The Effect of Repetitive Transcranial Magnetic Stimulation on Suicidal Ideation in Treatment-Resistant Depression: A Meta-Analysis

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ABSTRACT

Objective: To quantitatively synthesize the literature on the effects of repetitive transcranial magnetic stimulation (rTMS) on suicidal ideation (SI) in patients with treatment-resistant depression.

Data Sources: A literature search was conducted using PubMed, SCOPUS, Ovid, MEDLINE, Embase, and Web of Science from inception to January 11, 2021, for the keywords *repetitive transcranial magnetic stimulation, suicidal ideation, suicidality, treatment-resistant depression, refractory depression, transcranial magnetic stimulation,* and *brain stimulation*.

Study Selection: A total of 16 publications were eligible for inclusion. Studies were included that investigated the effects of rTMS in adolescents and/or adults 16 years or older diagnosed with unipolar or bipolar depression with suicidal ideation data before and after rTMS intervention.

Data Extraction: Data were extracted and managed using Covidence. Extracted data included authors, publication year, country of origin, study design, patient demographics, primary diagnosis, comorbidities, mean age, outcome assessment instruments, detailed stimulation parameters, sham control procedures, and any serious adverse events related to SI.

Results: A quantitative analysis of effect size using Hedges *g* was calculated for both randomized controlled trials and all other uncontrolled trials. We found a decrease in SI scores in randomized controlled trials ($g = 0.158$, 95% confidence interval [CI] = −0.078 to 0.393, $P = .191$), although the effect was not significant. There was a significant decrease in suicidal ideation scores for uncontrolled trials ($g = 0.692$, 95% CI = 0.463 to 0.922, $P < .001$).

Conclusions: Our findings suggest that rTMS may be an effective treatment for SI in individuals with treatment-resistant depression, although further investigation is warranted.

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Major depressive disorder (MDD) is the leading cause of disability worldwide, with more than 322 million people—4.4% of the world's population—afflicted.[1] More than 50% of MDD patients fail to remit after first-line therapy (psychotherapy, pharmacotherapy, or both).[2] In fact, a progressively smaller proportion of patients remit with each subsequent medication trial, with only 10%–15% of patients reaching remission after a fourth antidepressant trial.[3–5] A sizeable proportion of patients with MDD who do not respond to first-line treatment can go on to develop treatment-resistant depression (TRD).[6] This prolonged illness leads to decreases in productivity, diminished quality of life, more hospitalizations, increased health care costs, and a higher risk of suicidal ideation (SI).[7–11]

Suicidality, which includes SI, is a critical symptom in patients with major depressive episodes (MDEs) and impacts both the modality and intensity of treatment interventions.[12] The lifetime rate of deaths due to suicide is 15%–20% among patients with MDD or bipolar depression,[13] with an MDE as one of the significant risk factors for death by suicide.[14] Globally, suicide is the second leading cause of death in 15- to 29-year-olds; greater than 800,000 deaths due to suicide occur each year.[15] Approximately 30% of patients with TRD attempt suicide at least once,[16] which is twice the lifetime rate of patients with non-resistant depression.[14] SI in adolescents is a major public health concern, as SI and suicidal behavior in early life can be a predictor of similar behavior in adulthood.[17,18] In addition, suicide is a leading cause of death in adolescents worldwide,[15,19] but there are no standard, brain-based interventions for acute or chronic adolescent suicidality.[20,21]

Current treatment recommendations for TRD and suicidality include electroconvulsive therapy (ECT)[22,23] and pharmacologic options like lithium[24,25] or ketamine.[26] While ECT is the most effective treatment for TRD, its use is restricted by significant social stigma[27,28] and cognitive adverse effects.[29,30] Lithium is associated with reduced suicidality when used as a maintenance or augmentation treatment, but it is not specifically indicated for the treatment of acute SI.[31,32] While intranasal esketamine and intravenous ketamine are promising treatments, data around their efficacy are limited.[33,34] Additionally, first-line treatments such as pharmacotherapy or psychotherapy work over long periods of time, often taking a month or more to

Clinical Points

- There are few data on the clinical effectiveness of rTMS for suicidal ideation.
- For patients with treatment-resistant depression and suicidal ideation, rTMS can be a clinically effective treatment option.

take effect, which makes them less than ideal for the urgent resolution of SI.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neurostimulation treatment for TRD that induces lasting changes in the activity of brain regions involved in regulating thoughts, emotions, and behavior.[35,36] In rTMS treatment, an electromagnetic coil produces a powerful but brief magnetic field that passes through the skin, soft tissue, and skull and induces an electrical field that depolarizes neurons in the target cortical area.[37] By applying stimulation repetitively, TMS has been shown to alter the excitability of the stimulated area of the brain, which outlasts the period of stimulation.[38] Over 15 years of research has shown that rTMS, particularly when applied to the prefrontal cortex, is an effective antidepressant treatment.[38] The added benefit of rTMS is that it is typically performed on an outpatient basis, requires no anesthetic, and has a fairly benign side effect profile,[37] providing an accessible treatment option for patients with TRD and SI.

While the efficacy of rTMS as a treatment for MDD has been established, the literature reflects a wide variety of coil placements, stimulation parameters, and outcome measures.[39] In perhaps the most common form, an FDA-approved figure-of-eight coil is used to deliver 10 Hz stimulation over a treatment session of 20–40 minutes.[40] A newer form of rTMS called intermittent theta burst stimulation (iTBS) has been found to be as effective as the standard form of stimulation and uses the same coil to deliver treatments in just 3 minutes.[41,42] iTBS is a patterned form of rTMS that delivers treatment at frequencies that are similar to the brain's endogenous theta and gamma oscillatory rhythms and is associated with potent effects on synaptic long-term potentiation.[41] A second coil design, also approved by the FDA, was developed to enable to the direct modulation of relatively larger and deeper brain regions, termed deep transcranial magnetic stimulation (DTMS).[43] In more recent studies, the efficacy of delivering multiple rTMS treatments in 1 day—with a commensurate decrease in overall treatment length—has also been investigated.[44–47] Given the relative absence of studies examining the effects of rTMS on suicidal ideation, all brain targets, rTMS modalities, and stimulation parameters were included in this review.

Despite the growing interest in nonpharmacological options for patients with TRD, we were unable to identify any published meta-analyses examining the effect of rTMS on SI over the lifespan. Examining the effects of rTMS on SI has the potential to provide valuable information regarding the treatment of TRD and suicidality across age groups and developmental stages. As such, we undertook a quantitative meta-analysis of the literature looking at the effects of rTMS on SI in patients with depression across the lifespan. We hypothesized that active rTMS would demonstrate superior effects on reducing SI compared to sham across controlled studies.

METHODS

A systematic review of the literature on rTMS protocols for the treatment of SI in patients with TRD was executed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[48] This meta-analysis was registered with PROSPERO (ID number: CRD42020179805).

Literature Search Strategy

We searched the literature in the following databases: PubMed, SCOPUS, Ovid, MEDLINE, Embase, and Web of Science for keywords, text words, and medical subject headings related to rTMS treatment for TRD and SI. Our initial search was from inception up to April 10, 2020, and we subsequently updated the search up to January 11, 2021, for new publications. We checked the reference lists of identified studies as a supplement to our electronic search but did not identify any additional study that met our inclusion criteria.

Inclusion Criteria

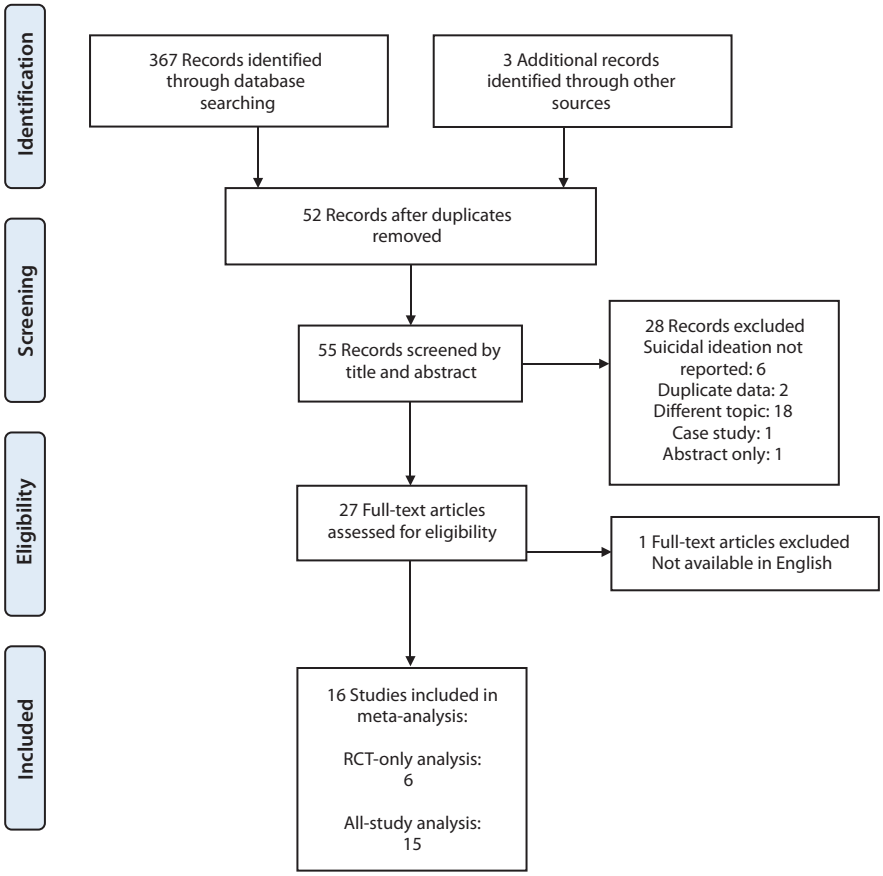
Selected studies were required to meet the following inclusion criteria:

1. Studies utilizing rTMS as an intervention in adolescents and/or adults ages ≥ 16 years
2. Studies either analyzed and reported suicide item scores taken from larger depression scales (eg, Hamilton Depression Rating Scale [HDRS][49]) or data from dedicated SI scales (eg, Beck Scale for Suicide Ideation [BSI][50])
3. A sample population with either bipolar or unipolar depression
4. The full study text was available in English

Due to the limited number of studies examining rTMS and SI, any form of rTMS intervention was included. Studies were not limited by the inclusion of comorbid Axis I disorders. Randomized controlled trials (RCTs) and uncontrolled (open) trials were included, as well as retrospective analyses of suicidal ideation data from larger clinical trials and case series. Only randomized controlled trials were included for primary quantitative analysis. A secondary quantitative analysis included active arms of randomized trials as well as the remaining uncontrolled trials, and a third exploratory analysis included only uncontrolled trials. Abstracts, individual case reports, reviews, and editorials were excluded.

All titles and abstracts identified by the literature search were independently reviewed for study inclusion by 2 authors, S.M. and G.K. Any disagreements were resolved

Figure 1. PRISMA Flow Diagram



through discussions with a third author, D.M.B. If the study details were unclear from the abstract, the full text was retrieved for further assessment.

Outcomes

The primary outcome of interest of this meta-analysis was change in SI score between study baseline and treatment end.

Data Abstraction

Data were extracted and managed using Covidence. Extracted data included (1) authors, (2) publication year, (3) country of origin, (4) study design, (5) patient demographics, (6) primary diagnosis, (7) comorbidities, (8) mean age, (9) outcome assessment instruments, (10) detailed stimulation parameters, (11) sham control procedures, and (12) any serious adverse events (SAEs) related to SI.

Quantitative Analysis

***Hedges* g.** Hedges *g*—standardized mean difference (*d*) multiplied by a correction factor (*J*)—was computed as an index of effect size for continuous outcome data. This approach uses the standard deviations to standardize the mean differences to a single scale and computes the study weights, making it possible to compare outcomes from different scales. An effect size of 0.2 is considered a small effect, 0.5 is considered medium, and 0.8 is considered a large effect.[51]

For studies that did not give the mean difference with standard deviation between posttreatment and baseline scores, an estimate of standard deviation was calculated using pre- and posttreatment values and an estimate of the pre–post correlation coefficient for the respective clinical scale. The sample size of the individual studies influenced the weight given to their means and SDs in the analyses.

Test of heterogeneity. Heterogeneity between studies was assessed with the total *Q* statistic, which estimates whether the variance of the effect sizes is greater than expected due to sampling error. A *P* value smaller than .01 provides indication of significant heterogeneity.[52] The I^2 statistic was performed for each analysis to indicate what percentage of the observed variance in effect sizes reflects real differences. I^2 values of 25%, 50%, and 75% represent little, moderate, and high heterogeneity, respectively.[51]

A funnel plot was visually inspected to assess potential publication bias. Analyses were conducted using Comprehensive Meta-Analysis,[53] and R[54] was used for data processing.

Risk of bias assessment. To determine the risk of bias in eligible randomized controlled trials, authors reviewed the adequacy of randomization, allocation concealment, blinding, and whether incomplete reporting of outcome data occurred. The Cochrane risk of bias tool was followed as a guideline.[51]

Table 1. Study Design and Demographic and Clinical Characteristics of Subjects Included in Analysis

Study	Study design	Country	Outcome scale	Sample size	Primary diagnosis	Comorbidities	Mean age (SD), y	Serious adverse events related to SI
Keshtkar et al 2011[57]	RCT	Iran	BDI	73	MDD (n = 73)	NA	34.0 (9.9)	None
George et al 2014[46]	RCT	US	BSI	41	Not specified	PTSD (n = 17), TBI (n = 1), both (n = 23), substance abuse (n = 40)	42.6 (15.7)	None
Desmyter et al 2016[47]	RCT	US	BSI	32	MDD (n = 32)	NA	41.9 (11.8)	None
Yesavage et al 2018[55]	RCT	US	BSI	164	MDD (n = 164)	PTSD (n = 81), substance abuse (n = 88)	55.2 (12.4)	None
Pan et al 2020[56]	RCT	China	BSI	42	MDD (n = 42)	NA	18.14 (3.94)	None
Rao et al 2020[58]	RCT	US	BSI	30	MDD (n = 30)	TBI (n = 30)	Active: 39.8 (14.2) Sham: 40.2 (14.6)	None reported
Bloch et al 2008[60]	Open label	Israel	SIQ	9	MDD (n = 9)	OCD (n = 2), PTSD (n = 3), ADHD (n = 3), borderline personality disorder (n = 5), ED (n = 3), SUB (n = 6), dysthymia (n = 2), panic disorder (n = 3), OCD (n = 3), GAD (n = 7)	17.2 (SD not reported)	1 participant attempted suicide 3 weeks after end of therapy; judged to be unrelated to therapy
Hadley et al 2009[59]	Open label	US	BSI	19	MDD (n = 11) BP (n = 8)	OCD (n = 3), GAD (n = 3), anxiety disorder NOS (n = 2), panic disorder (n = 4), social phobia (n = 1)	48.0 (16)	None
Berlim et al 2014[43]	Open label	Canada	BSI	17	MDD (n = 17)	Dysthymia (n = 2), panic disorder (n = 3), OCD (n = 3), GAD (n = 7)	47.12 (13.26)	None
Croarkin et al 2018[64]	Retrospective data analysis	US	C-SSRS	19	MDD (n = 19)	NA	16.0 (1.29)	None
Fitzgerald et al 2018[61]	Single blind	Australia	BSI	115	MDD (n = 115)	BP (n = 16)	49.0 (13.8)	None
Pan et al 2018[66]	Case series	China	BSI	3	MDD (n = 3)	NA	16.0 (SD not reported)	None
Weissman et al 2018[62]	Retrospective data analysis	Canada	HDRS	156	MDD (n = 156)	NA	47.9 (13.1)	None reported
Abdelnaim et al 2020[63]	Retrospective data analysis	Germany	HDRS	332	Not specified	NA	47.3 (12.3)	None reported
Cole et al 2020[45]	Open label	US	C-SSRS	21	MDD (n = 19), BPII (n = 2)	NA	44.86 (17.21)	None
Ozcan et al 2020[65]	Case series	Turkey	C-SSRS	30	MDD (n = 30)	NA	Not reported	None

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BP = bipolar disorder, BPII = bipolar disorder type II, BSI = Beck Scale for Suicide Ideation, C-SSRS = Columbia-Suicide Severity Rating Scale, ED = eating disorder, GAD = generalized anxiety disorder, HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, NA = not available, NOS = not otherwise specified, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, SIQ = Suicidal Ideation Questionnaire, SUB = substance abuse, TBI = traumatic brain injury.

RESULTS

A total of 16 publications met inclusion criteria (Figure 1). Stimulation parameters and study characteristics are summarized in Tables 1 and 2, respectively. Six publications were randomized controlled trials (Yesavage et al,[55] George et al,[46] Desmyter et al,[47] Pan et al,[56] Keshtkar et al,[57] Rao et al[58]), 4 were open-label trials (Berlim et al,[43] Hadley et al,[59] Bloch et al,[60] Cole et al[45]), 1 was a single-blind trial (Fitzgerald et al[61]), 3 were retrospective analyses of primary studies (Weissman et al,[62] Abdelnaim et al,[63] Croarkin et al[64]), and 2 were case series (Ozcan et al,[65] Pan et al[66]). Randomized controlled trials included a total of 506 patients for analysis, and the combined uncontrolled trials, single-blind trial, case series, retrospective analyses, and active arms of the RCT trials included a total of 833 patients for analysis.

Quantitative Analysis of rTMS vs Sham on SI in RCTs

Trials were included in this analysis if they compared rTMS treatment to sham. One of the RCTs (Keshtkar et al[57]) was not included in this analysis as the rTMS treatment was compared to ECT treatment, not sham. One retrospective analysis (Weissman et al[62]) was included as it compared active to sham rTMS treatment in its analysis.

All 5 RCTs included in the analysis collected SI data using the BSI (see Table 1). Weissman et al[62] was the only trial included that used the suicidal ideation item (item 3) of the HDRS-17. Yesavage et al[55] collected pre- and post-intervention data with both the BSI and the Columbia-Suicide Severity Rating Scale (C-SSRS). Only the BSI data were included in this analysis to remain consistent with the scales used by the other trials. Weissman et al[62] reported an analysis of both bilateral rTMS and unilateral rTMS vs sham treatment. Both these analyses were included separately in

Table 2. Detailed Treatment and Stimulation Parameters

Study	rTMS modality	Total no. of treatments	Pulses per session	Total no. of pulses	Laterality/ location	Frequency	Intensity	Trains
Keshtkar et al 2011[57]	Not specified	10	408	4,080	Left DLPFC	Not specified	90% rMT	Not specified
George et al 2014[46]	HFL (accelerated)	9	6,000	54,000	Left DLPFC	10 Hz	120% rMT	5 s train, 30 s intertrain interval
Desmyter et al 2016[47]	iTBS (accelerated)	5	1,620	8,100	Left DLPFC	50 Hz	110% rMT	2 s train, 8 s intertrain interval
Yesavage et al 2018[55]	HFL	20–30	4,000	80,000–120,000	Left DLPFC	10 Hz	120% rMT	Not specified
Pan et al 2020[56]	HFL	7	6,000	42,000	Left DLPFC	10 Hz	100% rMT	5 s train, 15 s intertrain interval
Rao et al 2020[58]	LFR	20	1,200	24,000	Right DLPFC	1 Hz	110% rMT	4 trains of 300 pulses, 60 s intertrain interval
Bloch et al 2008[60]	HFL	14	400	5,600	Left DLPFC	10 Hz	80% rMT	2 s train, 58 s intertrain interval
Hadley et al 2009[59]	HFL (accelerated)	10	6,800	68,000	Left DLPFC	10 Hz	120% rMT	5 s train, 10 s intertrain interval
Berlim et al 2014[43]	DTMS	20	3,000	60,000	Left DLPFC	20 Hz	120% rMT	2 s train, 20 s intertrain interval
Croarkin et al 2018[64]	HFL	30	3,000	90,000	Left DLPFC	10 Hz	120% rMT	4 s train, 15 s intertrain interval
Fitzgerald et al 2018[61]	HFL	20	3,150	63,000	Left DLPFC	10 Hz	120% rMT	4.2 s train, 25 s intertrain interval
	HFL (accelerated)	18	10,500	63,000	Left DLPFC	10 Hz	120% rMT	4.2 s train, 15 s intertrain interval
Pan et al 2018[66]	HFL	7	6,000	42,000	Left DLPFC	10 Hz	100% rMT	5 s train, 15 s intertrain interval
Weissman et al 2018[62]	HFL	15	Varied	Varied	Varied	Varied	Varied	Varied
Abdelnaim et al 2020[63]	HFL	30	Varied	120,000	Varied	Varied	Varied	Varied
Cole et al 2020[45]	iTBS (accelerated)	50	1,800	90,000	Left DLPFC	50 Hz	90% rMT	2 s train, 8 s intertrain interval
Ozcan et al 2020[65]	HFL	20–30	1,000	20,000–30,000	Left DLPFC	20 Hz	100% rMT	2 s train, 28 s intertrain interval

Abbreviations: DLPFC = dorsolateral prefrontal cortex, DTMS = deep transcranial magnetic stimulation, HFL = high frequency left, iTBS = intermittent theta burst stimulation, LFR = low frequency right, rMT = resting motor threshold, rTMS = repetitive transcranial magnetic stimulation.

the calculation of effect size, with the sham treatment data repeated for each analysis, as was performed in the original publication. Desmyter et al[47] employed a crossover study design, with one patient group receiving first active rTMS then sham and the second patient group receiving sham treatment before active rTMS. For the purposes of this review, only the data of the first half of the trial—before the crossover—were included, comparing the first group's active treatment scores to the second group's sham scores.

In the 6 trials analyzed, the cumulative effect size was 0.158 (95% CI = −0.078 to 0.393) (Figure 2A). The change in suicidal ideation scores for active treatment was not significantly greater than for sham ($P = .191$). It should be noted that the effect size of Pan et al[56] was significantly larger ($g = 1.060$) than the remaining studies in the RCT analysis. This result does not significantly affect the overall effect size for the RCT group, likely due to the relatively small sample size of this trial (n = 42).

The test for heterogeneity was moderate ($I^2 = 33.594\%$, $Q = 9.035$, $P = .172$), which supports using a random effects model, as the trials involved had significant clinical and methodological differences. However, both fixed and random effects models were computed, with no significant statistical difference in the results.

Quantitative Analysis of rTMS on SI in All Studies

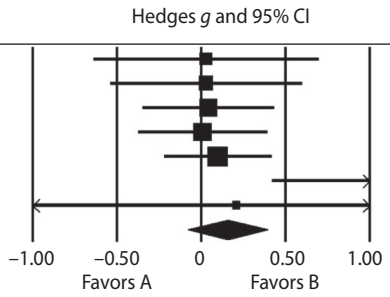
A secondary analysis was conducted with data from the remaining non-randomized studies and the active arms of the randomized trials. Fifteen of the 16 studies were included. Rao et al[58] could not be included in this analysis as there were no posttreatment data provided for the active treatment arm alone. Fitzgerald et al[61] employed a single-blind study design, randomizing participants to either an accelerated or standard 10 Hz treatment protocol (see Table 2 for detailed stimulation parameters), with assessment raters blind to the treatment condition. Each treatment protocol was included separately in this analysis, as presented in the original paper.

Of the studies included, 8 used the BSI (George et al,[46] Desmyter et al,[47] Berlim et al,[43] Hadley et al,[59] Fitzgerald et al,[61] Yesavage et al,[55] Pan et al,[56] and Pan et al[66]), 1 used the Suicidal Ideation Questionnaire (SIQ) (Bloch et al[60]), 3 used the C-SSRS (Ozcan et al,[65] Croarkin et al,[64] and Cole et al[45]), and 3 used the suicide item of the HDRS (Keshtkar et al,[57] Abdelnaim et al,[63] and Weissman et al[62]). Keshtkar et al[57] reported on SI data from both the Beck Depression Inventory (BDI) and HDRS, but only the HDRS data were included in the analysis in order to be as consistent as possible with the other publications. Croarkin et al[64] reported data

Figure 2. Forest Plots for Hedges *g* Analyses

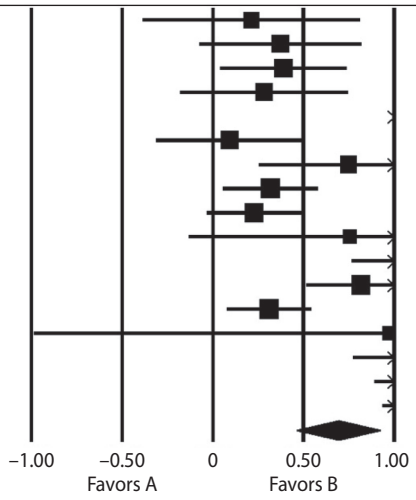
A. Analysis of RCT Studies

Study name	Hedges *g*	Standard error	Variance	Lower limit	Upper limit	*Z* value	*P* value
			Statistics for each study				
George 2014[46]	0.030	0.340	0.116	−0.636	0.697	0.089	.929
Desmyter 2016[47]	0.030	0.290	0.084	−0.538	0.599	0.105	.917
Weissman 2018 (bilateral)[62]	0.044	0.199	0.039	−0.345	0.434	0.223	.823
Weissman 2018 (unilateral)[62]	0.010	0.195	0038	−0.373	0.393	0.051	.959
Yesavage 2018[55]	0.100	0.163	0.026	−0.219	0.418	0.613	.540
Pan 2020[56]	1.060	0.324	0.105	0.424	1.695	3.270	.001
Rao 2020[58]	0.210	1.000	1.000	−1.750	2.170	0.210	.834
	0.158	0.120	0.014	−0.078	0.393	1.309	.191



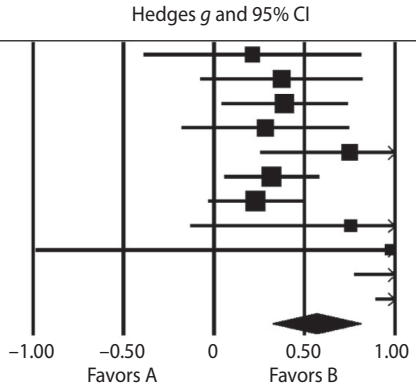
B. Analysis of All Studies

Study name	Hedges *g*	Standard error	Variance	Lower limit	Upper limit	*Z* value	*P* value
			Statistics for each study				
Bloch 2008[60]	0.212	0.305	0.093	−0.386	0.810	0.694	.488
Hadley 2009[59]	0.373	0.228	0.052	−0.074	0.820	1.636	.102
Keshtkar 2011[57]	0.390	0.177	0.031	0.043	0.736	2.206	.027
Berlim 2014[43]	0.283	0.236	0.056	−0.179	0.746	1.200	.230
George 2014[46]	2.576	0.548	0.300	1.502	3.650	4.701	.000
Desmyter 2016[47]	0.093	0.206	0.042	−0.311	0.497	0.451	.652
Croarkin 2018[64]	0.749	0.251	0.063	0.257	1.241	2.982	.003
Fitzgerald 2018 (accelerated)[61]	0.317	0.133	0.018	0.057	0.578	2.389	.017
Fitzgerald 2018 (standard)[61]	0.228	0.132	0.018	−0.032	0.487	1.720	.085
Pan 2018[66]	0.755	0.452	0.204	−0.130	1.640	1.672	.094
Weissman 2018 (bilateral)[62]	1.106	0.174	0.030	0.765	1.448	6.342	.000
Weissman 2018 (unilateral)[62]	0.817	0.153	0.023	0.518	1.116	5.349	.000
Yesavage 2018[55]	0.309	0.119	0.014	0.077	0.542	2.608	.009
Abdelnaim 2020[63]	0.973	0.998	0.995	−0.983	2.928	0.975	.330
Cole 2020[45]	1.413	0.326	0.106	0.774	2.051	4.337	.000
Ozcan 2020[65]	1.385	0.252	0.064	0.891	1.880	5.493	.000
Pan 2020[56]	1.563	0.320	0.102	0.936	2.190	4.889	.000
	0.692	0.117	0.014	0.463	0.922	5.913	.000



C. Analysis of Non-RCT Studies

Study name	Hedges *g*	Standard error	Variance	Lower limit	Upper limit	*Z* value	*P* value
			Statistics for each study				
Bloch 2008[60]	0.212	0.305	0.093	−0.386	0.810	0.694	.488
Hadley 2009[59]	0.373	0.228	0.052	−0.074	0.820	1.636	.102
Keshtkar 2011[57]	0.390	0.177	0.031	0.043	0.736	2.206	.027
Berlim 2014[43]	0.283	0.236	0.056	−0.179	0.746	1.200	.230
Croarkin 2018[64]	0.749	0.251	0.063	0.257	1.241	2.983	.003
Fitzgerald 2018 (accelerated)[61]	0.317	0.133	0.018	0.057	0.578	2.389	.017
Fitzgerald 2018 (standard)[61]	0.228	0.132	0.018	−0.032	0.487	1.720	.085
Pan 2018[66]	0.755	0.452	0.204	−0.130	1.640	1.672	.094
Abdelnaim 2020[63]	0.973	0.998	0.995	−0.983	2.928	0.975	.330
Cole 2020[45]	1.413	0.326	0.106	0.774	2.051	4.337	.000
Ozcan 2020[65]	1.385	0.252	0.064	0.891	1.880	5.493	.000
	0.565	0.124	0.015	0.322	0.807	4.564	.000



Abbreviation: RCT = randomized controlled trial.

from both the C-SSRS and the Children's Depression Rating Scale—Revised (CDRS-R); however, as above, only the C-SSRS was included in the analysis for consistency. Cole et al[45] reported the SI data from the C-SSRS, the HDRS-17, and the Montgomery-Asberg Depression Rating Scale (MADRS); however, in keeping with the above, only the data from the C-SSRS were used in this analysis.

For the combined random effects analysis, the cumulative effect size was 0.692 (95% CI = 0.463 to 0.922) (Figure 2B). There was a significant decrease in SI scores after rTMS treatment ($P < .001$). The test for heterogeneity was significant as expected ($I^2 = 79.450\%$, $Q = 77.859$, $P < .001$), so a random effects model was employed, although there was no significant difference between the fixed and random effect model.

Exploratory Analysis of rTMS on SI on All Studies Excluding RCTs

An exploratory analysis was conducted using all data except those from the RCTs. Ten of the studies were included. As stated above, Keshtkar et al[57] was not treated as an RCT as it compared the effect of rTMS vs ECT on SI, and as such was kept in this analysis. Again, both the accelerated and standard arms of the single-blind study from Fitzgerald et al[61] were included as separate entries in this analysis.

Of the studies included, 4 used the BSI (Hadley et al,[59] Berlim et al,[67] Fitzgerald et al,[61] and Pan et al[66]), 1 used the SIQ (Bloch et al.[60]), 2 used the HDRS (Keshtkar et al[57] and Abdelnaim et al[63]), and 3 used the C-SSRS (Cole et al,[45] Croarkin et al,[64] and Ozcan et al[65]). As mentioned above, Keshtkar et al[57] reported data from both the BDI and HDRS, but only the HDRS data were used in this analysis for consistency. Cole et al[45] reported the SI data from the C-SSRS, HDRS-17, and MADRS; however, in keeping with the above, only the data from the C-SSRS were used in this analysis. Croarkin et al[64] reported data from both the C-SSRS and the CDRS-R; however, as above, only the C-SSRS was included in the analysis for consistency.

For the combined random effects analysis, the cumulative effect size was 0.565 (95% CI = 0.322 to 0.807) (Figure 2C). There was a significant decrease in SI scores after rTMS treatment ($P < .001$). The test for heterogeneity was significant as expected ($I^2 = 66.426\%$, $Q = 29.785$, $P = .001$), so a random effects model was employed, although there was no significant difference between the fixed and random effect model.

DISCUSSION

To our knowledge, this is the first quantitative summary of the effects of rTMS on SI in TRD. We found that there was a significant reduction in SI scores after rTMS treatment in our analysis of the all studies group but not the RCT group. Previous studies have endeavored to systematically review the extant literature but did not attempt a quantitative analysis. Bozzay et al[68] conclude that there was preliminary promise for rTMS for SI but called for further suicide-specific research, as well as the development of mechanistic targets for SI. Serafini et al[69] conclude that rTMS has been found to attenuate multiple dimensions of suicidality but that further sham-controlled studies were needed.

The difference in effect size between our RCT analysis and the all-studies analysis was quite large, likely due to a combination of factors. A probable contributor to this disparity is the large effect size ($g = 0.973$) reported in Abdelnaim et al,[63] which may have had a disproportionate influence on the results due to its much larger sample size (n = 332). Additionally, the largest RCT included (Yesavage et al[55] [n = 150]) reported no significant difference in SI reduction compared to sham ($g = 0.10$), and many of the smaller RCTs were largely negative. Another factor that may have contributed to the disparity in results is the heterogeneity of the inclusion criteria with respect to baseline SI symptoms. Some of the trials were conducted in an inpatient setting where participants had been hospitalized for acute suicidality or attempted suicide, while some excluded high baseline SI, and others made no mention of baseline SI at all. The lack of standardization around baseline SI may also contribute to the variability in our results and obscures the interpretation of the discrete effects of rTMS on SI.

The studies in this review reflect the wide variation of techniques found in the rTMS literature. Optimal coil placement, stimulation frequency, rTMS modality, and treatment course length have yet to be established in clinical practice, although each modality included here (iTBS, 10 Hz, DTMS) has been shown to be efficacious.[43,47,62] This wide range of parameters may reflect the ability of rTMS to target different underlying brain circuitry and the likely heterogeneity underlying the biology of MDD. This is congruent with recent efforts in rTMS research to personalize treatment in a number of ways, including individualizing therapeutic parameters,[70] incorporating individual anatomic data in treatment,[71] selecting individual brain connectivity patterns,[72] or targeting depression "biotypes"—defined by homogeneous patterns of dysfunctional connectivity—based on brain network analyses.[73]

Treatment with rTMS addresses corticolimbic inhibitory-excitatory imbalances associated with MDD, an imbalance that is also a likely explanation for the emotional dysregulation and disrupted executive function associated with SI.[74] Further, there is evidence that rTMS has similar effects to ECT on a molecular level, including increased brain-derived neurotrophic factor (BDNF), increased monoamine turnover, and normalization of the hypothalamic-pituitary-adrenal axis.[75] One study included in this review, Weissman et al,[62] found a significant decrease in SI in the bilateral rTMS treatment group when compared to sham and posited that it was the targeting of the right dorsolateral prefrontal cortex (DLPFC), not the treatment modality, that decreased SI.[62,76] The vast majority of rTMS trials in the literature and in this review target the left DLPFC only, leaving alternative treatment locations as a parameter that warrants further investigation. Recent trends in the literature suggest that suicidal ideation can be thought of as its own symptom domain and treatment target. A large study (n = 660) conducted a factor analysis and found that the suicide and guilt items belonged to a "cognitive" factor, one of 3 factors for the HDRS-17.[77] A principal component analysis in a study of suicide attempters (n = 281) isolated the suicide item into one of 3 independent factors for the total HDRS-17.[78] SI as a separate symptom domain is an area of active research, and concerted efforts need to be made going forward to establish its underlying cause and most effective treatment approach.

The clinical and biological evidence of the effects of rTMS is encouraging, especially considering the burgeoning research into accelerated courses of rTMS, some of which were included in this review. Accelerated rTMS (arTMS) delivers multiple rTMS treatments per day, resulting in a

remarkably shortened treatment course, typically 1 week or less.[46,47,79] This new application of rTMS may address the need for rapid alleviation of SI symptoms and the desire for alternative treatment options to polypharmacy or convulsive therapy.

A focus on the treatment of SI in adolescence has great potential importance, due to the long-term impact of TRD across the lifespan,[7–9] as well as the gaps in knowledge created by frequent exclusion of adolescents with SI from research protocols.[20,80] The studies included in this review were insufficient for us to conduct an adolescent-only analysis. Croarkin et al[64] (n = 19) concluded that rTMS was safe and feasible in an adolescent population but found that the change in SI was statistically insignificant when adjusted for the change in overall depressive severity. Pan et al[66] (n = 3) employed an accelerated treatment course and also found it to be well tolerated. There was a significant decrease in SI over the treatment course; however, the very small sample size is a major limitation of this work. Bloch et al[60] (n = 9) did not find a significant decrease in SI after rTMS intervention but again found the treatment to be well tolerated. Larger randomized controlled trials are required to establish the efficacy of rTMS in treating SI in adolescents.

Limitations

This study has several limitations. First, the number of published studies examining the effects of rTMS on SI is limited, and many had small sample sizes. Due to the small number of published studies available, the criteria for the sample populations were kept broad, allowing for the inclusion of patients with a number of comorbidities. This prevents more effective pooling of data between studies. Additionally, some of the studies included in this review were designed to assess the effect of rTMS on depressive symptoms as a whole and reported SI data only as a secondary outcome.

The number of randomized, sham-controlled trials available to include in this review was small, in part due to the tendency to exclude those with elevated SI from rTMS for TRD studies. This practice often limits the assessment of suicidality to SI alone—which is the case in the majority of studies included in this review—and does not account for other dimensions such as suicidal behavior or attempts. This is often perpetuated by the use of assessment scales that are only designed to measure SI, such as the widely used BSI or C-SSRS. Both the BSI and C-SSRS have been found to be sensitive to change in SI symptoms,[50,81] but there are a variety of outcome assessments employed across the included trials. A number of included studies relied on a single item of a broader depression assessment scale to report changes in SI, most commonly the suicide item of the HDRS. Analyses of individual items of the HDRS have found the suicide item to be sensitive to change[82,83]—although there is not yet a consensus on its degree of sensitivity—and it only captures a narrow scope of the broader spectrum of suicidality symptoms.

There is evidence in the literature that SI may have distinct biological mechanisms compared to other depressive symptoms, yet the extent to which SI is independent from broader depressive symptoms is unclear. Some of the studies included in this review did not control for collinearity in change in SI within the context of overall depressive symptom change, which is a potential confound of this analysis. Previous rTMS trials have typically included only those patients who have demonstrated resistance to conventional first-line therapies (primarily pharmacotherapy). Therefore, the current analysis does not inform the effect that rTMS may have on SI in treatment-naive populations. This is a potential future avenue of research that remains to be explored.

The final limitation is the large variability in rTMS parameters between studies. A number of measures could be standardized to facilitate a more accurate comparison of change in SI across studies. Differences in coil placement, location of stimulation, number of treatments, number of pulses delivered per treatment, and frequency of stimulation all contribute to significant heterogeneity in the treatments included in this review. This variation is consistent with the realities of rTMS treatment in a clinical setting and reflects the lack of consensus as to optimal rTMS treatment parameters.

CONCLUSION

SI is not frequently singled out for analysis in large-scale rTMS clinical trials, as the majority of severe cases are immediately routed to more effective, although more invasive, treatments such as ECT and magnetic seizure therapy.[84] However, rTMS is an established alternative treatment for TRD. The added benefits of requiring no anesthesia, being available on an outpatient basis, and having minimal side effects make rTMS an increasingly attractive option to patients with TRD. The discrete effects on SI warrant further investigation. Concerted efforts to focus future research on populations with high depression symptom severity and suicidality along with dedicated measures of SI are needed. Efforts should be made to capture a complete picture of suicidality by assessing not only SI but behavior- and attempt-related outcomes as well. Since rTMS is becoming more widely integrated into treatment algorithms, patient registries may want to collect information on suicidal behavior and attempts as baseline risk factors that can be tracked over time. Since these are relatively rare outcomes, large-scale patient registries may be the only way to assess the impact of rTMS on these outcomes. Furthermore, unique biological mechanisms likely underlie SI; for example, there is evidence to suggest that loss of neuroplasticity may be a biological indictor of suicide risk.[85] Studies using biological assays such as functional neuroimaging and electroencephalography may help identify discrete brain targets of suicidal ideation in depressed patients. Despite increased severity portending worse outcomes with once daily rTMS, newer, more intensive and personalized protocols may successfully bridge this gap.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.