Effectiveness of Repetitive Transcranial Magnetic Stimulation in Depression, Schizophrenia, and Obsessive-Compulsive Disorder:

An Umbrella Meta-Analysis

Shweta Patel, MBBS, MPH(c); Suraiya Silvi, MD; Saral Desai, MD; Fayaz Rahman, MBBS; Nishitha Depa, MD(c), BSc; Sarah Hanif, MD; Syeda Rizvi, MD; Ya-Ching Hsieh MD, MPH, MBA; Preeti Malik, MD, MPH; Urvish Patel, MD, MPH; Zeeshan Mansuri; Rana Prathap Mercy Pathrose; Kapil Aedma, MD; and Tapan Parikh, MD, MPH

Abstract

Objective: To analyze the safety and efficacy of repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder, schizophrenia, and obsessive-compulsive disorder (OCD) via umbrella meta-analysis.

Data Sources: Meta-analysis studies were searched in PubMed from inception to May 2021 using the keywords *anxiety*, *depression*, *ADHD*, *schizophrenia*, *mood disorder*, *OCD*, *psychiatric disorders*, *GAD*, *bipolar disorders*, *ASD*, *PTSD*, *transcranial magnetic stimulation*, *transcranial*, *magnetic*, *stimulation*. PRISMA guidelines were followed.

Study Selection: Abstracts and full-length articles were reviewed for meta-analysis studies with data on the safety and efficacy of rTMS and sham and were collected for quantitative analysis. The full texts of all identified studies were independently screened and assessed to determine eligibility. Any disagreement was resolved through consensus.

Data Extraction: The descriptive variables extracted included the author names, study year, sample size, studies included in the meta-analysis, study period, and type of intervention.

Results: 28 meta-analyses were included; 13 were on treatment-resistant depression, 9 on schizophrenia, and 6 on OCD. In treatment-resistant depression, the rTMS group had higher odds of response compared to sham (odds ratio [OR]=3.27; 95% CI, 2.76–3.87; $P<.00001$) and higher odds of remission (secondary outcome) (OR=2.83; 95% CI, 2.33–3.45; $P<.00001$). rTMS was superior to sham in the reduction of negative symptoms of schizophrenia (mean difference [MD]: 0.47; 95% CI, 0.23–0.7; $P<.0001$). However, no significant difference was found between the effects of rTMS and sham on auditory hallucinations (MD: 0.24; 95% CI, 0.26–0.74; $P=.35$), which resulted in 94% heterogeneity. TMS was better than sham in reducing the severity of OCD symptoms (MD: 0.81; 95% CI, 0.53–1.10; $P<.00001$).

Conclusions: The effectiveness of rTMS for symptom reduction in various psychiatric disorders is associated with differences in neuropathology, disease-specific target site, and frequency of rTMS.

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Author affiliations are listed at the end of this article.

Transcranial magnetic stimulation (TMS) (also described as repetitive TMS [rTMS]) is a neuromodulation technique that was first indicated for depression but now has wider utility in a variety of mental health conditions. Numerous studies have been conducted on the use of TMS in a variety of conditions, and there are meta-analyses for each condition available as well that provide guidance on the effect size. With many meta-analyses at our disposal, a question remains about how to interpret these various combinations of individual studies. One of the statistical approaches that can be used to further understand the outcome of several studies is umbrella meta-analysis, which is an analysis of previously conducted meta-analyses. When the meta-analyses with overlapping studies are included in a new meta-analysis, the idea is that the overall impact of the individual effect sizes is already accounted for in the newly reported effect size.

Clinical Points

- In treatment-resistant depression, repetitive transcranial magnetic stimulation (rTMS) had higher odds of response and remission rates compared to sham.
- In schizophrenia, rTMS was superior to sham in the reduction of negative symptoms, but no significant difference was found between the effects of rTMS and sham on auditory hallucinations (ie, positive symptoms).
- rTMS was better than sham in reducing the severity of obsessive-compulsive disorder symptoms.

According to the National Institutes of Health, 7.1% of the US population suffers from a diagnosis of major depressive disorder (MDD), among which 63.8% have a severe impairment. Of this population, it was identified that only 65% of patients seek professional medical help.[1] Schizophrenia ranks among the top 15 causes of disability globally.[2] Approximately 50% of those with obsessive-compulsive disorder (OCD) have a serious impairment.[3] Although multiple treatment options are available for these psychiatric disorders, a few cases may be resistant to 1 or more treatments. In recent years, noninvasive brain stimulation (NIBS) has gained popularity when standard treatments such as medications and psychotherapy have not been effective.[4–8] NIBS refers to a set of technologies and techniques that modulate the excitability of the brain via transcranial stimulation to alter brain activity from the surface of the head without introducing instruments inside the body.

Two major types of NIBS are TMS and transcranial direct current stimulation.[9] TMS was developed in 1985, and it generates an electromagnetic field to induce an electric current in the brain.[10,11] rTMS is a type of TMS that uses electromagnetic pulses in rapid succession, causing a long-lasting effect.[12] The efficacy and safety of using these techniques have been studied in various disorders like anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), migraine, addiction, bipolar disorder, schizophrenia, and others.[9] Distinct frequencies of rTMS have different effects on the brain. Low-frequency rTMS has an inhibitory effect, while high-frequency rTMS has excitatory effects.[13] Various clinical trials and meta-analyses have been conducted over the years to assess the safety and efficacy of rTMS for psychiatric disorders.[14–18] In 2008, rTMS was approved by the US Food and Drug Administration (FDA) to treat MDD in patients who do not respond to at least 1 antidepressant medication in the current episode.[19]

For depression, it was shown that high-frequency rTMS has antidepressant properties when compared to sham rTMS; however, overall response and remission rates remain unclear.[20] For OCD, systematic review of randomized controlled trials (RCTs) found insufficient data to draw any conclusions regarding efficacy of transmagnetic stimulation in the treatment of OCD.[21] Hence, in this umbrella meta-analysis, also known as meta-meta-analysis, we aimed to evaluate the safety and efficacy of rTMS compared to sham treatment in treatment-resistant depression, OCD, and schizophrenia.

METHODS

Search Strategy and Selection Criteria

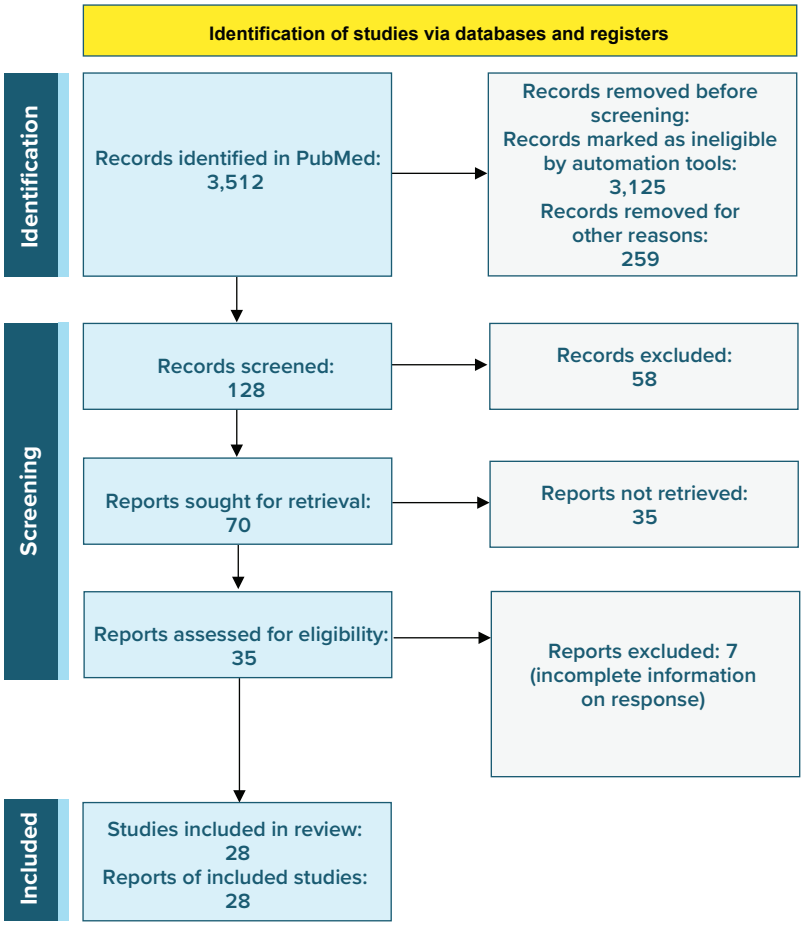
We followed PRISMA guidelines[22] in conducting the systematic review of meta-analysis studies comparing the safety and efficacy of rTMS and sham. Meta-analysis studies were searched in PubMed from inception to May 2021. The following keywords were used: ("anxiety"[Title/Abstract] OR "depression"[Title/Abstract] OR "ADHD"[Title/Abstract] OR "schizophrenia"[Title/Abstract] OR "mood disorder"[Title/Abstract] OR "OCD"[Title/Abstract] OR "psychiatric disorders"[Title/Abstract] OR "GAD"[Title/Abstract] OR "bipolar disorders"[Title/Abstract] OR "ASD"[Title/Abstract] OR "PTSD"[Title/Abstract]) AND ("transcranial magnetic stimulation"[MeSH Terms] OR ("transcranial"[All Fields] AND "magnetic"[All Fields] AND "stimulation"[All Fields]) OR "transcranial magnetic stimulation"[All Fields]). Meta-analyses comparing the safety and efficacy of rTMS versus sham in adult psychiatric disorders, including treatment-resistant depression, OCD, and schizophrenia, were included.

Meta-analyses that used rTMS as augmentation treatment and compared different types of rTMS were excluded. For depression, studies mainly included RCTs comparing rTMS to sham with no other antidepressants given during the trials. Additionally, studies not in English, observational studies, and those in pediatrics were excluded. The primary outcome was a clinical response defined as a 50% reduction in symptoms on the Hamilton Depression Rating Scale (HDRS)[23] or Montgomery-Asberg Depression Rating Scale (MADRS),[24] and remission (scores within normal range) was the secondary outcome. Other response scales used were the Yale-Brown Obsessive-Compulsive Scale (YBOCS),[25] Positive and Negative Syndrome Scale (PANSS),[26] Scale for the Assessment of Negative Symptoms (SANS),[27] Brief Psychiatric Rating Scale (BPRS),[28] and Auditory Hallucination Rating Scale (AHRS).[29] The flow diagram of the literature search and study selection process are provided in Figure 1.

Study Selection

We reviewed abstracts and full-length articles for meta-analysis studies with data on the safety and efficacy of rTMS and sham and collected them for quantitative analysis. All identified studies were independently screened (by S.P., S.S., F.R., Y-C.S.H.), and full texts were

Figure 1.
Flow Diagram of Literature Search and Selection Process of Included Studies



assessed to determine eligibility. Any disagreement was resolved through consensus (by T.P. and U.P.).

Data Extraction

Data were extracted (by S.P., S.S., F.R., and Y-C.S.H.). The descriptive variables extracted were author names, study year, sample size, studies included in the meta-analysis, study period, type of intervention, and various outcomes as described in Table 1.

Statistical Analysis

Review Manager version 5.3 software was used for analysis. We performed a random effects model irrespective of heterogeneity to estimate the pooled effect size (odds ratio and risk difference) and their respective 95% CI. I^2 values of 25%, 50%, and 75% represented low, medium, and high heterogeneity, respectively; $P < .05$ was considered statistically significant. The Newcastle-Ottawa Scale[54] was used to estimate the risk of bias among studies. Outlier studies were identified using funnel plot during sensitivity analysis, and leave-one-out method was used.

RESULTS

A total of 128 records were screened. Of these records, 35 articles were eligible after applying the inclusion and exclusion criteria. After the second round of data collection, 7 more studies were excluded due to incomplete/missing information. As of May 10, 2021, 28 meta-analysis studies were included for qualitative and quantitative analysis (Figure 1). Of these 28 studies, 13 meta-analyses were on treatment-resistant depression, 6 on OCD, and 9 on schizophrenia (negative symptoms and positive symptoms as measured by auditory hallucinations).

Depression

rTMS response. Seven meta-analysis studies reported their overall effect of response as an odds ratio (OR). In the meta-meta-analysis, we found that the rTMS

Table 1.

Meta-Analysis Studies Describing the Study Characteristics, Outcomes, and Complications for Individual Studies

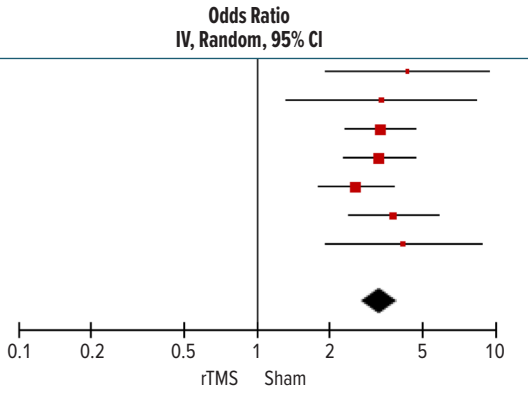
Study	Study Period	Studies Included in the Meta-Analysis	Sample Size, n	rTMS, n	Sham, n	Duration (sessions or weeks)	Diagnosis	Outcomes (scales used)
Depression								
Berlim et al, 2013[30]	January 1, 1995–July 20, 2012	7	279	162	117	Mean of 12.9 sessions	Depression	HDRS or MADRS response and remission
Berlim et al, 2013[31]	January 1, 1995–July 20, 2012	8	263	131	132	Mean of 12.6 sessions	Depression	HDRS or MADRS response and remission
Berlim et al, 2014[20]	1995–2012	29	1,371	730	641	Approximately 13 sessions	Depression	HDRS or MADRS response and remission
Brunoni et al, 2017[32]	Inception–October 1, 2016	81	4,233	NA	NA	≥10 sessions	Depression	HDRS or MADRS response and remission
Leggett et al, 2015[14]	Inception–January 2014	45	1,903	705	672	5–30 sessions over a period of 5 days to 6 weeks	Treatment-resistant Depression	HDRS or MADRS response and remission
Mutz et al, 2018[33]	Inception–May 1, 2018	56	3,058	1,598	1,460	≥1 sessions	Adult unipolar and bipolar depression	HDRS or MADRS response and remission
Zhang et al, 2015[34]	April 2012 (updated on January 2014)	10	634	164	114	1 to 6 weeks	Depression	HDRS or MADRS response and remission
Couturier, 2005[35]	1966–July 2003	6	68	37	31	5 to 10 days	Depression	HDRS or MADRS response and remission
Teng et al, 2017[36]	January 1990–June 2016	30	1,754	1,136	618	5 to 20 sessions	Depression	HDRS or MADRS response and remission
Kedzior et al, 2015[37]	Inception–September 30, 2013	16	495	253	242	5 to 15 sessions	Depression	HDRS or MADRS response and remission
Martin et al, 2003[15]	1966–March 2002	14	217	119	98	2 weeks	Depression	HDRS or MADRS response and remission
Lam et al, 2008[38]	September 2008	23	1,092	899	193	1 to 4 weeks	Depression	HDRS or MADRS response and remission
Sehatzadeh et al, 2019[39]	Inception–April 3, 2017	23				≥10 sessions	Depression	HDRS or MADRS response and remission
Obsessive-compulsive disorder								
Berlim et al, 2013[16]	1995–December 2012	10	282	161	121	≥5 sessions	OCD	YBOCS scores
Perera et al, 2021[40]	Inception–October 2020	26	781	413	368	≥5 sessions	OCD	YBOCS scores
Rehn et al, 2018[41]	Inception–December 2016	18	484	262	222	Mean of 14.63 sessions	OCD	YBOCS scores
Ma and Shi, 2014[42]	July 2014	9	290	154	136	≥5 sessions	OCD	YBOCS scores
Trevizol et al, 2016[43]	First RCT available–March 11, 2016	15	483	266	217	1 to 6 weeks	OCD	YBOCS scores
Zhou et al, 2017[44]	Inception–September 18, 2016	20	791	NA	NA	1 to 12 weeks	OCD	YBOCS scores
Schizophrenia								
Aleman et al, 2018[45]	Inception–December 2017	24	827	494	333	10 to 20 days	Schizophrenia	Negative symptom reduction using BPRS/SANS/PANSS
Freitas et al, 2009[46]	Inception–July 2008	8	107	63	44	4 to 20 sessions	Schizophrenia	Negative symptom reduction using BPRS/SANS/PANSS
He et al, 2017[47]	Inception– August 2015	7	412	235	177	≥5 or more sessions	Schizophrenia	Negative symptom reduction using BPRS/SANS/PANSS
Dlabač-de Lange et al, 2010[48]	1985–2008	9	213	NA	NA	NA	Schizophrenia	Negative symptom reduction using BPRS/SANS/PANSS
Shi et al 2014[49]	1998–2013	16	342	202	140	5 to 20 sessions	Schizophrenia	Negative symptom reduction using BPRS/SANS/PANSS
Aleman et al, 2007[50]	1999–2007	10	212	NA	NA	NA	Schizophrenia	Auditory hallucination reduction using AHRS
Freitas et al, 2009[46]	Inception–July 2008	9	178	122	94	4 to 20 sessions	Schizophrenia	Auditory hallucination reduction using AHRS
He et al, 2017[47]	Inception–August 2015	13	1,001	535	466	≥5 sessions	Schizophrenia	Auditory hallucination reduction using AHRS
Li et al, 2020[51]	1999–2018	11	278	145	133	10 to 20 sessions	Schizophrenia	Auditory hallucination reduction using AHRS
Otani et al, 2015[52]	1999–early 2013	10	284	147	137	4 to 20 sessions	Schizophrenia	Auditory hallucination reduction using AHRS
Zhang et al, 2013[53]	1985–2012	17	398	205	193	4 to 10 sessions	Schizophrenia	Auditory hallucination reduction using AHRS

Abbreviations: AHRS = Auditory Hallucination Rating Scale, BPRS = Brief Psychiatric Rating Scale, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable, OCD = obsessive-compulsive disorder, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, RCT = randomized controlled trial, rTMS = repetitive transcranial magnetic stimulation, YBOCS = Yale-Brown Obsessive-Compulsive Scale.

Figure 2.

Forest Plot of Depression Response Rate in rTMS and Sham Groups

Study or Subgroup	log[Odds Ratio]	SE	rTMS Total	Sham Total	Weight	Odds Ratio IV, Random, 95% CI
Berlim et al, 2013[30,a]	1.4586	0.4035	162	117	4.6%	4.30 [1.95–9.48]
Berlim et al, 2013[31,b]	1.209	0.4675	131	132	3.4%	3.35 [1.34–8.38]
Berlim et al, 2014[20,c]	1.1939	0.1732	730	641	24.8%	3.30 [2.35–4.63]
Brunoni et al, 2017[32,c]	1.1878	0.1745	0	0	24.5%	3.28 [2.33–4.62]
Leggett et al, 2015[14]	0.9603	0.1830	705	672	22.2%	2.61 [1.83–3.74]
Mutz et al, 2018[33,c]	1.3218	0.2193	1,598	1,460	15.5%	3.75 [2.44–5.76]
Zhang et al, 2015[34,a]	1.418	0.3851	164	114	5.0%	4.13 [1.94–8.78]
Total (95% CI)			**3,490**	**3,136**	**100.0%**	**3.27 [2.76–3.87]**



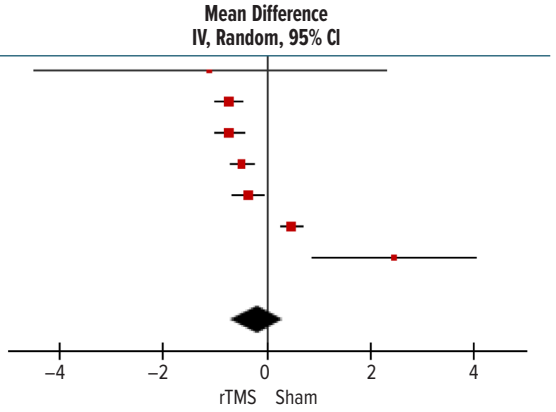
Heterogeneity: Tau² = 0.00; χ^2 = 2.73, *df* = 6 (*P* = .84); I^2 = 0%
Test for overall effect: *Z* = 13.72 (*P* < .00001)

[a]Bilateral rTMS. [b]Low-frequency rTMS. [c]High-frequency rTMS.
Abbreviations: rTMS = repetitive transcranial magnetic stimulation, SE = standard error.

Figure 3.

Forest Plot of Mean Difference in Depression Severity Scores in rTMS and Sham Groups

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Couturier, 2005[35]	–1.1	1.7347	1.9%	–1.10 [–4.50 to 2.30]
Teng et al, 2017[36]	–0.73	0.1378	18.2%	–0.73 [–1.00 to –0.46]
Mutz et al, 2018[33,a]	–0.72	0.1378	18.2%	–0.72 [–0.99 to –0.45]
Kedzior et al, 2015[37]	–0.48	0.1122	18.5%	–0.48 [–0.70 to –0.26]
Martin et al, 2003[15]	–0.35	0.1582	17.9%	–0.35 [–0.66 to –0.04]
Lam et al, 2008[38]	0.48	0.102	18.6%	0.48 [0.28 to 0.68]
Sehatzadeh et al, 2019[39]	2.47	0.801	6.6%	2.47 (0.90 to 4.04]
Total (95% CI)			**100.0%**	**–0.18 [–0.68 to 0.32]**



Heterogeneity: Tau² = 0.34; χ^2 = 91.35, *df* = 6 (*P* < .00001); I^2 = 93%
Test for overall effect: *Z* = 0.72 (*P* = .47)

[a]High-frequency rTMS.
Abbreviations: rTMS = repetitive transcranial magnetic stimulation, SE = standard error.

group has higher odds of response compared to the sham group (OR = 3.27; 95% CI, 2.76–3.87; *P* < .00001) with 0% heterogeneity (*P* = .84, I^2: 0%) (Figure 2). However, a meta-analysis of 7 studies that reported the effectiveness of rTMS on the response scale found no statistical significance between rTMS and the sham group (mean difference [MD]: –0.18; 95% CI, –0.68–0.32; *P* = .47) with 93% heterogeneity (*P* < .00001) (Figure 3). To account for heterogeneity, we conducted a sensitivity analysis by removing 2 outlying studies: Sehatzadeh et al[39] and Lam et al.[38] Results after sensitivity analysis showed significant overall effect on reduction in depression severity scores in the rTMS group compared to the sham group (MD: –0.57; 95% CI, –0.73 to –0.42; *P* < .00001) with 23% heterogeneity (*P* = .27).

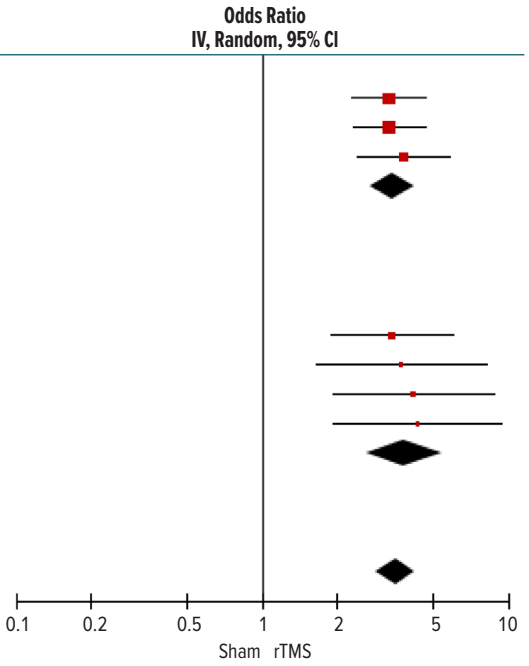
Subgroup analysis. In our subgroup analysis, 3 studies reported response outcomes using high-frequency rTMS and found that the high-frequency rTMS group had a higher response compared to the sham group in treatment-resistant depression (OR = 3.39; 95% CI, 2.75–4.19; *P* < .00001) with 0% heterogeneity (*P* = .87) (Figure 4). Furthermore, 5 meta-analyses found that bilateral rTMS had increased response compared to sham (OR = 3.77; 95% CI, 2.65–5.38; *P* < .00001) with 0% heterogeneity (*P* = .96, I^2: 0%) (Figure 4).

rTMS remission. Seven meta-analyses had remission as a secondary outcome. Our analysis found that the rTMS group had increased remission compared to the sham group (OR = 2.60; 95% CI, 1.83–3.69; *P* < .00001) with 63% heterogeneity (*P* = .01, I^2: 63%) (Figure 5). Sensitivity analysis was performed by removing one outlying study by Zhang et al.[34] Results after sensitivity analysis also showed significant remission in the rTMS group compared to the sham group (OR = 2.83; 95% CI, 2.33–3.45; *P* < .00001) with 0% heterogeneity (*P* = .52).

Figure 4.

Forest Plot of Depression Response Rate in High-Frequency rTMS and Bilateral rTMS Compared to Sham

Study or Subgroup	log[Odds Ratio]	SE	rTMS Total	Sham Total	Weight	Odds Ratio IV, Random, 95% CI
High-frequency rTMS						
Brunoni et al, 2017[32]	1.1878	0.1745	0	0	27.9%	3.28 [2.33–4.62]
Berlim et al, 2014[20]	1.1939	0.1732	730	641	28.3%	3.30 [2.35–4.63]
Mutz et al, 2018[33]	1.3218	0.2193	1,598	1,460	17.7%	3.75 [2.44–5.76]
Subtotal (95% CI)			**2,328**	**2,101**	**74.0%**	**3.39 [2.75–4.19]**
Heterogeneity: Tau² = 0.00; χ² = 0.27, *df* = 2 (*P* = .87); *I*² = 0%						
Test for overall effect: *Z* = 11.40 (*P* < .00001)						
Bilateral rTMS						
Brunoni et al, 2017[32]	1.2208	0.2927	0	0	9.9%	3.39 [1.91–6.02]
Mutz et al, 2018[33]	1.3029	0.4062	1,598	1,406	5.2%	3.68 [1.66–8.16]
Zhang et al, 2015[34]	1.418	0.3851	164	114	5.7%	4.13 [1.94–8.78]
Berlim et al, 2013[30]	1.4586	0.4035	162	117	5.2%	4.30 [1.95–9.48]
Subtotal (95% CI)			**1,924**	**1,637**	**26.0%**	**3.77 [2.65–5.38]**
Heterogeneity: Tau² = 0.00; χ² = 0.30, *df* = 3 (*P* = .96); *I*² = 0%						
Test for overall effect: Z = 7.35 (*P* < .00001)						
Total (95% CI)			**4,252**	**3,738**	**100.0%**	**3.49 [2.91–4.18]**
Heterogeneity: Tau² = 0.00; χ² = 0.82, *df* = 6 (*P* = .99); *I*² = 0%						
Test for overall effect: *Z* = 13.55 (*P* < .00001)						
Test for subgroup differences: χ² = 0.25, *df* = 1 (*P* = .61); *I*² = 0%						

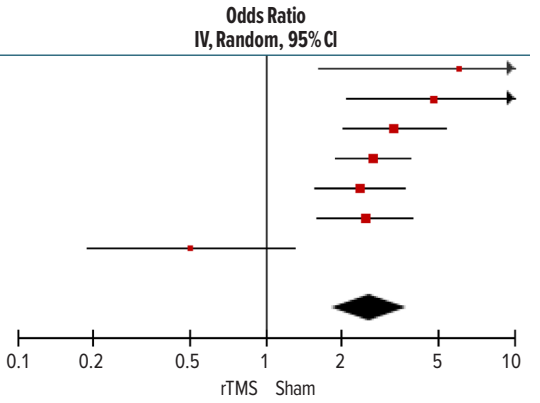


Abbreviations: rTMS = repetitive transcranial magnetic stimulation, SE = standard error.

Figure 5.

Forest Plot of Depression Remission Rate in rTMS and Sham Groups

Study or Subgroup	log[Odds Ratio]	SE	rTMS Total	Sham Total	Weight	Odds Ratio IV, Random, 95% CI
Berlim et al, 2013[30,a]	1.7918	0.6587	162	117	5.7%	6.00 [1.65–21.82]
Berlim et al, 2013[31,b]	1.5602	0.4103	131	132	10.9%	4.76 [2.13–10.64]
Berlim et al, 2014[20,c]	1.1939	0.2454	730	641	17.3%	3.30 [2.04–5.34]
Brunoni et al, 2017[32,c]	1.0006	0.1777	0	0	20.4%	2.72 [1.92–3.85]
Leggett et al, 2015[14]	0.877	0.2096	705	672	18.9%	2.40 [1.59–3.62]
Mutz et al, 2018[33,c]	0.9243	0.2254	1,598	1,460	18.2%	2.52 [1.62–3.92]
Zhang et al, 2015[34,a]	−0.6931	0.4937	164	114	8.6%	0.50 [0.19–1.32]
Total (95% CI)			**3,490**	**3,136**	**100.0%**	**2.60 (1.83–3.69]**
Heterogeneity: Tau² = 0.12; χ² = 16.07, *df* = 6 (*P* = .01); *I*² = 63%						
Test for overall effect: *Z* = 5.37 (*P* < .00001)						



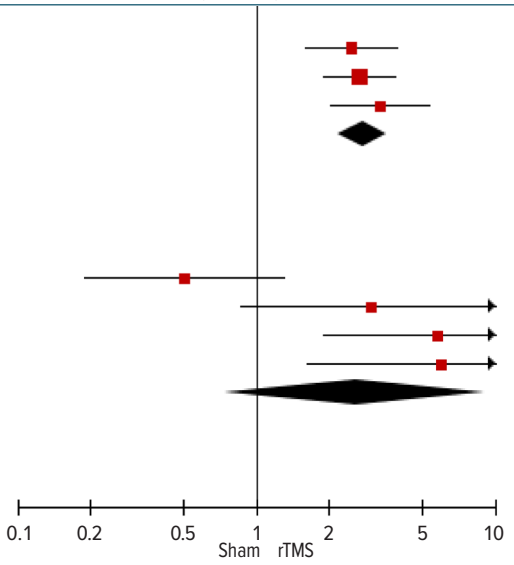
[a]Bilateral rTMS. [b]Low-frequency rTMS. [c]High-frequency rTMS.
Abbreviations: rTMS = repetitive transcranial magnetic stimulation, SE = standard error.

Subgroup analysis. In this subgroup analysis, 3 meta-analyses that reported remission data revealed the high-frequency rTMS subgroup had higher remission compared to the sham group in treatment-resistant depression (OR = 2.79; 95% CI, 2.20–3.54; *P* < .00001) with 0% heterogeneity (*P* = .71) (Figure 6). Furthermore, 4 meta-analyses found no significant effect between the 2 groups on remission (OR = 2.60; 95% CI, 0.74–9.15; *P* = .14) with 79% heterogeneity (*P* = .002) (Figure 6). We performed sensitivity analysis on a bilateral rTMS subgroup by removing the outlying study by Zhang et al.[34] Results after sensitivity analysis showed significant remission in the rTMS group compared to the sham group (OR = 4.79; 95% CI, 2.39–9.60; *P* < .00001) with 0% heterogeneity (*P* = .70).

Figure 6.

Forest Plot of Depression Remission Rate in High-Frequency rTMS and Bilateral rTMS Compared to Sham

Study or Subgroup	log[Odds Ratio]	SE	rTMS Total	Sham Total	Weight	Odds Ratio IV, Random, 95% CI
High-frequency rTMS						
Mutz et al, 2018[33]	0.9243	0.2254	1,598	1,460	29.0%	2.52 [1.62–3.92]
Brunoni et al, 2017[32]	1.0006	0.1777	0	0	46.6%	2.72 [1.92–3.85]
Berlim et al, 2014[20]	1.1939	0.2454	730	641	24.4%	3.30 [2.04–5.34]
Subtotal (95% CI)			**2,328**	**2,101**	**100.0%**	**2.79 [2.20–3.54]**
Heterogeneity: Tau² = 0.00; χ^2 = 0.69, *df* = 2 (*P* = .71); I^2 = 0%						
Test for overall effect: Z = 8.46 (*P* < .00001)						
Bilateral rTMS						
Zhang et al, 2015[34]	–0.6931	0.4937	164	114	26.7%	0.50 [0.19–1.32]
Mutz et al, 2018[33]	1.1151	0.64	1,598	1,406	24.1%	3.05 [0.87–10.69]
Brunoni et al, 2017[32]	1.7492	0.557	0	0	25.6%	5.75 [1.93–17.13]
Berlim et al, 2013[30]	1.7918	0.6587	162	117	23.7%	6.00 [1.65–21.82]
Subtotal (95% CI)			**1,924**	**1,637**	**100.0%**	**2.60 [0.74–9.15]**
Heterogeneity: Tau² = 1.30; χ^2 = 14.56, *df* = 3 (*P* = .002); I^2 = 79%						
Test for overall effect: Z = 1.49 (*P* = .14)						
Test for subgroup differences: χ^2 = 0.01, *df* = 1 (*P* = .91); I^2 = 0%						

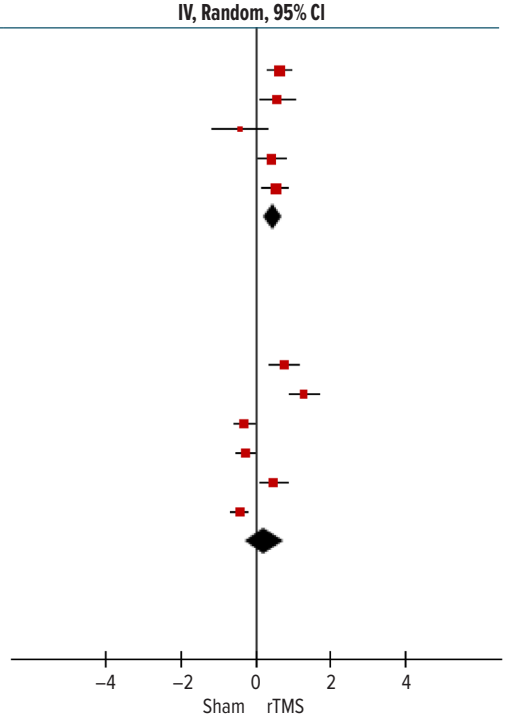


Abbreviations: rTMS = repetitive transcranial magnetic stimulation, SE = standard error.

Figure 7.

Forest Plot of Mean Difference in the BPRS, SANS, PANSS, and AHRS in Negative Symptoms and Auditory Hallucinations on Depression Severity Score in rTMS and Sham Groups

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Negative Symptoms				
Aleman et al, 2018[45]	0.64	0.1633	26.8%	0.64 [0.32 to 0.96]
Freitas et al, 2009[46]	0.58	0.2398	17.2%	0.58 [0.11 to 1.05]
He et al, 2017[47]	–0.41	0.3827	8.5%	–0.41 [–1.16 to 0.34]
Dlabač-de Lange et al, 2010[48]	0.43	0.1939	22.4%	0.43 [0.05 to 0.81]
Shi et al, 2014[49]	0.53	0.1735	25.2%	0.53 [0.19 to 0.87]
Subtotal (95% CI)			**100.0%**	**0.47 [0.23 to 0.70]**
Heterogeneity: Tau² = 0.03; χ^2 = 6.66, *df* = 4 (*P* = .16); I^2 = 40%				
Test for overall effect: *Z* = 3.82 (*P* = .0001)				
Auditory Hallucinations				
Aleman et al, 2007[50]	0.76	0.2041	16.1%	0.76 [0.36 to 1.16]
Freitas et al, 2009[46]	1.28	0.199	16.2%	1.28 [0.89 to 1.67]
He et al, 2017[47]	–0.29	0.1429	17.0%	–0.29 [–0.57 to –0.01]
Li et al, 2020[51]	–0.27	0.1225	17.2%	–0.27 [–0.51 to –0.03]
Otani et al, 2015[52]	0.49	0.1939	16.3%	0.49 [0.11 to 0.87]
Zhang et al, 2013[53]	–0.42	0.1122	17.3%	–0.42 [–0.64 to –0.20]
Subtotal (95% CI)			**100.0%**	**0.24 [–0.26 to 0.74]**
Heterogeneity: Tau² = 0.37; χ^2 = 84.60, *df* = 5 (*P* < .00001); I^2 = 94%				
Test for overall effect: *Z* = 0.93 (*P* = .35)				
Test for subgroup differences: χ^2 = 0.63, *df* = 1 (*P* = .43); I^2 = 0%				



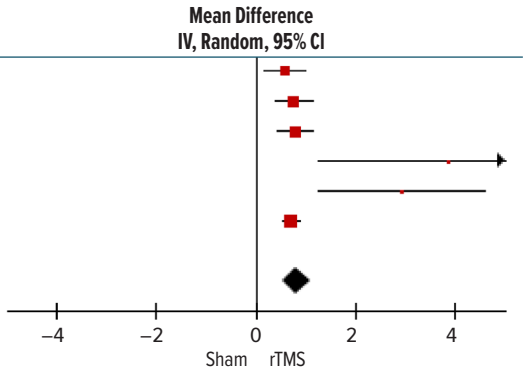
Abbreviations: AHRS = Auditory Hallucination Rating Scale, BPRS = Brief Psychiatric Rating Scale, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, SE = standard error, rTMS = repetitive transcranial magnetic stimulation.

Figure 8.

Forest Plot of Mean Difference in YBOCS Scores on OCD Symptom Reduction in rTMS and Sham Groups

Study or Subgroup	Mean Difference	SE	rTMS Total	Sham Total	Weight	Mean Difference IV, Random, 95% CI
Berlim et al, 2013[16]	0.59	0.2143	161	121	19.9%	0.59 [0.17–1.01]
Perera et al, 2021[40]	0.77	0.1837	413	368	22.5%	0.77 [0.41–1.13]
Rehn et al, 2018[41]	0.79	0.1837	262	222	22.5%	0.79 [0.43–1.15]
Ma and Shi, 2014[42]	3.89	1.3368	154	136	1.2%	3.89 [1.27–6.51]
Trevizol et al, 2016[43]	2.94	0.8572	266	217	2.7%	2.94 [1.26–4.62]
Zhou et al, 2017[44]	0.71	0.0816	0	0	31.3%	0.71 [0.55–0.87]
Total (95% CI)			**1,256**	**1,064**	**100.0%**	**0.81 [0.53–1.10]**

Heterogeneity: Tau² = 0.06; χ^2 = 12.86, *df* = 5 (*P* = .02); I^2 = 61%
Test for overall effect: *Z* = 5.56 (*P* < .00001)



Abbreviations: OCD = obsessive-compulsive disorder, rTMS = repetitive transcranial magnetic stimulation, SE = standard error, YBOCS = Yale-Brown Obsessive-Compulsive Scale.

Schizophrenia

Our meta-meta-analysis included 5 studies that reported effectiveness as the mean difference of rTMS on negative symptoms. We found that rTMS was superior compared to sham TMS in reduction of negative symptoms (MD: 0.47; 95% CI, 0.23–0.70; *P* = .0001) with 40% heterogeneity (*P* = .16, I^2: 40%). A meta-meta-analysis of 6 meta-analyses showed no statistically significant difference between the effectiveness of rTMS and sham on auditory hallucinations (MD: 0.24; 95% CI, −0.26 to 0.74; *P* = .35) with 94% heterogeneity (*P* < .00001, I^2: 94%) (Figure 7). All negative symptoms were included, whereas positive symptoms were measured by the effect of rTMS on auditory hallucinations.

OCD

In our meta-meta-analysis, we analyzed the data from 6 meta-analyses that reported a reduction in OCD symptoms using YBOCS scores and found that rTMS was superior to sham TMS in reducing the severity of OCD symptoms (MD: 0.81; 95% CI, 0.53–1.10; *P* < .00001) with 61% heterogeneity (*P* = .02, I^2: 61%) (Figure 8).

DISCUSSION

The results of our meta-meta-analysis demonstrate that rTMS was more effective for treatment-resistant depression, as well as for reducing negative symptoms and auditory hallucinations in schizophrenia and OCD symptoms compared to sham treatment. In the subgroup analysis of treatment-resistant depression, we also found that high-frequency rTMS and bilateral rTMS compared to sham showed increased efficacy in clinical response and remission rates. Depending on the frequency of rTMS, it could either activate or inhibit the targeted brain region.[55] For example, high-frequency rTMS has been shown to increase cerebral blood flow in targeted brain regions, whereas low-frequency rTMS reduces cerebral blood flow in targeted brain regions.[56]

In our meta-meta-analysis, a response is defined as a 50% reduction of HDRS or MADRS scores, and remission is defined as scores within the normal limits on the HDRS or MADRS. Our results suggest that rTMS is more effective in achieving a response (OR = 3.27) and remission (OR = 2.60) in treatment-resistant depression than sham rTMS. A study[57] found that rTMS can be helpful in treatment-resistant depression by changing the metabolism in different parts of the brain. Concerto et al[58] suggest that the efficacy and duration of rTMS can be based on its ability to change the excitability of the cerebral cortex and mood regulatory areas based on the frequency of rTMS. The authors[58] also found that high-frequency rTMS was superior to sham in producing long-lasting antidepressant effects. We also found bilateral and high-frequency rTMS to be more effective in treatment-resistant depression. An RCT with 74 subjects by Blumberger et al[59] reported bilateral rTMS was more effective in treatment-resistant depression. All the included studies show rTMS to be safe and well tolerated (Table 1). More studies are required to know the exact duration of the effect of rTMS.

rTMS over the dorsolateral prefrontal cortex (DLPFC) causes changes in functional connectivity between the anterior cingulate cortex (ACC) and frontoparietal neuronal circuits.[60] It is believed that rTMS achieves these changes in brain connectivity by inducing neuroplastic changes such as long-term potentiation mediated by *N*-methyl-D-aspartate glutamate receptors.[61] rTMS also promotes neurogenesis in brain regions such as the hippocampus by activating brain-derived neurotropic factor/tropomyosin receptor kinase B pathways.[62]

Previous studies[63] have shown that depression is associated with impaired neurogenesis in the hippocampus. Thus, rTMS-induced changes in functional connectivity between critical brain regions involved in regulation of mood and cognition and neurogenesis in the hippocampus might explain the potential benefits of rTMS in reducing depressive symptoms.

In our meta-meta-analysis, we found that rTMS was superior to sham TMS in the reduction of negative symptoms (MD: 0.47, $P = .0001$); we found no statistically significant difference between the effects of rTMS and sham TMS on positive symptoms as measured by auditory hallucinations (MD: 0.24, $P = .35$). A systematic review and meta-analysis by Kennedy et al[64] of 30 RCTs on rTMS (involving 768 participants) demonstrated that compared to sham, rTMS improved hallucinations and negative symptoms but was associated with modest, nonsignificant worsening of positive symptoms. The study[64] also revealed that higher pulse frequency (> 10 Hz), motor threshold intensity of 110%, left prefrontal cortical treatment site, and trial duration over 3 weeks were associated with improvement in negative symptoms and worsening in positive symptoms (all $P < .03$). The symptom dimensions in schizophrenia may respond differently to brain stimulation interventions. A study by Stanford et al[65] demonstrated that rTMS produces targeted changes in neurophysiologic measures in some brain regions, which can be the reason for its efficacy. Factors such as sex, patient subtype, pathophysiology (eg, confidence interval, electroencephalogram), accurate anatomic and functional coil localization, dose of rTMS, and duration of treatment may all affect the reduction in negative symptoms with rTMS.[65]

Negative symptoms of schizophrenia are largely believed to be hypo-functioning of prefrontal cortical brain regions, which are also attributed to executive dysfunction seen in schizophrenia.[66] The functional magnetic resonance imaging (fMRI) evidence suggests that treatment with rTMS targeting the prefrontal cortex in schizophrenia patients results in an increase in task-specific activation of these brain regions, correlating with a reduction in negative symptoms.[67]

Our meta-meta-analysis results demonstrate that rTMS is a more effective treatment compared to sham TMS for OCD symptoms (MD: 0.81; 95% CI, 0.53–1.10; $P < .00001$). Heterogeneity for our results was 61% ($P = .02$, I^2: 61%). A study by Tandt et al[68] found that twice-daily low-frequency rTMS targeting dorsomedial prefrontal cortex in treatment-resistant OCD significantly decreased YBOCS scores ($Z = -3.061$, $P = .002$) in 12 patients after 10 days of treatment. Rostami et al[69] found that patients who were treatment resistant and had low scores in the obsession severity, disturbance, and resistance factors of the YBOCS might benefit more from rTMS.

The ability of rTMS to alter functional connectivity between brain regions could also explain the benefits of rTMS in reducing obsessive-compulsive symptoms. Unmedicated individuals with OCD show abnormally high connectivity between the orbitofrontal cortex and putamen.[70] Unlike depression, DLPFC may not be an ideal target for treating OCD, as rTMS-induced neuronal firing in this brain region has been shown to induce obsessive-compulsive symptoms.[71] rTMS, especially in low frequency, targeting primary motor and orbitofrontal areas has been most promising in reducing OCD symptoms.[72] The fMRI studies have shown a reduction in cortico-striatal hyperconnectivity seen in OCD following rTMS, which correlated to a decrease in YBOCS scores.[73]

Advantages and Disadvantages of rTMS

The most common side effects of rTMS during treatment are transient head or scalp discomfort and skin redness at or around the location where TMS pulses are applied. The patient may experience discomfort and twitching or movement of adjacent areas of the face, ipsilateral eye, ear, nose, and jaw during stimulation trains due to excitation of superficial nerve branches and contraction of superficial muscle groups.[74] Headache is another common side effect, but procedural pain and headache typically decrease due to habituation or the direct antinociceptive effect of TMS.[75] Seizures (ie, the most serious TMS-related acute adverse effect) have been extremely rare, with most of the few new cases receiving rTMS exceeding previous guidelines, often in patients under treatment with drugs that potentially lower the seizure threshold.[76] An uncommon side effect of rTMS is the induction of mania or hypomania.[77]

Future Directions of TMS

Intermittent theta-burst stimulation (iTBS), which can be conceptualized as a second-generation form of TMS, allows an entire therapeutic "dose" equivalent of stimulation to be delivered in 3–10 minutes, a fraction of the time required for standard TMS.[78] Stanford Accelerated Intelligent Neuromodulation Therapy is an accelerated, high-dose resting-state functional connectivity MRI–guided iTBS protocol for treatment-resistant depression. The treatment produced very high levels of clinical remission, exceeding those observed in more traditional TMS studies, and the majority of the remissions occurred in the first 3 days of a 5-day course of treatment.[79] In 2018, the FDA approved a new TMS device called sTMS that delivers a single pulse to the brain of those suffering from frequent debilitating migraines, and researchers found that sTMS helped reduce the days people had headaches by one-third.[80,81]

Limitations and Strengths

Meta-analyses can be poorly conducted; abstracting and summarizing large sets of data points can lead to inappropriate conclusions, failing to consider variation in data. Bias from the analysts, overgeneralizations, and

overarching statements that lack precision could be some of the overall issues. The heterogeneity of the studies, the possible inclusion of noncomparable variables, and the omission of some of the subtle conclusions of individual studies are other issues. All these limitations, to some extent, apply to our analysis as well; however, we have attempted to be accurate in abstracting and summarizing. The strengths of meta-analyses lie with increased sample size and thus greater power of the integrated data. This approach allows one to summarize and quantify results and conclusions from numerous individual studies. We found meta-analysis studies only on depression, schizophrenia, and OCD that were analyzable from the umbrella meta-analysis perspective.

CONCLUSION

The results of the meta-meta-analysis revealed that rTMS exerts its effects by altering functional connectivity between brain regions by activating or inhibiting the targeted brain region depending on the frequency of rTMS used. Since different mental illnesses are associated with differences in neuropathology, disease-specific target site and frequency of rTMS are 2 of the most important parameters related to the efficacy of rTMS in symptom reduction in various psychiatric disorders. Future studies that lead the field toward more individualized and personalized treatment guided by objective parameters such as imaging would add to the existing knowledge base.

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Author Affiliations: Department of Epidemiology, New York University, New York (S. Patel); Department of Psychiatry, Millwood Hospital, Arlington, Texas (Silvi); Department of Psychiatry, Tower Health/Phoenixville Hospital, Phoenixville, Pennsylvania (Desai); Karuna Medical College, Palakkad, Kerala, India (Rahman); St. George's University School of Medicine, St. George's, Grenada, West Indies (Depa); Department of Child and Adolescent Psychiatry, Tulane University School of Medicine, New Orleans, Louisiana (Hanif); Department of Child and Adolescent Psychiatry, BronxCare Health System, New York (Rizvi); Department of Public Health, Icahn School of Medicine at Mount Sinai, New York (Hsieh); Department of Pathology, Montefiore Medical Center, New York (Malik); Department of Public Health, Icahn School of Medicine at Mount Sinai, New York (U. Patel); Department of Psychiatry, Boston Children's Hospital/Harvard Medical School, Massachusetts (Mansuri); Department of Psychiatry, Indiana University Health Ball Memorial Hospital, Muncie (Pathrose); Department of Psychiatry, Unitypoint Health, Peoria, Illinois (Aedma); Department of Psychiatry, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Parikh).

Corresponding Author: Saral Desai, MD, Department of Psychiatry, Tower Health/Phoenixville Hospital, 140 Nutt Rd, Phoenixville, PA 19460 (srd342@drexel.edu).

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