Washington State Health Care Authority

Transcranial Magnetic Stimulation for Treatment of Selected Behavioral Disorders

Final Evidence Report

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Health Technology Assessment Program (HTA)

Washington State Health Care Authority

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This evidence report is based on research conducted by the RTI–University of North Carolina Evidence-based Practice Center through a contract between RTI International and the State of Washington Health Care Authority (HCA). The findings and conclusions in this document are those of the authors, who are responsible for its contents. The findings and conclusions do not represent the views of the Washington HCA, and no statement in this report should be construed as an official position of Washington HCA.

The information in this report is intended to help the State of Washington's independent Health Technology Clinical Committee make well-informed coverage determinations. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Contents

List of Appendices

List of Figures

List of Tables

List of Abbreviations

ACC	Anterior cingulate cortex
ADM	Antidepressant medication
AE	Adverse event
ANOVA	Analysis of variance
APGAR	Appearance, Pulse, Grimace, Activity, and Respiration
ARD	Absolute risk difference
AUD	Alcohol use disorder
AUDIT	Alcohol use disorders identification test
BDI	Beck Depression Inventory
BE	Beech EH
BSI	Beck Scale for Suicide Ideation
BVMT	Brief Visual Spatial Memory Test
CAPS	Clinician Administered PTSD Scale
CGI	Clinical Global Impression Scale-Improvement
CI	Confidence interval
CIHR	Canadian Institutes of Health Research
COWAT	Controlled Word Association Test
CPRS	Comprehensive Psychopathological Rating Scale
CPT	Cognitive processing therapy
CQ	Cost research question
CQR	Continuous quit rate
DLPFC	Dorsal lateral prefrontal cortex
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
EPC	Evidence-based Practice Center
EQ	Efficacy research question
FAB	Frontal Assessment Battery
FDA	Food and Drug Administration
FTND	Fagerstrom Test of Nicotine Dependence
GAD	Generalized anxiety disorder
GAF	Global Assessment of Functioning
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HARS	Hamilton Anxiety Rating Scale
HCA	Health Care Authority
HDD	Heavy drinking days
HDI	Human Development Index
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat

LNS	Letter number sequencing
MADRS	Montgomery–Åsberg Depression Rating Scale
MCID	Minimal Clinically Important Differences
MD	Mean differences
MDD	Major depressive disorder
MeSH	Medical subject headings
MMSE	Mini-Mental State Examination
MPSS	Modified PTSD Symptom Scale
NAMI	National Alliance on Mental Illness
NARSAD	National Alliance for Research on Schizophrenia and Depression
NHMRC	National Health and Medical Research Council
OCD	Obsessive-compulsive disorder
OMHF	Ontario Mental Health Foundation
PAS	Paired associative stimulation
PCL	PTSD Checklist
PTSD	Posttraumatic stress disorder
QALY	Quality-adjusted life-year
RAVLT	Rey Auditory Verbal Learning Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomized controlled trial
RDLPFC	Right dorsolateral prefrontal cortex
RMT	Resting motor threshold
RoB	Risk of bias
RR	Risk ratio
SAE	Serious adverse event
SMA	Supplementary motor area
SMD	Standardized mean difference
SOE	Strength of evidence
SQ	Safety research question
SSRI	Selective serotonin reuptake inhibitor
SUD	Substance use disorder
TBS	Theta-burst stimulation
TMS	Transcranial magnetic stimulation
TQD	Target quit date
WTAR	Wechsler Test of Adult Reading
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale

Executive Summary

Structured Abstract

Purpose: To conduct a health technology assessment (HTA) on the efficacy, safety, and cost-effectiveness of transcranial magnetic stimulation (TMS) for the treatment of selected behavioral health disorders, including generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), major depressive disorder (MDD), posttraumatic stress disorder (PTSD), smoking cessation, and substance use disorder (SUD).

Data Sources: PubMed, PsycInfo, and Cochrane Library from inception through May 24, 2022; clinical trial registry; government, payor, and clinical specialty organization websites; hand searches of systematic reviews.

Study Selection: Using a priori criteria, we selected English-language primary research studies that were conducted in very highly developed countries that reported effectiveness, safety, or cost-effectiveness outcomes for the 6 behavioral health disorders included in this HTA. We selected randomized controlled trials (RCTs) or controlled clinical trials; we also included cost analyses. Interventions included TMS (repetitive [r], deep [d], or theta-burst stimulation [TBS]) with or without concurrent pharmaco- or psychotherapy, delivered over more than 1 session and the comparator was sham TMS. Eligible study outcomes included clinical response, remission, loss of diagnosis, or change in severity of symptoms as measured by validated instruments or clinical evaluation for efficacy outcomes; serious adverse events, adverse events, or side effects for safety outcomes; and cost-effectiveness of TMS interventions from studies that used U.S.-based cost data.

Data Abstraction and Analysis: One research team member extracted data, and a second checked for accuracy. Two investigators independently assessed the risk of bias of included studies. When quantitative synthesis was appropriate, we used random-effects models to generate pooled estimates of effect. We graded the strength of evidence (SOE) for each clinical condition and category of outcomes using the Agency for Healthcare Research and Quality Evidence-based Practice Center SOE approach, which is based on the Grading of Recommendations Assessment, Development, and Evaluation approach.

Data Synthesis: We included 64 RCTs; some studies included multiple intervention arms. Sixty-one studies provided evidence on efficacy outcomes, 58 studies provided evidence for safety outcomes, and 3 studies provided evidence on cost-effectiveness outcomes. Most studies evaluated outcomes at posttreatment only. The disease severity of study populations ranged from moderate to severe for GAD and PTSD, very severe for OCD, severe for MDD, and variable for smoking cessation and SUD. OCD and MDD populations were primarily treatment resistant, while treatment resistance was often not specified for the other conditions. All but 1 study in MDD was conducted in adults. Most studies used rTMS, though some also used dTMS, and TBS. The number of treatment sessions generally ranged from 10 to 30. Two studies reported on the impact of rTMS compared to sham for the treatment of GAD; evidence for the effects of TMS on remission or response was judged as insufficient; however, TMS may reduce symptom

severity (SOE: low, favor TMS). Nine RCTs evaluated TMS for individuals with OCD; overall effects favored TMS with low SOE for reduction in symptom severity and for response to therapy (pooled risk ratio [RR] 1.96; 95% confidence interval [CI], 0.94 to 4.09; 281 participants; 7 RCTs). Evidence for the 1 study with cost-effectiveness outcomes was judged as insufficient. Thirty-six studies focused on TMS for the treatment of MDD. In general, there was moderate to high SOE favoring TMS compared to sham for remission, response, and reduction in symptom severity. For rTMS, the pooled RR was 1.86 (95% CI, 1.26 to 2.75; 1,469 participants; 15 RCTs), and for TBS, the RR was 4.68 (95% CI, 1.79 to 12.21; 197 participants; 3 RCTs). Evidence from 2 cost-effectiveness studies was judged as low SOE. Four RCTs reported on the impact of TMS on PTSD; there was low SOE favoring TMS for reducing symptoms but insufficient evidence for response and remission. Five RCTs reported on TMS for smoking cessation, and 6 studies reported on TMS for SUD, including alcohol and cocaine use disorders. TMS was favored for outcomes of smoking abstinence, reduced nicotine use, and reduced substance use (SOE: Low), but evidence was insufficient for other outcomes. The strength of evidence for harms, both any adverse events and serious adverse events, was low (favoring sham or no difference between groups) or insufficient, depending on the condition.

Limitations: The evidence base included many RCTs with high risk of bias and studies with small sample sizes, resulting in imprecise effect estimates, particularly for nondepression indications for TMS. The trials included in this HTA infrequently reported on race or ethnicity, and further understanding of how TMS performs in specific populations is unavailable. A limited number of studies reported outcomes at a follow-up time point beyond the immediate posttreatment period, many only evaluating patients up to a few weeks after treatment. This review did not include unpublished data and did not address comparative effectiveness of alternative TMS protocols or comparisons to other active treatments. Studies with fewer than 10 participants in each study arm were excluded.

Conclusions: This HTA examined the efficacy, safety, and cost-effectiveness of active TMS compared to sham TMS for selected behavioral health conditions. TMS has low SOE for benefit in OCD at posttreatment and moderate to high SOE for benefit in MDD. Evidence for benefit for the other conditions (GAD, PTSD, smoking cessation, SUD) ranges from insufficient to low for benefit depending on the outcome assessed. Data on the efficacy of TMS at longer follow-up assessments were lacking across all conditions. There was less robust evidence for safety outcomes, although studies generally reported fewer adverse events for sham TMS; few serious adverse events were reported for either active or sham TMS. Evidence is lacking with respect to cost-effectiveness outcomes.

ES 1. Background

This health technology assessment (HTA) reviews the efficacy, safety, and cost-effectiveness of transcranial magnetic stimulation (TMS) to assist the State of Washington's Health Technology Clinical Committee in determining coverage of TMS for selected behavioral health disorders including generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), major depressive disorder (MDD), posttraumatic stress disorder (PTSD), smoking cessation, and substance use disorder (SUD).

ES 1.1 Condition Description

Behavioral health disorders affect a large proportion of the American population. According to a 2020 national survey, over 14 million adults (14.2%) are estimated to have serious mental illness, defined as a mental, behavioral, or emotional disorder causing serious functional impairment interfering with 1 or more major life activities.[1] A growing number of studies in the pandemic era reported a rise in the prevalence of several mental health conditions. In a survey administered in June 2020, over 40% of respondents reported at least 1 behavioral health condition, including anxiety and depression (30.9%), trauma-related or stress disorder (26.3%), and the initiation or exacerbation of substance use.[2]

ES 1.2 Disease Burden

Behavioral health disorders can affect physical health, function, and quality of life. Depressive disorders are associated with elevated risk of chronic medical conditions, early mortality, and reduced role functioning at work and in relationships.[3] OCD and PTSD cause significant personal and interpersonal distress to individuals with these conditions, affecting social and occupational function.[4-6] Similarly, patients with GAD have lower health-related quality of life, increased health care utilization, and comorbid medical and mental health conditions.[7-10] Smoking contributes to nearly half a million deaths per year in the United States, $170 billion is spent on direct medical care related to smoking, and lost productivity totals $160 billion.[11,12]

ES 1.3 Technology Description

This HTA includes an evaluation of TMS. TMS is an outpatient neuromodulation procedure, often administered by a nurse, physician's assistant, or medical assistant with a physician present on site, and unlike electroconvulsive therapy (ECT) it does not require sedation. Treatments typically last 20 to 40 minutes, and patients may leave when finished without an observation period. During the procedure, patients may experience a small tapping sensation and clicking sounds associated with tensing of the coil used to induce the magnetic field. Safety protocols include offering hearing protection and may include having anti-epileptics and oxygen on hand.[13]

ES 1.4 Regulatory Status

Currently, 8 TMS devices have obtained U.S. Food and Drug Administration (FDA) 510k clearance. Indications for TMS for which the FDA has issued 510k clearance include depression, OCD, smoking cessation, treatment of anxiety symptoms in those with depression, and acute and prophylactic treatment of migraine with aura. Most FDA indications specify failure of 1 prior

medication only. TMS is not currently cleared by the FDA for use in the following conditions of interest in this review: GAD, PTSD, and SUD.

ES 1.5 State of Washington Utilization Data

The State of Washington Health Care Authority provided data on transcranial magnetic stimulation utilization in the State of Washington from 2018 to 2021. The data provided included utilization and costs for Medicaid (fee for service and managed care organization), Department of Labor and Industries Workers' Compensation Program, and the Public Employee Benefit Board Uniform Medical Plan. Detailed information is provided in ***Appendix A***.

ES 1.6 Policy Context

The State of Washington Health Care Authority selected TMS for selected behavioral health conditions for an HTA because of medium concerns of safety and high concerns for efficacy and cost.

ES 2. Methods

This section describes the methods we used to conduct this HTA.

ES 2.1 Research Questions and Analytic Framework

We developed the following research questions to guide this HTA (***Figure ES-1***):

Efficacy Question 1 (EQ 1). What is the efficacy of TMS for the treatment of selected behavioral disorders?

Safety Question 1 (SQ 1). What are the harms associated with TMS for the treatment of selected behavioral disorders?

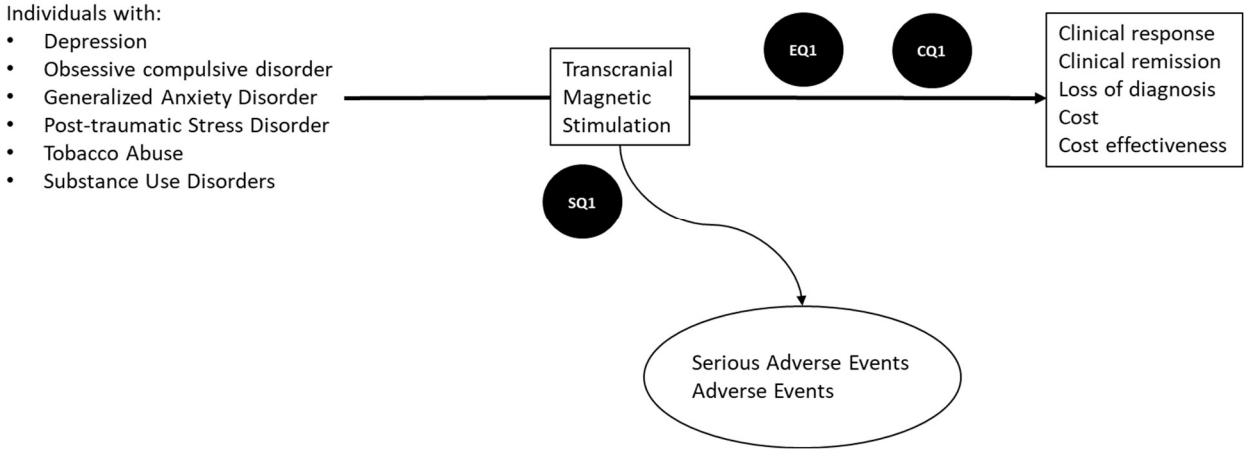
Cost Question 1 (CQ 1). What are the costs and cost-effectiveness of TMS for the treatment of selected behavioral disorders?

The State of Washington HTA Program posted a draft of these research questions and proposed scope for public comment from July 8 to July 22, 2022. The final key questions and response to public comments on the draft key questions were published on the Program's website on August 23, 2022.[14] A draft of this report underwent external peer review and was posted for public comment between January 5, 2023 and February 6, 2023.

ES 2.1.1 Data Sources and Search

We searched PubMed, the Cochrane Library, and PsycInfo for relevant studies published in English from inception to May 24, 2022. We also conducted an addendum search of the same databases for cost studies on June 29, 2022. In addition, we reviewed the reference lists of relevant studies, systematic reviews, practice guidelines, and other HTAs on the topic to identify any relevant primary research studies not found through the electronic search. The detailed search strategy is in ***Appendix B***.

Figure ES-1. Analytic Framework Depicting Scope of This HTA on TMS for Treatment of Selected Behavioral Health Disorders



Abbreviations: CQ = cost question; EQ = efficacy question; HTA = health technology assessment; SQ = safety question; TMS = transcranial magnetic stimulation.

ES 2.1.2 Study Selection

Two reviewers independently screened titles and abstracts and full-text articles based on the following study inclusion criteria. (Complete details are in ***Table 2*** of the Full Technical Report.)

- **Population**: Individuals of any age with a clinical diagnosis of MDD, OCD, GAD, PTSD, tobacco use disorder, or SUD. We excluded studies with study populations, including a mix of eligible and ineligible conditions (e.g., MDD and bipolar disorder) where results were not stratified by the population of interest to this review. Although TMS is usually reserved for treatment-resistant persons, we did not limit study selection by this characteristic. Special populations of interest included individuals who are peri- or postpartum, elderly, younger than 18 years. We also looked for subgroup analyses by age, sex or gender, race or ethnicity, and disability.

- **Intervention(s):** Repetitive TMS (rTMS), including deep TMS (dTMS) or theta-burst stimulation (TBS), with or without concurrent pharmaco- or psychotherapy, delivered over more than 1 session.

- **Comparator(s):** Sham TMS with or without concurrent pharmaco- or psychotherapy. We excluded studies where the comparator was no treatment, usual care, or wait-list control.

- **Outcomes:** Primary study outcomes of clinical response (e.g., based on validated symptom scales or indices), remission, loss of diagnosis, or change in severity of illness as measured by validated instruments or clinical evaluation (EQ); serious adverse events (SAEs), adverse events (AEs), or side effects, including device-related complications (SQ); and cost-effectiveness of TMS interventions from studies that used U.S.-based cost data (CQ).

- **Study design**: Randomized controlled trials (RCTs), nonrandomized controlled trials, and crossover trials (EQ and SQ); cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis studies that were performed from the societal or payor perspective (CQ). Systematic reviews were not included, but we searched their reference lists to identify relevant primary research studies potentially missed by our search.

- **Setting:** Studies in any care setting conducted in countries with a development rating designated as *very high* by the United Nations Human Development Index.[15]

- **Other:** English-language only

ES 2.1.3 What Is Excluded From This HTA

This review did not include studies published in languages other than English or conducted in countries that are not very highly developed based on the United Nations Human Development Index.[15] This review also did not include studies solely focused on head-to-head comparisons between alternative TMS protocols or comparisons between TMS and medication. Studies with multiple intervention arms were included if an eligible control group was also included; only data from the comparisons between eligible intervention groups and eligible control groups were included in this HTA.

ES 2.1.4 Data Abstraction and Risk-of-Bias Assessment

One team member extracted relevant study data into a structured abstraction form in DistillerSR, and a senior investigator checked those data for accuracy. Two team members conducted independent risk-of-bias assessments on all included studies. We used the Cochrane Risk of Bias (RoB 2.0) tool to assess the risk of bias for each included RCT.[16] We used the Quality of Health Economic Studies Instrument to assess the risk of bias of included cost analyses.[17]

ES 2.1.5 Data Synthesis and Quality-of-Evidence Assessment

We qualitatively synthesized study characteristics and results for each research question by clinical diagnosis category in tabular and narrative formats. When quantitative synthesis was determined to be appropriate using established guidance,[18,19] we employed random-effects models using the inverse variance method of DerSimionian and Laird to generate pooled mean differences (MDs) or standardized mean differences (SMDs) for continuous outcomes and risk ratios (RRs) for categorical outcomes.[20] We graded the strength of evidence (SOE) for each clinical condition and category of outcomes using the Agency for Healthcare Research and Quality Evidence-based Practice Center (EPC) SOE approach,[21,22] which is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[21-23] We combined multiple outcome measures within the same outcome domain and graded SOE for the outcomes of remission, response, disease-specific continuous outcomes, non-disease-specific outcomes, safety, and cost-effectiveness. SOE can be graded as *insufficient*, *low*, *moderate*, or *high* and reflects our level of confidence in the findings.

ES 3. Results

ES 3.1 Literature Search and Overview of Measures Reported

We included a total of 64 studies reported in 70 articles published between 2001 and 2022. Sixty-one studies provided evidence on effectiveness (EQ 1), 58 studies provided evidence for safety outcomes (SQ 1), and 3 studies provided evidence on cost outcomes (CQ 1). ***Table 4*** in the full technical report summarizes the most commonly reported scales and indices used to report findings related to the EQ across the included conditions. ***Table ES-1*** summarizes disease severity and treatment resistance of the included study populations, and ***Figure ES-2*** illustrates the range in number of sessions by condition. ***Table ES-2*** includes the number of studies and participants for each outcome.

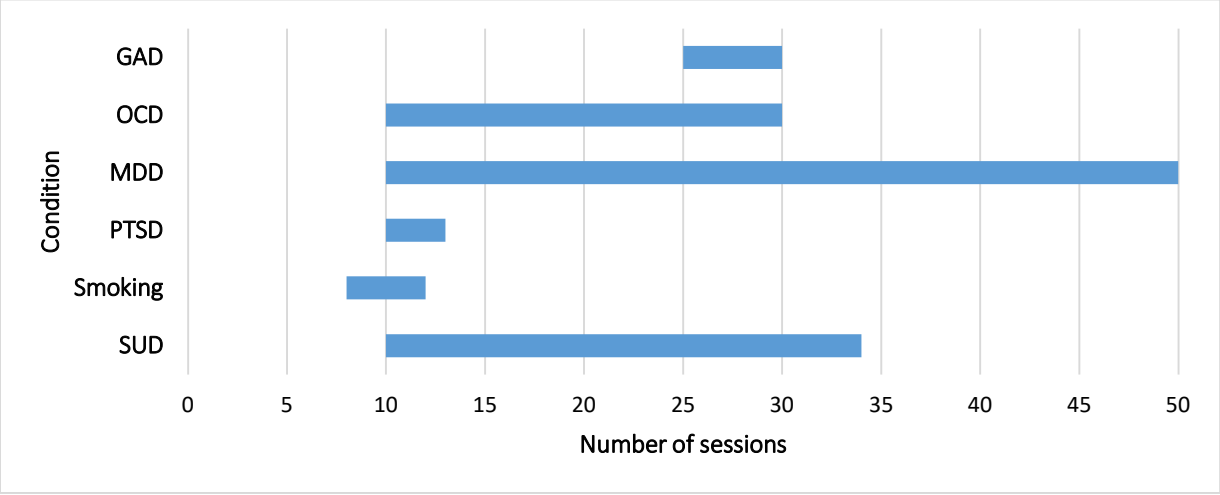
Table ES-1. Disease Severity and Treatment Resistance of Included Study Populations by Condition

Condition	Disease Severity[a]	Number of Studies in Treatment-Resistant Population	Number of Studies in Treatment-Naïve Population	Number of Studies in Both Treatment-Resistant and -Naïve Population	Number of Studies with Treatment Resistance Unspecified
GAD	Moderate-severe	0	0	0	2
OCD	Very severe	8	0	0	1
MDD	Severe	25	1	3	7
PTSD	Moderate-severe	1	0	1	2
Smoking cessation	Variable reporting	1	0	0	4
SUD	Variable reporting	0	0	1	5

Notes: [a] Disease severity based on validated clinical severity score among majority of studies for that condition.

Abbreviations: GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder; SUD=substance use disorder.

Figure ES-2. Number of TMS Sessions by Condition



Abbreviations: GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder; SUD=substance use disorder; TMS=transcranial magnetic stimulation.

ES 3.2 Generalized Anxiety Disorder

We identified 2 parallel-assignment RCTs that focused on rTMS stimulation compared to sham stimulation for the treatment of GAD in adults.[24,25] Both studies recruited patients with moderate to severe anxiety, but neither study specified whether participants were treatment-resistant. The interventions varied in terms of TMS protocol and number of sessions. Both studies provided treatment sessions for a duration of 6 weeks and measured outcomes posttreatment and at 12-weeks' follow-up. Key findings are as follows:

- Two RCTs[24,25] reported on remission and clinical response, defined in different ways. However, only 1 study reported statistically significant findings,[25] where response was improved immediately posttreatment and at 12 weeks' follow-up, but remission was only significantly improved at 12-weeks' follow-up. (SOE: Insufficient for both response and remission)

- Two RCTs[24,25] reported on the change in Hamilton Anxiety Rating Scale (HARS) scores from baseline to end of treatment and last follow-up time points, both with statistically significant results and both favoring TMS (SOE: Low, favor TMS). One study also reported on Clinical Global Impression–Severity scale (CGI-S) results at posttreatment and follow-up. (SOE: Insufficient)

- Two RCTs[24,25] reported on safety outcomes (SOE: Insufficient). Two studies reported SAEs for 1 patient each, both in the TMS group. Facial twitching was the most common specific AE reported.

- No studies reported cost-effectiveness outcomes or findings for special populations or subgroup analyses of interest.

ES 3.3 Obsessive-Compulsive Disorder

We identified 9 parallel-assignment RCTs [26-34] that evaluated TMS compared to sham among adult individuals diagnosed with OCD. All studies enrolled participants with at least moderate OCD, and all but 1 study[32] enrolled persons considered treatment resistant. Six studies evaluated rTMS, [29-34] 2 studies evaluated dTMS,[26,27] and 1 study evaluated continuous theta-burst stimulation (cTBS).[28] The number of TMS sessions and treatment duration varied among studies. Outcome measures used were consistent, but the timing of treatments, timing of the outcome measurements, and duration of follow-up varied. Key findings are as follows:

- Seven RCTs[24-29,32] reported clinical response, defined as a decrease in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of 25% or more; pooled relative risk (RR) 1.96 (95% confidence interval [CI], 0.94 to 4.09; 281 participants; I^2=47.1%); absolute risk difference (ARD) 155 more clinical responses per 1,000 participants (95% CI, from 9 fewer to 487 more) for TMS compared to sham. (SOE: Low, favor TMS)

- Nine RCTs[26-34] reported using Y-BOCS. Change in severity of OCD symptoms from Y-BOCS was the primary outcome in all but 1 study. Results were mixed: 5 studies

reported that TMS was associated with improvement in symptom severity (statistically significant in 4 studies), 1 study favored sham (nonsignificant), and 3 studies did not report the direction of effect of TMS treatment on OCD symptom severity. (SOE: Low, favor TMS)

- Eight RCTs[26-29,31-34] reported on AEs. There were no differences in any AEs or SAEs. Headache and localized scalp pain were the most frequently reported side effects across groups. (SOE: Low, no difference)

- Two studies reported results by subgroups of age or sex.[27,29] In 1 study, there was no significant difference in treatment effect by age (interaction term treatment*age, $P>0.05$).[29] In the other study, male individuals with OCD were more likely to be treatment responders than female individuals with OCD (66% vs. 14%, $P<0.05$).[27]

- One study based on U.S. data reported cost-effectiveness outcomes.[35] Compared to monotherapy with antidepressant medication, dTMS cost more (incremental cost $6,425) but was more effective (incremental reduction in Y-BOCS score of 3.9 points) for an incremental cost-effectiveness ratio of $1,647 per unit reduction in Y-BOCS.[35] A minimal clinically important difference for severe OCD is approximately a Y-BOCS change of 8. A similar ratio was observed when compared to combination antidepressant and antipsychotic medication. (SOE: Insufficient)

ES 3.4 Major Depressive Disorder

We identified 36 RCTs in 40 publications that focused on TMS stimulation compared to sham stimulation for the treatment of MDD. Most studies enrolled persons with at least moderate MDD, and most were conducted in treatment-resistant persons, most often defined as persons failing at least 2 medications. All studies were conducted in adults, with the exception of 1 study of adolescents.[36] The interventions varied in terms of type of TMS, protocol, number of sessions, duration over which the sessions were provided, and timing of outcome measure at follow-up. In general, few studies had follow-up data beyond the immediate posttreatment period. Key findings are as follows:

- Nineteen RCTs reported on remission, defined by different symptom severity surveys and cut-off points.[36-54] Pooled analyses favored remission for individuals undergoing rTMS compared to sham (RR, 1.86; 95% CI, 1.26 to 2.75; 15 RCTs) and for TBS compared to sham (RR, 4.68; 95% CI, 1.79 to 12.21; 3 RCTs). Absolute risk differences for rTMS and TBS were 96 more remissions per 1,000 individuals (95% CI, 26 to 196 more remissions per 1,000) and 194 more remissions per 1,000 individuals (95% CI, 40 to 500 more remissions per 1,000), respectively. Two studies of dTMS also favored active treatment over sham for remission. (SOE: High, favor rTMS; moderate, favor TBS; low, favor dTMS)

- Twenty-six RCTs reported on response, defined by different symptom severity surveys and cut-off points.[36,37,39-62] Pooled analyses favored response among

individuals undergoing rTMS and TBS compared to sham (rTMS: RR, 1.90; 95% CI, 1.45 to 2.49; 20 RCTs; TBS: RR, 3.92; 95% CI, 2.28 to 6.73; 5 RCTs). Absolute risk differences for rTMS and TBS were 109 more responses per 1,000 individuals (95% CI, 50 to 186 more responses per 1,000) and 302 more responses per 1,000 individuals (95% CI, 132 to 593 more responses per 1,000), respectively. Two studies of dTMS also favored active treatment over sham for MDD response. (SOE: High, favor rTMS; moderate, favor TBS; low, favor dTMS)

- Thirty-six RCTs reported on change in symptom severity score.[36-71] A pooled analysis of change in severity score over baseline favored TMS treatment compared to sham for posttreatment times ranging from 2 to 11 weeks (SMD, -0.65; 95% CI, -0.91 to -0.39; 20 rTMS RCTs and 1 dTMS RCT), which was estimated to be clinically meaningful for the most common measure used (Hamilton Depression Rating Scale-17 item [HAMD17]) to estimate symptom severity. (SOE: Moderate, favor TMS)

- Twenty studies reported on AEs.[37,39,41,42,47,48,51-54,57,58,60-62,64,65,67,68,72] One study reported a greater number of any AEs in the active TMS group compared to sham (41% vs. 29%, no significance testing reported).[53] The remaining studies reported no difference in any AEs between active TMS and sham groups. (SOE: Low, favor sham) Most studies reported 0 events for serious AEs. (SOE: Low, no difference)

- We identified 3 studies that reported outcomes for subgroups of age, sex, and comorbidity.[38,47,59] There was no difference in clinical response by age,[47,59] or sex.[38,47,59] In a study of veterans with MDD, rates of remission were higher for individuals with MDD (without PTSD) for active TMS groups compared to sham condition, whereas there was little difference between groups for individuals with MDD and comorbid PTSD (P=0.03).[38] One study each was identified for the following special populations: adolescents (n=103),[36] pregnant individuals (n=26),[40] and older adults (n=52);[54] there was no difference between TMS and sham for these 3 studies.

- Two studies based on U.S. data reported cost-effectiveness outcomes.[73,74] In the base case for both studies, rTMS was the dominant strategy compared to pharmacotherapy, meaning that it cost less and was more effective.[73,74] In the study using a 1-year time horizon, the cost savings per quality adjusted life-year (QALY) gained was $746 without productivity costs and was $7,243 when productivity costs were considered.[73] In the study using a lifetime horizon, the cost savings per QALY gained ranged from $9,225 to $25,907 depending on the age at diagnosis, and more savings accumulated for younger age groups.[74] (SOE: Low)

ES 3.5 Posttraumatic Stress Disorder

We identified 4 parallel-assignment RCTs that focused on TMS[75-77] or TBS[78] compared to sham stimulation for the indication of PTSD in adults. Enrolled participants had at least moderate disease, but only 1 exclusively enrolled treatment-resistant participants; the others enrolled either

a mix of treatment-naïve and -resistant persons or did not specify treatment history. The interventions varied in terms of protocol, number of sessions, duration over which the sessions were provided, and timing of outcome measure follow-up. Key findings are as follows:

- One RCT[75] reported on remission and response. The study reported very low remission rates that did not differ statistically between groups. Likewise, for response to treatment, defined as at least a 50% decrease in the Clinician Administered PTSD Scale (CAPS), results were not statistically significant. (SOE: Insufficient for remission and response)

- Four RCTs[75-78] reported on the change from baseline in the CAPS score to either end of treatment or last follow-up. Two studies using low frequency repetitive transcranial magnetic stimulation (LF-rTMS) showed improvement in CAPS scores for TMS vs. sham, but the improvement was only statistically significant in the larger study (n=103).[76] One study of intermittent theta-burst stimulation (iTBS) showed no difference from sham, and 1 study favored sham over dTMS, although the results were not statistically significant. (SOE: Low, favors TMS)

- Three RCTs[75,76,78] reported on safety outcomes. One study reported no difference in AEs across groups, 1 study reported no serious AEs, and another reported 2 SAEs in the TMS group. Headache and treatment site discomfort were the most common specific AEs reported. (SOE for AE: Low, no difference; SOE for SAE: Insufficient)

- No studies reported cost-effectiveness outcomes or findings for special populations or subgroup analyses of interest.

ES 3.6 Smoking Cessation

We identified 5 parallel-assignment RCTs in 5 publications that focused on rTMS stimulation compared to sham stimulation for the indication of smoking cessation in adults.[79-83] Disease severity was reported in a variety of ways, including number of cigarettes smoked[80,83] and nicotine dependence as measured by the Fagerstrom Test of Nicotine Dependence (FTND) score.[80,83] Only 1 study specified the treatment history of the study population, specifically a history of at least 2 unsuccessful quit attempts.[81] The interventions varied in terms of protocol, number of sessions, duration over which the sessions were provided, and timing of outcome measure follow-up. Key findings are as follows:

- Five RCTs[79-83] reported on remission. Although various measures of abstinence from smoking generally favored TMS over sham, findings were statistically significant in only 3 studies at the posttreatment time point and durable beyond posttreatment for 1 study. (SOE: Low, favor TMS)

- Two RCTs[80,83] reported lower nicotine use as measured by self-report or nicotine biomarkers, statistically significant posttreatment for both studies and at follow-up for 1 study. (SOE: Low, favors TMS) One of these studies also reported a 50% decrease in number of cigarettes smoked for TMS compared to sham; however, the study was

small and had a high risk of bias (SOE: Insufficient).[80] Both studies also reported measures of nicotine dependence, which improved in the TMS group compared to sham, statistically significant in 1 study. (SOE: Low, favor TMS)

- Four RCTs[79-81,83] reported on safety outcomes. One study reported no AEs, 2 studies reported no difference in AEs across groups, and the largest trial found more AEs in the TMS group compared to sham. Headache was the most common specific AE reported. (SOE: Low, favor sham)

- No studies reported cost-effectiveness outcomes or findings for special populations or subgroup analyses of interest.

ES 3.7 Substance Use Disorder

We identified 6 parallel-assignment RCTs in 6 publications that focused on rTMS or deep TMS stimulation compared to sham stimulation for the treatment of alcohol use disorder and cocaine use in adults. Two studies enrolled persons with moderate to severe SUD, while the others did not indicate severity; 1 study enrolled both treatment-naïve and treatment-resistant persons, while the others did not specify treatment history. The interventions varied in terms of protocol, number of sessions, duration over which the sessions were provided, and timing of outcome measure follow-up. Key findings are as follows:

- Two RCTs reported on abstinence, 1 for alcohol use at 12 months' posttreatment[84] and 1 for cocaine use at 3 months' posttreatment.[85] In the alcohol use study,[84] the difference in total number of abstinent days was statistically significant between rTMS and sham (P=0.00), but there was no difference in percentage abstinence (P=0.126). Findings were not statistically significant for differences between TMS and sham in the cocaine use study.[85] (SOE: Insufficient)

- Four RCTs reported on substance use based on results of urine or blood tests, 2 for AUD[86,87] and 2 for cocaine use disorder.[85,88] Both AUD studies showed no statistically significant differences between TMS and sham treatment, although 1 study favored TMS for percentage of positive urine ethyl glucuronide samples at 12 weeks' posttreatment (P=0.069, actual values NR).[86] The other AUD study showed no differences in biomarkers during treatment at weeks 1, 2, and 3 (P=0.6) and favored TMS posttreatment at 2, 4, 8, and 12 weeks' follow-up (P=0.8).[87] Differences in positive tests favored TMS in both cocaine use disorder studies, but were not statistically significant (SOE: Low, favor TMS)

- Six RCTs reported on safety outcomes, 4 for alcohol use[84,86,87,89] and 2 for cocaine use.[85,88] Among the 3 studies that reported on SAEs,[84-86] no SAEs occurred. (SOE: Insufficient)

- One study on cocaine use disorder[85] reported a statistically significant difference favoring TMS for days of cocaine use (P<0.05) among the subgroup of participants

with higher depression levels (MADRS score >20). This study found no other correlations between demographic or clinical variables and treatment outcomes.

- No studies reported cost-effectiveness outcomes.

ES 4. Discussion

ES 4.1 Summary of the Evidence

The SOE ratings for the effectiveness, safety, and cost-effectiveness of TMS for the conditions included in this HTA ranged from insufficient to high (***Table ES-2***).

Table ES-2. Summary of SOE Ratings for TMS for Indications Included in This HTA

Condition	Outcome	No. Studies (No. Participants)	Strength of Evidence[a]	Direction
GAD	Remission	2 RCTs (76)	●○○○	Unable to determine
	Response	2 RCTs (76)	●○○○	Unable to determine
	Symptom severity	2 RCTs (76)	●●○○	Favor TMS
	Any SAEs	2 RCTs (76)	●○○○	Unable to determine
OCD	Response	7 RCTs (281)	●●○○	Favor TMS
	Symptom severity	9 RCTs (337)	●●○○	Favor TMS
	Any AEs	8 RCTs (315)	●●○○	No difference
	Any SAEs	8 RCTs (315)	●●○○	No difference
	Cost-effectiveness	1 DA (NA)	●○○○	NA
MDD	Remission (rTMS)	15 RCTs (1,469)	●●●●	Favors TMS
	Remission (TBS)	3 RCTs (197)	●●●○	Favors TMS
	Remission (dTMS)	2 RCTs (269)	●●○○	Favor TMS
	Response (rTMS)	20 RCTs (1,386)	●●●●	Favors TMS
	Response (TBS)	5 RCTs (259)	●●●○	Favors TMS
	Response (dTMS)	2 RCTs (264)	●●○○	Favor TMS
	Symptom severity	36 RTCs (2,615)	●●●○	Favors TMS
	Any AEs	8 RCTs (594)	●●○○	Favor Sham
	Any SAEs	14 RCTs (1,266)	●●○○	No difference
	Cost-effectiveness	2 DAs (NA)	●●○○	NA
PTSD	Remission	1 RCT (134)	●○○○	Unable to determine
	Response	1 RCT (134)	●○○○	Unable to determine
	Symptom severity	4 RCTs (307)	●●○○	Favor TMS
	Any AEs	1 RCT (134)	●●○○	No difference
	Any SAEs	3 RCTs (287)	●○○○	Unable to determine
Smoking cessation	Remission (smoking cessation)	5 RCTs (444)	●●○○	Favor TMS
	Response	1 RCT (42)	●○○○	Unable to determine
	Symptom severity (nicotine use)	2 RCTs (304)	●●○○	Favor TMS
	Any AEs	3 RCTs (370)	●●○○	Favor Sham
	Any SAEs	2 RCTs (299)	●○○○	Unable to determine
Substance abuse	Remission (abstinence)	2 RCTs (114)	●○○○	Unable to determine
	Symptom severity (substance use)	5 RCTs (283)	●●○○	Favor TMS
	Any SAEs	3 RCTs (165)	●○○○	Unable to determine

Notes: [a] SOE ratings: ●○○○ Insufficient, ●●○○ Low, ●●●○ Moderate, ●●●● High

Abbreviations: AE = adverse event; DA = decision analysis; dTMS = deep TMS; GAD = generalized anxiety disorder; HTA = health technology assessment; MDD = major depressive disorder; NA = not applicable; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SAE = serious adverse event; SOE = Strength of Evidence; TBS = theta-burst stimulation TMS; TMS = transcranial magnetic stimulation.

The largest body of evidence was for MDD, and nearly all of these studies enrolled patients with moderate to severe depression with treatment resistance to medications. Although many trials enrolled small numbers of participants, our pooled results for remission, response, and change in severity of symptoms suggested high SOE for benefit of TMS by the end of a course of treatment. In the 1 study of individuals who were specifically naïve to treatment,[46] TMS had greater magnitude of benefit for measures of remission, response, and reduction of disease severity compared to the pooled estimate, although CIs were very wide for all estimates, precluding conclusions about the benefit of TMS in non-treatment-resistant populations. We also found few studies examining special populations such as children, elderly persons, and pregnant persons or subgroups based on sex or race/ethnicity.

The remaining conditions had much smaller evidence bases, ranging from 2 to 9 studies each and with SOE ratings of low or insufficient for all outcomes we evaluated. Compared to the studies evaluating MDD, studies evaluating other conditions were more varied with respect to TMS protocol used, including brain location target, numbers of sessions per treatment course, numbers of pulses per session, durations of treatment, types of TMS used, and co-treatments.

Evidence was also limited with respect to longer term follow-up across all conditions. The durability of TMS benefits was mixed among the handful of studies reporting at time points beyond the end of a course of treatment, which ranged from 2 to 24 weeks posttreatment. For each condition, we found only 1 to 2 studies with follow-up of 3 months or longer. In general, results were durable at 3 months for this handful of studies with respect to remission, response, or reduction in symptom severity for GAD,[25] OCD,[32] MDD,[52,67] and SUD.[84,86] One study of smoking cessation found abstinence rates were durable at 18 weeks, though absolute rates of remission were < 20%.[83] Only 2 studies evaluated outcomes at 20 weeks and 24 weeks; these studies examined changes in symptom severity in MDD and found results were durable for 1 study,[52] and statistical testing was not reported for the other.[67]

For each condition, harms were graded as low (no difference or favored sham) or insufficient, often because of imprecision or study limitations related to deficiencies in how harms were ascertained and reported, which was highly variable within and across conditions, thus limiting our ability to pool these data. We have no biologic reason to believe that harms from TMS would be condition specific, and at this time, we interpreted the evidence as suggesting a low risk of AEs or SAEs for TMS as a procedure. More robust and systematic ascertainment of harms in future studies would facilitate pooling across conditions and would likely increase the SOE ratings that could be assigned to harm outcomes.

Depression findings were largely consistent with findings from other systematic reviews of TMS for the treatment of depression. An HTA authored by Ontario Health found similar remission and response benefits, and another systematic review observed a similar safety profile for TMS.[90,91] Systematic reviews of TMS for GAD, OCD, and PTSD have generally found greater benefit in symptom severity from baseline than our HTA; however, these reviews often included study designs that were ineligible for this HTA, including comparative effectiveness research, open-label studies, and uncontrolled studies and sample sizes fewer than 10 per study arm.[49,92,93]

Systematic reviews of substance abuse often included only TMS among other nonpharmacologic treatments or reported on the intermediate outcome of craving as the primary outcome.[94,95]

ES 4.2 Limitations of the Evidence Base

This HTA included many RCTs with high risk of bias and studies with small sample sizes, resulting in imprecise effect estimates, particularly for nondepression indications for TMS. The trials included in this HTA infrequently reported on race or ethnicity, and further understanding of how TMS performs in populations defined by race or ethnicity is unavailable. Similarly, a minority of studies reported on variation in treatment effect by other psychiatric comorbidities, and few studies performed subgroup analyses for comorbid conditions that commonly present in patients (e.g., GAD and MDD). For nondepression indications, there was a broader range of protocols for TMS, including several different brain targets, suggesting further research into the neural networks underlying these diseases is needed to determine optimal treatment parameters. For studies of participants with tobacco use disorder and SUD, disease severity was defined in variable ways, and prior treatment trials were rarely documented. Measuring and reporting these population characteristics will clarify which individuals may gain greater benefits from this treatment. Finally, a limited number of studies reported outcomes at a follow-up time point beyond a few weeks after the end of treatment. Understanding of the durability of TMS therapy would help guide clinical decision making on the use of this therapy.

ES 4.3 Clinical Practice Guidelines

Clinical practice guidelines and recommendations for the use of TMS for selected behavioral disorders are found in ***Tables 20, 21, and 22.*** The largest number of guidelines with recommendations for the use of TMS was for depression, although these guidelines ranged from general to specific about when and how to use TMS for treatment. Fewer guidelines were found for GAD, OCD, PTSD, and SUD. Smoking cessation guidelines or recommendations from the American Heart Association, American College of Cardiology, American Association of Chest Physicians, the American Thoracic Society, and the U.S. Preventive Services Task Force did not include TMS in treatment recommendations. Likewise, the American Society of Addiction Medicine did not include TMS in its 2020 National Practice Guideline Update.

ES 4.4 Payer Coverage

No Medicare national coverage determination for TMS exists, but we did identify local coverage determinations for some Medicare contractors. All payors cover TMS for depression and some cover TMS for OCD (***Table 23***). However, payor coverage policies vary in the required clinical criteria for coverage (***Table 24***). Coverage policies often required multiple criteria, most commonly 2 to 4 medication trials from at least 2 classes or adjunctive treatment with psychotherapy, additional medications, or both. Inability to tolerate ECT and prior favorable clinical response to TMS were also criteria for TMS coverage.

ES 4.5 Limitations of This HTA

This HTA was limited to peer-reviewed studies published in English. We did not include data or results presented solely in conference abstracts. Our research questions did not include

comparative effectiveness of various TMS types or comparisons between TMS and other treatment options (e.g., ECT, medication). For practical reasons, we excluded studies with fewer than 10 participants in each study arm and abstracted only symptom severity scores for the primary indication for TMS (e.g., depression scores for MDD studies). TMS may have also affected symptoms associated with comorbid conditions (e.g., anxiety in MDD), but we did not capture impact on comorbid conditions unless there was a formal subgroup analysis. Additionally, we did not abstract quality-of-life outcomes or cognitive outcomes.

We ultimately included only trial study designs, which generally have a short follow-up and cannot offer evidence concerning the durability of TMS on longer term clinical benefits or adverse effects. A comprehensive assessment of longer-term benefits and harms may require broader evidence base that includes observational or registry-based studies. Additionally, for harms we did not use data from the FDA Manufacturer and User Facility Device Experience (MAUDE) database to assess safety because passive surveillance systems such as MAUDE include incomplete, inaccurate, untimely, and unverified data.[96] Studies conducted in countries other than *very high* on the United Nations' Human Development Index were outside the scope of this review.

ES 4.6 Ongoing and Future Research

We identified 744 clinical trials registered in clinicaltrials.gov that are relevant to this HTA. ***Table 25*** summarizes these trials by study status and intervention category. Depression and SUD were the conditions most frequently found to have active trials.

The evidence based for TMS is more mature for MDD as compared to the other conditions included in this HTA. Research on conditions other than depression may require additional work to determine the optimal brain target and TMS treatment parameters that can then be evaluated in larger, sham-controlled effectiveness trials. Future effectiveness trials should seek to address limitations of the current evidence base, including adequately powered designs with robust execution to minimize risk of bias from attrition, outcome assessment, deviations from protocol, and post hoc analyses. For all conditions, trials should include longer term outcomes to evaluate the durability of treatment effect and to identify harms that may only emerge later to elucidate the role of TMS among treatment options. Additionally, all trials should include a measure of disease severity and treatment resistance to support clinical decision making on when to use TMS compared to another therapy, such as further medication management or ECT. The role of co-treatment with cognitive therapies or medication therapies, particularly for nondepression conditions such as tobacco use disorder or SUD, remains an area where further research could elucidate the role of TMS in treatment. Another future focus of research is to determine regimens for maintenance therapy after an initial course of TMS treatment. Lastly, trials that enroll diverse racial and ethnic populations or that are specifically designed to evaluate the effect of psychiatric comorbidities on treatment effect would advance our understanding of the applicability of this evidence to broader populations.

ES 5. Conclusion

This HTA examined the efficacy, safety, and cost-effectiveness of active TMS compared to sham TMS for selected behavioral health conditions. TMS has moderate to high SOE for benefit in MDD and low SOE for benefit in OCD at posttreatment. Evidence for benefit for the other conditions (GAD, PTSD, smoking cessation, SUD) ranges from insufficient to low for benefit depending on the outcome assessed. Data on the efficacy of TMS at longer follow-up assessment are lacking across all conditions. There was less robust evidence for safety outcomes, although studies generally reported fewer AEs for sham TMS; few SAEs were reported for either active or sham TMS. Evidence is lacking with respect to cost-effectiveness outcomes.

Full Technical Report

1. Background

Current treatment approaches for behavioral health disorders often begin with psychotherapy, pharmacotherapy, or both. However, many people do not achieve adequate clinical responses after the initial treatment attempt, and second- and third-line medications or procedures (e.g., electroconvulsive therapy [ECT]) carry risk of adverse side effects that many individuals do not tolerate. Transcranial magnetic stimulation (TMS) is a noninvasive procedure that has been cleared by the U.S. Food and Drug Administration (FDA) for some behavioral health and neurologic conditions. The growing evidence base that TMS can be efficacious with fewer and more tolerable side effects than other therapies has led to growing interest in applying TMS to a broader set of conditions.

This health technology assessment (HTA) reviews the efficacy, safety, and cost-effectiveness of TMS to assist the State of Washington's Health Technology Clinical Committee in determining coverage of TMS for selected behavioral health disorders including generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), major depressive disorder (MDD), posttraumatic stress disorder (PTSD), smoking cessation, and substance use disorder (SUD).

1.1 Epidemiology

Behavioral health disorders affect a large proportion of the American population. According to a 2020 national survey, over 14 million adults (14.2%) are estimated to have serious mental illness in the past year, defined as a mental, behavioral, or emotional disorder causing serious functional impairment interfering with 1 or more major life activities.[1] With regard to disease-specific prevalence, national surveys using validated survey instruments have found 8.1% of Americans over the age of 20 years and 15.6% over the age of 18 years experienced symptoms of depression and anxiety, respectively, consistent with clinical diagnoses of these disorders.[97,98] OCD, a chronic, debilitating condition, affects approximately 2 to 3% of the U.S. population,[5] while national surveys estimate PTSD has a prevalence of nearly 7%, reaching 23% in a veteran populations.[99,100] In 2020, over 47 million U.S. adults (19%) used any commercial tobacco product, including cigarettes.[101] The opiate epidemic has fueled years of drug overdose deaths, although nonopiates like cocaine and stimulants account for growing numbers of death over the last decade.[102] A growing number of studies in the pandemic era report a rise in prevalence of several mental health conditions. In a survey administered in June 2020, over 40% of respondents reported at least 1 behavioral health condition, including anxiety and depression (30.9%), trauma-related or stress disorder (26.3%), and the initiation or exacerbation of substance use.[2]

1.2 Disease Burden

Behavioral health disorders can affect physical health, function, and quality of life. Depressive disorders are associated with elevated risk of chronic medical conditions, early mortality, and reduced role functioning at work and relationships.[3] The burden of disease often increases with

condition severity. Patients with treatment-resistant depression are twice as likely to be hospitalized, incur direct medical costs 2 to 6 times higher compared to other individuals with treatment-responsive depressive disorder, and report a mean quality of life 25 to 40% lower than individuals with treated depression.[103-105] OCD and PTSD cause significant personal and interpersonal distress to individuals with these conditions, affecting social and occupational function.[5] Similarly, patients with GAD have lower health-related quality of life, increased health care utilization, and comorbid medical and mental health conditions.[10] Smoking contributes to nearly half a million deaths per year in the United States, with $170 billion spent on direct medical care related to smoking, and $160 billion in lost productivity.[11,12]

1.3 Treatment

Despite the significant prevalence of behavioral health disorders, over a third of individuals with mental health illness and with serious impaired function remained untreated.[106] The several barriers to treatment included cost or lack of insurance, lack of access to mental health services, perceived stigma, and structural barriers for certain racial and ethnic groups.[107] However, even for those receiving services, an adequate medication trial may still have had partial or no response. For example, for individuals with depression receiving adequate treatment, only 30% went on to have a full recovery or remission, while 20% had a partial response, and 50% had no response at all and were considered treatment resistant.[108] About one-third of individuals with PTSD were resistant to treatment; the nonresponse rates for cognitive behavioral therapy were up to 50% and 20 to 40% for pharmacotherapy. Likewise, an estimated 40 to 60% of patients with OCD and 50% with GAD remained resistant to treatment. Among FDA-approved pharmacotherapy, nicotine replacement therapy and varenicline had a 6-month abstinence rate of only 19% and 33%, respectively.[109] SUDs also had a high rate of relapse.

The 3 core components of treatment resistance are 1) establishment of the correct diagnosis, 2) adequate treatment in terms of dose and duration, and 3) inadequate response.[110] In a systematic review of treatment-resistant definitions for psychiatric disorders, there was considerable heterogeneity in the definition of treatment resistance between behavioral health disorders of depression and OCD, as well as within different guidelines for the same condition.[110] The investigators of this review did not identify consensus definitions for treatment-resistant PTSD, GAD, or SUD. Another systematic review aiming to define treatment-resistant depression found a common definition of failure of 2 medications of adequate dose and duration, although, similarly, no consensus for dose and duration, if these components are mentioned at all.[111]

There is considerable interest in neuromodulation therapies for behavioral health disorders, particularly for individuals who have not responded to typical first-line available psychotherapy and medications. TMS stands out as an option because it is noninvasive with relatively tolerable side effects. Other neuromodulation techniques include ECT, deep brain stimulation, and vagal nerve stimulation and are not the focus of this HTA. In the following section we give an overview of TMS technology.

1.4 Technology Description

Neuromodulation techniques like TMS are a separate therapeutic category, distinct from pharmacotherapy or psychotherapy. TMS is an outpatient neuromodulation procedure that is prescribed and monitored by a physician who has adequate training in the disease condition being treated, expertise in the indications and contraindications of the technology, and knowledge of the current FDA status of the treatment being offered. (***Figure 1***) TMS is often administered by a nurse, physician's assistant, or medical assistant; a physician may be present on site; and, unlike ECT, it does not require sedation. For depression, patients typically undergo treatments that last 20 to 40 minutes, and patients may leave when finished without an observation period. Patients may experience a small tapping sensation and clicking sounds associated with tensing of the coil used to induce the magnetic field. Safety protocols include offering hearing protection and potentially having anti-epileptics and oxygen on hand.[13] Typically, 5 sessions are delivered each week for 4 to 6 weeks.

Figure 1. Patient Receiving rTMS for Depression

Image source: CloudTMS.[112] This is an illustrative example of how TMS is administered and is not an endorsement for the specific device shown in the image.

During the TMS procedure, a wand (which may also be referred to as a coil) composed of a coiled wire in a protective covering is placed against the patient's scalp. An electric current in the coil creates a focal magnetic field that travels through the skull, about 2 to 3 centimeters in depth for a standard figure-eight coil. The focal magnetic field causes neurons on the cortical surface of the brain to depolarize, which can trigger activity in larger neural circuits and functional neural networks in the brain.[113,114] TMS can deliver a single pulse or multiple pulses ("a train") and is typically delivered as multiple trains, referred to as repetitive TMS (rTMS). Pertinent treatment parameters include the following:

(1) Frequency of magnetic pulses per second (Hz) in which high frequencies (>1 Hz, usually 5, 10, or 20 Hz) stimulate neurologic activity and low frequencies (≤1 Hz) inhibit activity, though impact on cortical activity can vary across individuals

(2) Intensity, which is usually set to 100% to 120% of a resting threshold, which is defined as the amount of energy to produce a visible twitch in a small muscle of the hand 50% of the time

(3) Number of pulses per session

(4) The stimulation site, which in most studies of depression target the left or right dorsal lateral prefrontal cortex (DLPFC) site, although several other stimulation sites have been or are under study, particularly for nondepression conditions

Although many TMS protocols, particularly for depression, use parameters outlined above for acute treatment, the stimulation protocols for optimal efficacy are unknown and under ongoing study. Similarly, standardized protocols for duration of active treatment, use of concurrent medications, and maintenance therapy are not established for depression, nor for any of the other indications covered in this review.[115]

Subsets of rTMS include deep TMS (dTMS) and theta-burst stimulation (TBS). dTMS involves the use of a different type of coil to create magnetic fields that can penetrate deeper brain structures. TBS is a higher intensity treatment (50 Hz) delivered in pulses that mimics theta brain waves;[115] in general, TBS treatments are shorter and are hypothesized to have a faster and more powerful effect.[50] Further, several experimental protocols and techniques are under study to accelerate the treatment course.[115] The rationales for accelerated protocols include a potential stronger impact on clinical disease, faster time to effect, and greater patient acceptability of and retention with shorter treatment times.

Contraindications to TMS include cochlear implants and implanted metal devices such as pacemakers. Seizure is a rare but serious adverse event (SAE), and some providers may taper medications that lower the seizure threshold (e.g., bupropion) before using TMS. Other common side effects include headache and scalp pain; hearing loss and vasovagal syncope are rare adverse events (AEs); hearing loss can be prevented by wearing hearing protection during treatment sessions.[37]

1.5 Regulatory Status

The first TMS device (Neurostar TMS System)[116] was initially submitted to the FDA as a Class III device under the 510K clearance pathway, citing ECT as the predicate device for TMS.[117] The FDA determined that TMS was not a substantial equivalent to ECT, and the sponsor subsequently submitted TMS under the De Novo Classification pathway as a class II device for individuals with MDD that had failed 1 antidepressant medication. The first TMS device was subsequently approved under this pathway in 2008, and this approval has served as the predicate device for 510k clearance of subsequent devices. Currently, 8 TMS devices have obtained FDA 510k clearance for indications of depression, OCD, and smoking cessation treatment. A list of

the 8 device manufacturers and indications obtained from the FDA website[118] can be found in ***Table 1***. Indications for TMS for which the FDA has issued 510k clearance include depression, OCD, smoking cessation, treatment of anxiety symptoms in those with depression, and acute and prophylactic treatment of migraine with aura. Most FDA indications specify failure of 1 prior medication only. TMS is not currently cleared by the FDA for use in the following conditions of interest in this review: GAD, PTSD, and SUD.

Table 1. FDA-Approved TMS Devices

Applicant	Product(s)	Indication(s)	De Novo or 510K Number	Clearance Date
Neuronetics	Neurostar TMS Therapy System, model 1.1, NeuroStar TMS Therapy System 3.0, Neurosoft TMS	Treatment of MDD in adult patients who have failed to achieve satisfactory improvement from 1 prior antidepressant medication at or above the minimal effective dose and duration in the current episode	DEN070003/ K061053 K083538 K130233 K133408 K160703 K161519 K160309	10/07/2008 10/07/2008 12/16/2008 04/30/2013 03/28/2014 06/10/2016 09/11/2016 12/22/2016
	NeuroStar Advanced Therapy	Adjunct for the treatment of adult patients suffering from OCD	K212289	05/06/2022
Brainsway Deep	Brainsway Deep TMS System	Treatment of depressive episodes in adult patients suffering from MDD who failed to achieve satisfactory improvement from previous antidepressant medication treatment in the current episode	K122288 K173540 K203735	01/07/2013 05/03/2018 04/23/2021
		Adjunct for the treatment of adult patients suffering from OCD	DEN170078 K183303	08/17/2018 03/08/2019
		Aid in short-term smoking cessation for adults	K200957 K203616	08/21/2020 04/16/2021
		Treatment of depressive episodes and for decreasing anxiety symptoms for those who may exhibit comorbid anxiety symptoms in adult patients suffering from MDD and who failed to achieve satisfactory improvement from previous antidepressant medication treatment in the current episode	K210201	08/17/2021
Eneura Therapeutics	SpringTMS total Migraine System, sTMS mini	Acute treatment of pain associated with migraine headache with aura	K140094 K161663	05/21/2014 08/23/2016
	SpringTMS	Acute and prophylactic treatment of migraine headache	K162797	06/26/2017
		Acute and prophylactic treatment of migraine headache in adolescents (aged 12 or older) and adults	K182976	02/25/2019
Tonica Elektronik A/S	MagVita TMS Therapy System, MagVita TMS Therapy with MagPro R20, Mag Vita TMS Therapy System w/Theta Burst Stimulation	Treatment of MDD in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode	K150641 K170114 K171481 K171967 K172667 K173620	07/31/2015 05/01/2017 06/16/2017 07/25/2017 10/05/2017 08/14/2018

Applicant	Product(s)	Indication(s)	De Novo or 510K Number	Clearance Date
	MagVenture TMS Therapy for treatment of OCD, MagVenture TMS Therapy system	Adjunct for the treatment of adult patients suffering from OCD	K193006	08/09/2020
TeleEMG, LLC	Neurosoft TMS (also CloudTMS)	Treatment of MDD in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode	K173441	12/13/2017
Mag & More GmbH	Apollo TMS Therapy System	Treatment of MDD in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode	K180313	05/04/2018
Magstim Company Ltd.	Horizon TMS Therapy System, Horizon TMS Therapy System with Navigation, Magstim Horizon 3.0 TMS Therapy System, Horizon 3.0 System, Horizon 3.0, Horizon 3.0 with Navigation	Treatment of MDD in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode	K180907 K182853 K183376 K211389	08/03/2018 03/15/2019 04/03/2019 09/14/2021
REMED Co.	ALTMS Magnetic Stimulation Therapy System	Treatment of MDD in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode	K202537	11/26/2021

Abbreviations: MDD = major depressive disorder; OCD = obsessive-compulsive disorder; TMS = transcranial magnetic stimulation.

1.5 Policy Context

The State of Washington Health Care Authority selected TMS for selected behavioral health conditions for an HTA because of medium concerns of safety and high concerns for efficacy and cost.

1.6 Washington State Agency Utilization Data

The State of Washington Health Care Authority provided data on TMS utilization in the State of Washington from 2018 to 2021. This data is provided in ***Appendix A***. The data provided includes utilization and costs for Medicaid (fee for service and managed care organization), Department of Labor and Industries Workers' Compensation Program, and the Public Employee Benefit Board Uniform Medical Plan.

2. Methods

This section describes the methods we used to conduct this HTA.

2.1 Research Questions and Analytic Framework

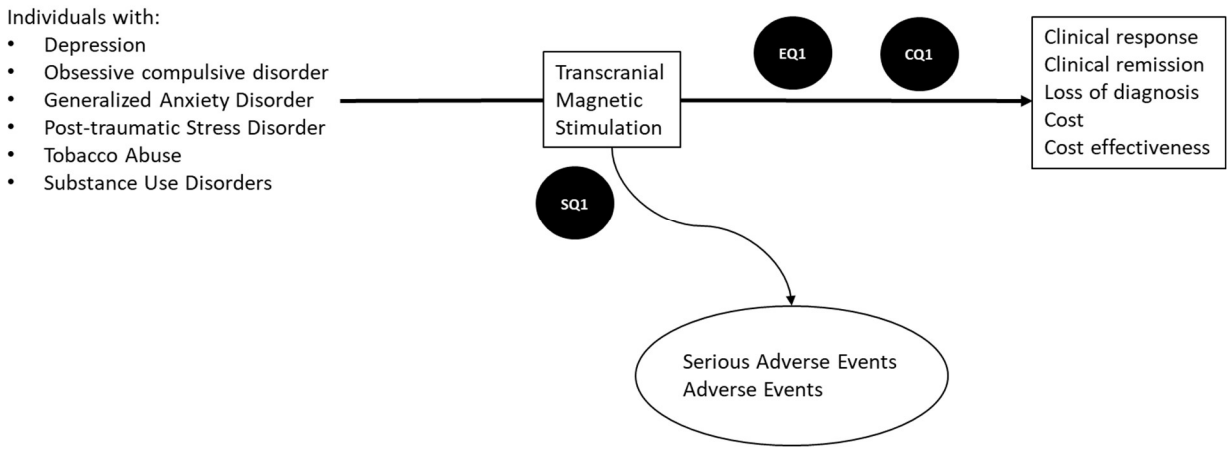
We developed the following research questions and analytic framework (***Figure 2)*** to guide the systematic evidence review of primary research studies:

Efficacy Question 1 (EQ 1). What is the efficacy of TMS for the treatment of selected behavioral disorders?

Safety Question 1 (SQ 1). What are the harms associated with TMS for the treatment of selected behavioral disorders?

Cost Question 1 (CQ 1). What are the costs and cost-effectiveness of TMS for the treatment of selected behavioral disorders?

Figure 2. Analytic Framework Depicting Scope of this HTA on TMS for Treatment of Selected Behavioral Health Disorders



Abbreviations: CQ = cost question; EQ = efficacy question; HTA = health technology assessment; SQ = safety question; TMS = transcranial magnetic stimulation.

The State of Washington HTA Program posted a draft of these research questions and proposed scope for public comment from July 8 to July 22, 2022. The final key questions and response to public comments on the draft key questions were published on the Program's website on August 23, 2022.[14] A draft of this report underwent external peer review and was posted for public comment between January 5, 2023 and February 6, 2023.

2.2 Data Sources and Searches

We searched PubMed, the Cochrane Library, and PsycInfo for relevant studies published in English from inception to May 24, 2022. We also conducted an addendum search of the same databases for cost studies on June 29, 2022. To ensure comprehensive identification of studies of relevant interventions, we used medical subject headings (MeSH terms) and keyword terms. The detailed search strategy is presented in ***Appendix B***. In addition, we reviewed the reference lists of relevant studies, systematic reviews, practice guidelines, and other HTAs on the topic to identify any relevant primary research studies not found through the electronic search.

2.3 Study Selection

Table 2 summarizes the study selection criteria related to the population, intervention, comparator, outcomes, timing, study design, and setting that defined the scope of this HTA,

which are further described in the sections following the table. Two review team members independently screened titles, abstracts, and full-text articles based on these study selection criteria using DistillerSR version 2.35 (DistillerSR, Inc.). Discrepancies in study selection at the full-text level were adjudicated by a senior investigator or, in some cases, by consensus among the team.

Table 2. Population, Intervention, Comparator, Outcome, Timing, and Setting for HTA on TMS for Treatment of Selected Behavioral Health Disorders

PICOTS	Include	Exclude
Population	Individuals of all ages with eligible clinical diagnosis: • GAD • OCD • MDD • PTSD • Tobacco use disorder or regular smoker • SUD Subgroups of special interest: Individuals who are peri- or postpartum, elderly, aged < 18 years	• Individuals with ineligible mental health diagnoses, including mixed populations of eligible and ineligible diagnoses for which results are not stratified • Individuals with no mental health diagnosis (e.g., healthy controls) • Individuals with a primary medical (i.e., nonpsychiatric) diagnosis as the TMS indication • Studies conducted in animals, in vitro, or in silico
Intervention	• rTMS, dTMS, and TBS with or without concurrent pharmaco- or psychotherapy delivered over more than 1 session	• Single-session TMS • Other noninvasive neuromodulation procedures (e.g., transcranial direct current stimulation, neurofeedback, transcutaneous vagus nerve stimulation) • Invasive neuromodulation therapies (e.g., implanted vagus nerve stimulation, deep brain stimulation, brain surface implants) • Experimental therapies (e.g., synchronized TMS)
Comparator	• For EQ and SQ: Sham TMS with or without concurrent pharmaco- or psychotherapy • For CQ: Sham TMS, medication, ECT, or other standard-of-care therapies for treatment-resistant depression	EQ and SQ: • Head-to-head comparisons of TMS with alternative TMS protocols, medications, psychotherapy, other neuromodulation procedures (e.g., ECT), or complementary or alternative therapies • Wait-list control • No comparator
Outcomes	• EQ: Primary study outcome or outcome used for determining power or sample size must be a clinical outcome: response (e.g., symptom scales or indices), remission, or loss of diagnosis as measured by validated instruments or clinical evaluation. For smoking, validated measures of abstinence. Clinical outcomes from studies where the primary outcome was an intermediate or biomarker but that also reported a validated clinical outcome will only be included if the study was also adequately powered for the clinical outcome.	• Nonvalidated measures of clinical response or remission • Individual symptom response outside of a validated scale (e.g., guilt, hopelessness) • Intermediate or biomarker outcomes, such as electrophysiologic or functional imaging outcomes, craving measures, and lab measures with the exception of cotinine and carbon monoxide measures of abstinence • Clinical outcomes that do not measure the primary indication for TMS (e.g., anxiety measures in MDD population)

PICOTS	Include	Exclude
	• SQ: SAEs (e.g., seizure), AEs (e.g., headache), side effects including device-related complications (e.g., scalp pain) • CQ: Cost, cost-effectiveness	• Quality-of-life outcomes (e.g., SF-12)
Timing and Language	• No timing restrictions • English-language articles	• No timing exclusions • Non-English-language articles
Study Design	• EQ: RCTs, nonrandomized controlled trials, crossover trials • SQ: Same as EQ; plus we will consider prospective controlled cohort studies if there are not enough trials to synthesize • CQ: CEA, CUA, or CBA performed from the societal or payor perspective	• Editorials, commentaries, narrative reviews, or letters; conference abstracts; case reports or case series; retrospective controlled cohort studies; case-control studies; other observational study designs without a comparator group not already specified • Relevant systematic reviews will be excluded but will be hand searched to identify potentially eligible primary studies. • Studies with fewer than 10 individuals in any arm will be excluded.
Setting	• For EQ and SQ: Countries categorized as "very high human development" on the United Nations Development Programme's HDI Report[15,a] • For CQ: Studies conducted based on U.S. cost data • Inpatient settings, outpatient settings, community and residential (e.g., group homes, long-term care facilities)	• For EQ and SQ: Countries not categorized as "very high human development" according to the United Nations Development Programme's Human Development Report[15] • For CQ: Studies conducted using non-U.S.-based cost data • No exclusions based on care setting

Note.

[a] Andorra, Argentina, Australia, Austria, Bahamas, Bahrain, Barbados, Belarus, Belgium, Brunei Darussalam, Bulgaria, Canada, Chile, Costa Rica, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hong Kong China (SAR), Hungary, Iceland, Ireland, Israel, Italy, Japan, Kazakhstan, Korea (Republic of), Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malaysia, Malta, Mauritius, Montenegro, Netherlands, New Zealand, Norway, Oman, Palau, Panama, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Turkey, United Arab Emirates, United Kingdom, United States, Uruguay.

Abbreviations: CBA = cost-benefit analysis; CEA = cost-effectiveness analysis; CQ = cost question; CUA = cost-utility analysis; EQ = efficacy question; PICOTS = population, intervention, comparator, outcome, timing, and setting; RCT = randomized controlled trial; SQ = safety question; TMS = transcranial magnetic stimulation.

2.3.1 Population

We selected studies that enrolled individuals of any age with a clinical diagnosis of GAD, OCD, MDD, PTSD, tobacco use disorder, or SUD. We excluded studies that enrolled individuals with no mental health diagnosis (e.g., healthy controls), individuals with TMS indication based on a primary medical diagnosis (i.e., nonpsychiatric diagnosis), or study populations including a mix of eligible and ineligible conditions (e.g., MDD and bipolar disorder) where results were not stratified by the population of interest to this review. Although TMS is usually reserved to treat individuals who have failed prior treatment (i.e., treatment-resistant individuals), this HTA also considered study populations of treatment-naïve individuals or a mix of treatment-naïve and treatment-resistant individuals. Populations of special interest included pregnant, peri- or postpartum, and elderly individuals and persons younger than 18 years. We also looked for subgroup analyses based on age, sex or gender, race or ethnicity, or disability.

2.3.2 Intervention and Comparator

We selected studies that used rTMS, dTMS, or TBS with or without concurrent pharmaco- or psychotherapy delivered over more than 1 session; we excluded other noninvasive neuromodulation procedures and invasive neuromodulation therapies. For comparators, we required that studies used a sham TMS comparator group with or without concurrent pharmaco- or psychotherapy. We excluded active comparators of medication or other TMS protocols for EQ 1 and SQ 1 because the purpose of this HTA was to review the efficacy and safety of TMS. We allowed other comparators for CQ 1.

2.3.3 Outcomes

For the efficacy research question (EQ 1), we selected studies with primary study outcomes of clinical response (e.g., generally based on a specified threshold decrease in score on validated symptom scales or indices), remission (a period of improvement where the individual is virtually asymptomatic), loss of diagnosis (based on clinically assessed diagnostic criteria), or change in severity of illness as measured by validated instruments or clinical evaluation. Clinical outcomes from studies where the primary outcome was an intermediate or biomarker but that also reported a validated clinical outcome were only included if the study was also adequately powered for the clinical outcome. We did not include clinical outcomes that did not measure the primary clinical indication for TMS in the study (e.g., we did not include anxiety severity scores for individuals with MDD).

For the safety research question (SQ 1), we selected studies that reported SAEs, AEs, or side effects including device-related complications. We did not require studies to report these types of outcomes based on any prespecified taxonomy or definitions.

For the cost research question (CQ 1), we selected studies that reported on the cost-effectiveness of TMS interventions from studies that used U.S.-based cost data.

2.3.4 Settings

Studies in any care setting were eligible. For efficacy and safety research questions, we selected studies that were conducted in countries with a development rating designated as *very high* on the United Nations Human Development Index in August 2022 for selection because these countries (e.g., Canada, Europe, Australia, New Zealand, Japan, South Korea, Singapore, Hong Kong, and others) are like the United States with respect to standards of medical practice.[15] We excluded studies conducted in countries with a development rating designated as less than *very high*. For cost studies, we selected only studies conducted in the United States.

2.3.5 Study Design

For EQ 1, we selected studies that used randomized controlled trials (RCTs), nonrandomized controlled trials, and crossover trials.

For SQ 1, we selected studies that used RCTs, nonrandomized controlled trials, and crossover trials. We initially planned to consider prospective controlled cohort studies if the number of trials was too low to synthesize; however, we did not identify any such studies for any conditions other than MDD for which we had an adequate number of trials.

For both EQ 1 and SQ 1, we excluded eligible designs with fewer than 10 individuals in any arm. We also excluded case-control studies, retrospective controlled cohort studies, case reports, other observational study designs without a comparator group, editorials, comments, letters, conference abstracts, and narrative reviews. We did not include systematic reviews but did search their reference lists to identify relevant primary studies that our electronic database search may have missed.

For CQ 1, we included cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis studies that were performed from the societal or payor perspective.

2.3.6 Time Period

We selected studies regardless of date of publication or years when the study was conducted.

2.3.7 What Is Excluded From This HTA

This review did not include studies published in languages other than English or conducted in countries that are not very highly developed based on the United Nations Human Development Index.[15] This review also did not include studies solely focused on head-to-head comparisons between alternative TMS protocols or comparisons between TMS and medication. Studies with multiple intervention arms were included if an eligible control group was also included; only data from the comparisons between eligible intervention groups and eligible control groups were included in this HTA.

2.4 Data Abstraction and Risk-of-Bias Assessment

One team member extracted relevant study data into a structured abstraction form in DistillerSR, and a senior investigator checked those data for accuracy. Two team members conducted independent risk-of-bias assessments on all included studies; discrepancies were resolved by discussion. We used the Cochrane Risk of Bias (RoB 2.0) tool to assess the risk of bias for each included RCT.[16] Domains assessed with this tool included bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcomes data, bias in measurement of the outcomes, and bias in selection of the reported results. Risk of bias was assessed as "high," "some concerns," or "low" at the study level, unless different outcomes within a single study required outcome-level risk-of-bias ratings. We used the Quality of Health Economic Studies Instrument to assess the risk of bias of included cost analyses.[17] We considered studies with scores on this instrument of 90 or above to have low risk of bias, studies with scores between 60 and 89 to have some concerns for bias, and studies with scores below 60 to have high risk of bias.

2.5 Data Synthesis and Strength-of-Evidence Rating

We qualitatively synthesized study characteristics and results for each research question by clinical diagnosis category in tabular and narrative formats.

To determine whether quantitative synthesis was appropriate, we assessed the number of studies and the clinical and methodological heterogeneity present based on established guidance.[18,19] We required a minimum of 3 studies to conduct meta-analyses. We also required at least 50% of

studies for a condition with a similar intervention and comparator with the same outcome measured at approximately the same follow-up time point to calculate a pooled treatment effect for that comparison. For meta-analyses, we used random-effects models using the inverse variance method of DerSimonian and Laird to generate pooled mean differences (MDs) or Cohen's d standardized mean differences (SMDs) for continuous outcomes and risk ratios (RRs) for categorical outcomes.[20] We re-expressed pooled RR estimates as absolute risk differences (ARDs) per 1,000 participants. When studies reported more than 1 outcome for symptom severity, response, or remission, we selected the outcome most commonly reported across the set of studies for use in pooled estimates. For studies with multiple intervention arms and 1 control group, 1 active group was picked for the main analyses, and a sensitivity analysis was performed including the alternative active arm; results from sensitivity analyses were similar and the main results are reported. Statistical significance was assumed when 95% confidence intervals (CIs) of pooled results did not include the null effect (i.e., 1.0 for RRs, 0 for MDs and SMDs). For all quantitative syntheses, the I^2 statistic was calculated to assess statistical heterogeneity in effects between studies.[119,120] An I^2 from 0 to 40 percent might not be important, 30 to 60 percent may represent moderate heterogeneity, 50 to 90 percent may represent substantial heterogeneity, and 75 percent or greater represents considerable heterogeneity.[119,120] All testing was two-sided. For pooled analyses, we performed sensitivity analyses removing studies with high risk of bias. Stata version 17 (Stata Corp) was used to conduct all quantitative analyses.[121]

We graded the strength of evidence (SOE) for each clinical condition and category of outcomes using the Agency for Healthcare Research and Quality Evidence-based Practice Center (EPC) SOE approach,[21,22] which is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[23] We combined multiple outcome measures within the same outcome domain and graded SOE for the outcomes of remission, response, disease-specific continuous outcomes, non-disease-specific outcomes, safety, and cost-effectiveness.[23] SOE can be graded as *insufficient*, *low*, *moderate*, or *high* and reflects our confidence in the findings; ***Table 3*** defines these levels. Bodies of RCT evidence began with a *high* rating and were downgraded based on domains relating to study limitations (i.e., risk of bias), consistency, precision, directness, and reporting bias. To assess the consistency domain, we evaluated both the consistency in the direction and magnitude of the treatment effect. Single study bodies of evidence were rated as "Consistency NA" and downgraded 1 level. To assess the precision domain, we evaluated the width of the CI for pooled estimates; when pooled estimates were not available, we evaluated the overall sample size relative to optimal information size based on a single adequately powered study and variance of individual studies contributing to the evidence base for the comparison. When CIs were either not provided or could not exclude a meaningful benefit or harm, we downgraded for imprecision. Our study selection criteria only selected for outcomes and comparisons that we considered direct. We captured reporting bias as part of study limitations.

Table 3. SOE Grades and Definitions[21,22]

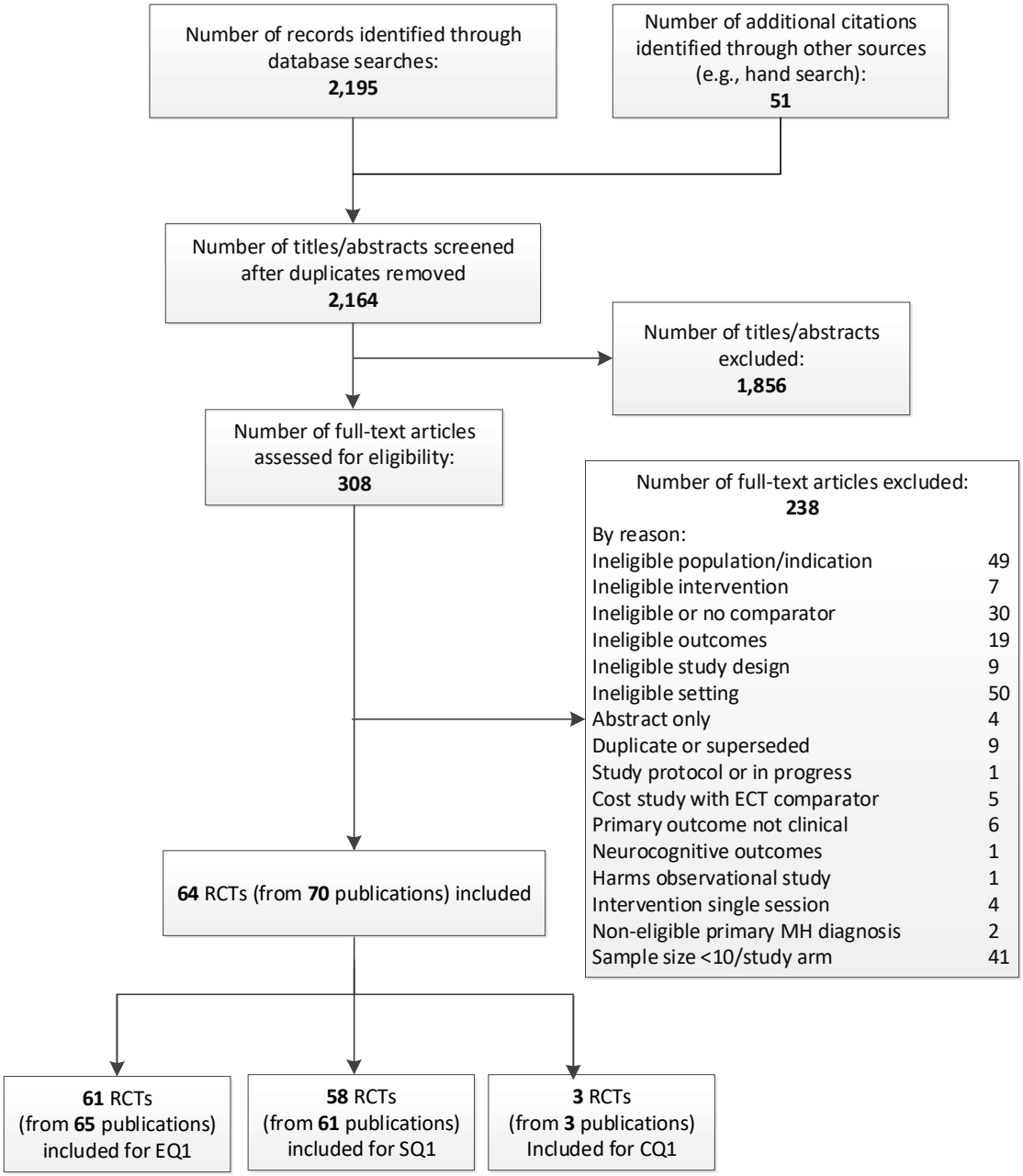
GRADE	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, that is, another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome.** No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

3. Results

3.1 Literature Search and Overview of Measures Reported

Figure 3 depicts the study flow diagram. We identified and screened 2,164 unique citations. We excluded 1,856 citations after title and abstract review. We reviewed the full text of 308 articles and included a total of 64 studies reported in 70 articles published between 2001 and 2022. Sixty-one RCTs were included for EQ 1, 58 RCTs for SQ 1, and 3 RCTs for CQ 1.

Figure 3. Study Flow Diagram for HTA on TMS for Treatment of Selected Behavioral Health Disorders



Abbreviations: CQ = cost question; ECT = electroconvulsive therapy; EQ = efficacy question; MH = mental health; RCT = randomized controlled trial; SQ = safety question.

Individual study and population characteristics and findings for all included studies are summarized in ***Appendix C***. The list of articles we screened at the full-text stage, but which we excluded, is provided in ***Appendix D***. Note that articles may have been excluded for more than 1 reason, but we report only 1 reason. We also include a list of single arm studies that were excluded. We report our individual study risk-of-bias assessments for included studies in ***Appendix E***.

Table 4 details the most commonly reported scales and indices used to report findings related to the EQ across the included conditions. In the next section, we present results organized by clinical condition.

Table 4. Summary of Validated Measures Reported by Included Studies

Instrument	Description	Score Range	Directionality of Scale	Minimally Important Difference
Disease-Specific Measures				
Depression				
Beck Depression Inventory (BDI)[122]	21 items measuring characteristic attitudes and symptoms of depression	0–63: 0–13 minimal depression, 14–19 mild depression, 20–28 moderate depression, 29–63 severe depression	Higher scores indicate worse depression	5 points or 17.5–30% reduction in score
Hamilton Rating Scale for Depression (HAMD)[123]	Versions range from 17 to 24 items; items are scored on a 5-point scale	0–7 normal; 8–13 mild, 14–18; moderate, 19–22 severe, ≥ 23 very severe depression	Higher scores indicate worse depression	2 to 3 points or 27–28% reduction
Montgomery–Åsberg Depression Rating Scale (MADRS)[124]	10-item measure assessing the severity of depression among patients with a diagnosis of depression; designed to be sensitive to change resulting from antidepressant therapy	0–60: 0–6 absence of symptoms, 7–19 mild depression; 20–34 moderate depression, 35–60 severe depression	Higher scores indicate more severe depression	6- to 9-point reduction in score
Non-depression conditions				
Clinician Administered PTSD Scale (CAPS)[125]	Structured interview of 30 items to rate symptoms of PTSD described in the DSM manual on both frequency and intensity	0–80: A PTSD diagnosis is made if there is at least 1 "B" symptom, 3 "C" symptoms, and 2 "D" symptoms as well as meeting the other diagnostic criteria	Higher scores indicate greater severity of PTSD	7- to 13-point reduction in score
Fagerstrom Test For Nicotine Dependence (FTND)[126]	Six-item instrument for assessing the intensity of physical addiction to nicotine, including the quantity of cigarette consumption, the compulsion to use, and dependence	0–10: 0–2 very low, 3–4 low, 5 moderate, 6–7 high, 8–10 very high	Higher scores indicate more intense physical dependence on nicotine	Unclear
Hamilton Anxiety Rating Scale (HARS)[127]	14 items, each scored on a scale of 0 (not present) to 4 (severe), assessing severity of anxiety symptoms	0–56: <17 mild severity, 18–24 mild to moderate severity, 25–30 moderate to severe	Higher scores indicate worse anxiety	Unclear
Yale–Brown Obsessive-Compulsive Scale (Y-BOCS)[128]	10-item measure assessing severity of obsessive-compulsive symptoms over the past week, including time occupied, associated distress, impairment, resistance, control of obsessions and compulsions	0–40: < 13 mild, 14–24 moderate, 25–30 moderate-severe, > 30 severe symptoms.	Higher scores indicate more severe disease	35% decrease from baseline
Global Measures				
Clinical Global Impression Scale-Improvement (CGI-I)[129]	Structured interview question measuring the patient's experienced change in response to treatment; the improvement scale is on a 7-point scale	1–7: 1 very much improved, 3 minimally improved, 4 no change, 5 minimally worse; 7 very much worse	Higher scores indicate worsening of condition	Unclear
Clinical Global Impression Scale-Severity (CGI-S)[129]	Structured interview question measuring the severity of illness on a 7-point scale	1–7: 1 normal, 2 borderline ill, 3 mildly ill, 4 moderately ill, 5 markedly ill, 6 severely ill, 7 among the most extremely ill patients	Higher scores indicate greater severity of condition	Unclear

Abbreviations: DSM-IV = *Diagnostic and Statistical Manual*, 4th edition; PTSD = posttraumatic stress disorder.

3.2 Generalized Anxiety Disorder

We identified 2 parallel-assignment RCTs that focused on rTMS stimulation compared to sham stimulation for the treatment of GAD. The interventions varied in terms of TMS protocol and number of sessions. Both studies provided treatment sessions for a duration of 6 weeks and measured outcomes posttreatment and at 12-weeks' follow-up. Key findings are as follows:

- Two RCTs[24,25] reported on remission and clinical response, defined in different ways. However, only 1 study reported statistically significant findings,[25] where response was improved immediately posttreatment and at 12 weeks follow-up, but remission was only significantly improved at 12-weeks' follow-up. (SOE: Insufficient for both response and remission)

- Two RCTs[24,25] reported on the change in HARS scores from baseline to end of treatment and last follow-up time points, both with statistically significant results and both favoring TMS (SOE: low, favor TMS). One study also reported on Clinical Global Impression – Severity scale (CGI-S) results at posttreatment and follow-up (SOE: Insufficient).

- Two RCTs[24,25] reported on safety outcomes (SOE: Insufficient). Two studies reported SAEs for 1 patient each, both in the TMS group. Facial twitching was the most common specific AE reported.

The rest of this section provides detailed study characteristics and results.

3.2.1 Study and Population Characteristics

One of the 2 trials was conducted from 2008 to 2012,[24] and the other study was conducted from 2012 to 2014.[25] We assessed 1 trial as having some risk of bias for differences in baseline anxiety severity between groups that did not appear to be adjusted for in the analysis[25] and 1 trial as having high risk of bias for high overall attrition, differential attrition, and lack of transparency in reporting of patient flow.[24] One trial was conducted in the United States,[25] and 1 trial was conducted in Canada and Bulgaria.[24] One study received partial industry support,[25] and the other study did not report their sponsorship.[24] ***Table 5*** summarizes the characteristics of included rTMS trials; additional details are found in ***Appendix C***, ***Tables C-1, C-2,*** and ***C-3***.

Both studies recruited patients with moderate to severe anxiety: 1 based on eligibility criteria of HARS score ≥18, with mean baseline HARS score ranging from 20 to 25.[25] The other study eligibility criteria did not require a minimum HARS score, but the mean baseline HARS score ranged from 29 to 32.[24] Neither study specified if participants were resistant to prior treatment trials. The study sample sizes ranged from 26 to 50 participants. The mean age of included populations ranged from 34 to 44.6 years. All studies included both male and female participants, and only 1 study[25] provided data about participant race: over 90% of the participants were White. One study reported on mental health comorbidities, specifically anxiety and depressive disorders.[25]

The active intervention in all RCTs was rTMS, although there was variation in the rTMS protocol used in the 2 studies. One study was conducted using high-frequency rTMS of the right DLPFC,[24] and 1 study was conducted using low-frequency rTMS of the right DLPFC.[25] Studies also varied in the number of pulses administered during a single session (range 900 to 3,600) and in the stimulation intensity used (range 90 to 110% motor threshold). Both studies provided active or sham treatment over 6 weeks (number of sessions ranging from 2 to 5 sessions per week) and a follow-up duration of 12 weeks. Both studies included co-interventions; 1 study provided medication per treatment as usual,[25] and 1 study provided medication and psychotherapy per treatment as usual.[24] The studies included a variety of sham rTMS controls.

Table 5. Summary of Study Characteristics of Included Studies of TMS for Treatment of GAD

Author, Year Country RoB	Intervention and Comparator (N Randomized)	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions	Mean Age (SD)	N (%) Female
Dilkov et al., 2017[24] Canada, Bulgaria High	HF-rTMS (25) Sham TMS (25)	50	6 weeks;[b] 12 weeks	Medication and psychotherapy per treatment as usual	TMS: 34 (7) Sham: 38 (10)	TMS: 6 (15) Sham: 13 (33)
Diefenbach et al., 2016[25] U.S. Some concerns	LF-rTMS (14) Sham TMS (12)	26	6 weeks;[c] 12 weeks	Medication per treatment as usual	TMS: 44.0 (12.0) Sham: 44.6 (14.8)	TMS: 11 (84.6) Sham: 8 (66.7)

Notes: [a] "Last follow-up" indicates last follow-up time point eligible for this HTA (e.g., blinded phase eligible only of a multiphase study with open-label phases). A study may have reported outcomes at follow-up time points that were subsequent to what is reported in this column, although they were not eligible for review (e.g., open-label phase).
[b] 5 sessions/week for 4 weeks, then 3 sessions/week for 1 week, then 2 sessions/week for final week.
[c] 5 sessions/week.

Abbreviations: GAD = generalized anxiety disorder; HF = high frequency, LF = low frequency, N = number; RoB = risk of bias; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; TMS = transcranial magnetic stimulation; U.S. = United States.

3.2.2 Findings

Detailed findings are provided in ***Appendix C, Tables C-4*** and ***C-5***. A summary of findings and the SOE are provided in ***Table 6***. Both studies showed differences in remission, response, and other measures favoring the active TMS group, although most statistically significant results were for later follow-up time points only. The following section provides detailed results for each category of outcome measure.

Table 6. Summary of Findings and SOE for TMS Compared to Sham Stimulation for GAD

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall SOE/ Direction
Remission of GAD symptoms at posttreatment and last follow-up						
2 RCTs[24,25]/76	One study reported remission measures favoring TMS immediately after treatment, which was not statistically significant; however, there was a statistically significant difference in remission favoring TMS at the12-week follow-up time point. One study reported remission measures favoring TMS immediately after treatment and at the 12-week follow-up time point, but information on statistical significance was not reported for either time points.	Consistent	Imprecise	Direct	High (1 SC, 1 High RoB)	Insufficient[a,b]
Response of GAD symptoms at posttreatment and last follow-up						
2 RCTs[24,25]/76	One study reported response to treatment as statistically significantly higher in participants allocated to active TMS compared to sham TMS immediately posttreatment and at 12-week follow-up. One study reported a more favorable response to treatment in the TMS group at posttreatment and 12-week follow-up, but information on statistical significance was not reported.	Consistent	Imprecise	Direct	High (1 SC, 1 High RoB)	Insufficient[a,b]
HARS score at posttreatment or last follow-up						
2 RCTs[24,25]/76	Both studies reported HARS scores, which favored TMS with statistically significance differences at reported time points (actual differences NR).	Consistent	Imprecise	Direct	High (1 SC, 1 High RoB)	Low[b,c] Favor TMS
CGI-S score at posttreatment and last follow-up						
1 RCT[24]/50	At posttreatment and 12-week follow-up, participants in the TMS group were reported to have a lower CGI-S score than those in the sham group, which was statistically significant.	Consistency NA (single study)	Imprecise	Direct	High (1 High RoB)	Insufficient[b,c,d]

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall SOE/ Direction
Safety (total AEs)						
2 RCTs[24,25]/76	Studies only reported specific AEs; did not report total AEs by group. Frequently reported AEs include facial twitching, headache, and dizziness. Unable to assess SOE.	NA	NA	NA	NA	NA
Safety (SAEs)						
2 RCTs[24,25]/76	Both studies reported 1 SAE in the TMS group only; 1 study reported generalized tonic-clonic seizure, and the other study reported chest pain, which was determined to be unrelated to the study intervention.	Consistent	Imprecise	Direct	High (1 High, 1 SC)	Insufficient[a,b]

Notes: [a] Downgrade 2 levels for imprecision. [b] Downgrade 1 level for study limitations. [c] Downgrade 1 level for imprecision. [d] Downgrade 1 level for single study body of evidence.

Abbreviations: AE = adverse event; CGI-S = clinical global impression scale-severity; GAD = generalized anxiety disorder; HARS = Hamilton Anxiety Rating Scale; NA = not applicable; NR = not reported; RoB = risk of bias; SAE = serious adverse event; SC= some concerns; SOE = strength of evidence; TMS = transcranial magnetic stimulation.

Remission of GAD Symptoms

Two RCTs[24,25] reported on remission. Remission was defined as a HARS score of less than 10 for 1 study[24] and a HARS score of less than 8 and a CGI-I score of 1 or 2 for the other study.[25] One study[25] reported increased remission in the TMS group immediately posttreatment, although it did not achieve statistical significance. However, this result remained durable and became statistically significant at 12-week follow-up (P=0.003). Remission measures for the other study[24] showed improvement at posttreatment (80%) and 12-week (100%) follow-up time points for the intervention group, although outcomes for the control group and statistical significance were not reported for either time point.

Response to Treatment

Two RCTs[24,25] reported on response to treatment, defined as at least a 50% improvement on HARS scores. One RCT[25] found that participants in the TMS group were more likely to have a response to treatment (61.5%) than those in the sham group posttreatment (16.7%; P=0.022). This result remained durable at 12-week follow-up (P=0.001), where 61.5% of participants in the TMS group had a response to treatment compared to 0% of those in the sham group. One RCT[24] reported increased response in the TMS group at posttreatment and 12-week follow-up, but statistical testing was not reported for either time point.

Other Measures

Change in HARS Score

Two RCTs[24,25] reported on HARS scores, both of which favored TMS. One study[24] reported statistically significantly higher change in HARS score from baseline to posttreatment in participants allocated to active TMS compared to sham TMS (P<0.001). Another study[25] reported a lower HARS score for the TMS group at posttreatment (12.1 vs. 14.4) and 12-week follow-up (10.4 vs. 18.0) compared to the sham group (Group x Time interaction: P<0.001).

CGI-S Scores

One RCT[24] reported on CGI-S scores at posttreatment and 6 weeks posttreatment. At both time points (immediately posttreatment and at 12 weeks), participants in the TMS group had a lower CGI-S score than those in the sham group (P<0.001).

Safety Measures

Two RCTs[24,25] reported on safety outcomes, although the specific outcomes reported varied. Two studies reported on SAEs; 1 study[24] reported 1 SAE (generalized tonic-clonic seizure) in the TMS group, and 1 study[25] reported 1 SAE (chest pain, which was determined to be unrelated to the study intervention) in the TMS group. The most frequently reported specific AE was facial twitching, which occurred in all patients for 1 study[24] and in 46% of patients in the TMS group for the other study (P<0.01).[25] Differences between all other reported specific AEs between groups, including headache and dizziness, were not statistically significant.

3.3 Obsessive-Compulsive Disorder

We identified 9 parallel-assignment RCTs[26-34] that evaluated TMS compared to sham among individuals diagnosed with OCD and 1 decision analysis (DA) reporting on cost-effectiveness.

Six studies evaluated repetitive TMS (rTMS),[29-34] 2 studies evaluated dTMS,[26,27] and 1 study evaluated continuous theta-burst stimulation (cTBS).[28] The number of TMS sessions and treatment duration varied among studies. Outcome measures used were consistent, but the timing of treatments, timing of the outcome measurements, and duration of follow-up varied. Key findings are as follows:

- Seven RCTs[26-31,34] reported clinical response, defined as a decrease in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score of 25% or more; pooled RR 1.96 (95% CI, 0.94 to 4.09; 281 participants; I^2=47.1%); ARD 155 more clinical responses per 1,000 participants (95% CI, from 9 fewer to 487 more) for TMS compared to sham. (SOE: Low, favor TMS)

- Nine RCTs[26-34] reported using Y-BOCS. Change in severity of OCD symptoms from the Y-BOCS was the primary outcome in all but 1 study. Results were mixed with 5 studies reporting that TMS was associated with symptom severity improvement (statistically significant in 4 studies), 1 study favoring sham (non-significant) and 3 studies that did not report direction of effect of TMS treatment on OCD symptom severity. (SOE: Low, favor TMS)

- Eight RCTs[26-29,31-34] reported on AEs. There were no differences in any AEs or severe AEs between groups. Headache and localized scalp pain were the most frequently reported side effects across groups. (SOE: Low, no difference)

- One DA reported incremental cost-effectiveness ratios (ICERs) ranging from $1,002 to $1,647 per unit improvement in Y-BOCS score compared to antidepressant monotherapy and antidepressant therapy in combination with antipsychotic therapy respectively (SOE: insufficient).

The rest of this section provides detailed study characteristics and results.

3.3.1 Study Population and Characteristics

Studies were conducted between 2006 and 2018. We assessed 7 of these trials as having some risk of bias,[26,28-32,34] and 2 as high risk of bias.[27,33] Four studies lacked a description of allocation concealment contributing to an overall assessment of some concerns[30,32,34] or high risk of bias.[33] Failure to include all eligible randomized participants in the analyses[26,27,31,33] and absence of a trial registry record or evidence that the analyses were preplanned (i.e., a study protocol)[28,29,33,34] were additional reasons for overall ratings of some concerns or high risk of bias. Two studies were multicountry studies; 1 was conducted in the United States, Israel, and Canada,[26] and the other was conducted in Turkey and Bulgaria.[30] Of those conducted in a single country, 2 trials were conducted in France;[28,29] 2 in South Korea;[31,34] and 1 each in Canada,[32] the Czech Republic,[33] and Israel.[27] One study, which recruited the highest number of participants,[26] was fully supported by industry, and 2 smaller studies were partially industry supported.[27,34] Five studies reported no industry support,[29-33] and 1 did not disclose source of funding.[28] ***Table 7*** summarizes the characteristics of included TMS trials for treating OCD; additional details are found in ***Appendix C***, ***Tables C-6***, ***C-7,*** and ***C-8***.

Six studies enrolled patients with a minimum YBOCS ranging from at least 15 to 20, corresponding to moderate OCD.[26-30,34] The remaining 3 studies did not have a threshold YBOCS requirement to enter the study, though baseline YBOCs scores indicated moderate to severe OCD.[31-33] All but 1 study[32] enrolled participants who were treatment resistant, generally defined as failing at least 1 to 2 medication trials. Two studies also required that participants had failed a trial of CBT.[26,27] The study sample sizes ranged from 21 to 100 participants; almost all studies[27-34] enrolled fewer than 50 participants. The mean age of included populations ranged from 26 to 48 years. All studies included both male and female participants; the percentage of female participants ranged from 10% to 64%. Only 1 study[26] provided data about participant race, of which 83% of the sample was White. Almost half of the included studies (n=4)[28,29,31,34] included participants with comorbid MDD with rates ranging from 12% to over 80%. Participants continued usual medication treatment;[26-31,33,34] psychotherapy;[27] or, in 1 study,[32] a maximum of 1 selective serotonin reuptake inhibitor (SSRI) or selective serotonin–noradrenaline reuptake inhibitor maintained at a stable regimen throughout treatment.

The active intervention was repetitive TMS (rTMS) in 6 studies,[29-34] deep TMS (dTMS) in 2 studies,[26,27] and continuous TBS in 1 study.[28] Studies varied in the number of pulses administered during a single session, in the frequency used, in the stimulation intensity used, and in the location of the stimulation coil relative to the scalp. In 4 studies, the targeted area included the supplementary motor area (SMA) or pre-SMA;[28-31] in 3 studies the right or left DLPFC was the target,[31,33,34] and the targeted areas for the remaining studies were the anterior cingulate cortex (ACC) and the medial prefrontal cortex (mPFC).[26,27,32] Three studies employed TBS or dTMS;[26-28] the remainder used low- frequency TMS.[29-34] The number of treatment days ranged from 10 to 30, and almost all administered TMS once per day. One study administered TMS over 2 sessions per day.[32] Median pulses were 1,500 with a range from 600 to 2,400. Two studies incorporated personalized OCD provocation before treatment.[26,27] All studies included a sham TMS arm that varied across studies.

Table 7. Summary of Study Characteristics of Included Studies of TMS for Treatment of OCD

Author, Year Country RoB	Intervention and Comparator (N Randomized)	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions; Exposure Therapy (Y/N)	Mean Age (SD)	N (%) Female
Carmi et al. (2019)[26] U.S., Israel, Canada Some concerns	dTMS (47) Sham dTMS (47)	100	6 weeks;[b] 4 weeks posttreatment (10 weeks)	Medication per treatment as usual; yes	38.8 (11.85)	39 (42)
Carmi et al. (2018)[27] Israel High	dTMS (18) Sham dTMS (15)	41	5 weeks;[c] 4 weeks posttreatment (9 weeks)	Medication and psychotherapy per treatment as usual; yes	IG1: 36 (2.1) CG: 35 (3.5)	IG1: 7 (44) CG: 7 (50)
Harika-Germaneau et al. (2019)[28] France Some concerns	cTBS (14) Sham cTBS (16)	30	6 weeks;[c] 6 weeks posttreatment (12 weeks)	Medication per treatment as usual; no	IG: 46.3 (10.1) CG: 48.2 (12.9)	IG: 9 (64) CG: 6 (43)

Author, Year Country RoB	Intervention and Comparator (N Randomized)	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions; Exposure Therapy (Y/N)	Mean Age (SD)	N (%) Female
Hawken et al. (2016)[30] Turkey, Bulgaria Some concerns	LF-rTMS (10) Sham rTMS (12)	22	6 weeks;[d] no additional follow-up (6 weeks)	Medication per treatment as usual; no	IG: 33.0 (10.0) CG: 34.0 (14.0)	11 (50)
Kang et al. (2009)[31] Korea Some concerns	LF-rTMS (11) Sham rTMS (10)	21	2 weeks;[c] 2 weeks posttreatment (4 weeks)	Medication per treatment as usual; no	IG: 28.6 (12.7) CG: 26.2 (10.5)	IG: 2 (20) CG: 1 (10)
Meek et al. (2021)[32] Canada Some concerns	LF-rTMS (12) Sham (11)	23	2 weeks;[e] 12 weeks posttreatment (14 weeks)	Medication per treatment as usual;[f] no	IG: 45.0 (16.7) CG: 38.3 (11.5)	IG: 6 (60) CG: 4 (40)
Pelissolo et al. (2016)[29] France Some concerns	LF-rTMS (20) Sham rTMS (19)	39	4 weeks;[c] no additional follow-up (4 weeks)	Medication per treatment as usual; no	41.5 (10.7)	23 (58)
Prasko et al. (2006)[33] Czech Republic High	LF-rTMS (18) Sham rTMS (12)	33	2 weeks;[c] 2 weeks posttreatment (4 weeks)	Medication per treatment as usual; no	IG: 28.9 (7.7) CG: 33.4 (8.7)	12 (36)
Seo et al. (2016)[34] Korea Some concerns	LF-rTMS (14) Sham rTMS (13)	28	3 weeks;[c] no additional follow-up (3 weeks)	Medication per treatment as usual; no	IG: 34.6 (9.8) CG: 36.3 (12.5)	13 (48)

Notes: [a] "Last follow-up" indicates last follow-up time point eligible for this HTA (e.g., blinded phase eligible only of a multiphase study with open-label phases). A study may have reported outcomes at follow-up time points that were subsequent to what is reported in this column though were not eligible for review (e.g., open-label phase).
[b] 5 sessions per week for 5 weeks and 4 sessions in the 6th week.
[c] 5 sessions per week.
[d] 5 sessions per week for 4 weeks, 3 sessions in 5th week, and 2 sessions in the 6th week.
[e] 2 sessions per day, 5 days per week.
[f] Participants were allowed a maximum of 1 SSRI maintained at a stable regimen throughout treatment or SNRI

Abbreviations: CG = control group; cTBS = continuous theta-burst stimulation; dTMS = deep transcranial magnetic stimulation; HF = high frequency; HTA = health technology assessment; IG = intervention group; LF = low frequency; N = number; OCD = obsessive-compulsive disorder; RoB = risk of bias; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; SNRI = serotonin-norepinephrine reuptake inhibitor; TMS = transcranial magnetic stimulation; U.S. = United States.

3.3.2 Findings

Detailed findings are provided in ***Appendix C, Tables C-9*** and ***C-10***. A summary of findings and the SOE are provided in ***Table 8***. This section provides detailed results for each category of outcome measure.

Table 8. Summary of Findings and SOE for TMS Compared to Control (Sham Stimulation for RCTs, medication for DA) for OCD

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall SOE/ Direction
Clinical response posttreatment and at various follow-up time points						
7 RCTs[26-31,34]/281	Decrease in Y-BOCS score of 25% to 30% or more; pooled RR, 1.96 (95% CI, 0.94 to 4.09). In the 2 studies with significant results favoring TMS posttreatment, durability of response up to 4 weeks after the end of treatment was observed.	Consistent (I^2=47%)	Imprecise	Direct	Some concerns (6 SC, 1 high RoB)	Low[a] Favor TMS
Symptom severity at posttreatment and various follow-up time points as measured by Y-BOCS						
9 RCTs[26-34]/337	At posttreatment, 5 of 9 studies reported symptom severity improvements in TMS vs. sham (statistically significant improvements in 4 of 5). There were no statistically significant results in other 4 studies, 1 study favored sham but was not significant, 3 studies did not provide follow-up values to judge direction of effect.	Consistent	Imprecise	Direct	High (7 SC, 2 high RoB)	Low[b,c] Favor TMS
Clinical Global Impression–Severity (CGI-S) at posttreatment and various follow-up time points						
5 RCTs[26,28,29,33,34]/230	Two studies reported statistically significant improvements for TMS vs. sham at posttreatment, while 2 studies reported no difference between groups, and 1 did not provide follow-up value to judge direction of effect. One study reported that global severity improvement was significantly higher for TMS vs. sham at 4 weeks' posttreatment.	Consistent	Imprecise	Direct	High (4 SC, 1 high RoB)	Low[b,c] Favor TMS

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall SOE/ Direction
Clinical Global Impression–Improvement (CGI-I) at posttreatment and various follow-up time points						
3 RCTs[26,27,29]/ 180	Two studies reported a statistically significant effect of TMS compared to sham at posttreatment, while 1 study showed no difference between groups (CGI-I 3.6 vs. 3.5). Of the 2 studies with improvement, 1 study reported that CGI-I score improvement persisted at 4 weeks and was statistically significant, while the other had statistically significant improvement for the TMS group when compared to sham at 1-week follow-up but not significant at 4-week follow-up.	Consistent	Imprecise	Direct	Some concerns (2 SC, 1 high RoB)	Low[a] Favor TMS
Any AEs up to 3 months' posttreatment						
8 RCTs[26-29,31-34]/315	AE reporting highly variable; only 2 studies reported overall AEs between groups; 73% (TMS) vs. 69% (sham); *P*=0.639 in 1 study; 7% (TMS) vs. 14% (sham) in other study. The remaining studies reported specific harms only; frequently reported AEs in the other studies included headache and localized scalp discomfort.	Consistent	Imprecise	Direct	High (6 SC, 2 high RoB)	Low[b,c] No difference
Safety (SAEs) up to 3 months' posttreatment						
8 RCTs[26-29,31-34]/315	All but 1 study reported 0 events across both groups. The exception was 1 study reporting 1 participant with suicidal ideation requiring hospitalization before treatment. (TMS group)	Consistent	Imprecise	Direct	High (6 SC, 2 high RoB)	Low[b,c] No difference

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall SOE/ Direction
Cost-effectiveness over 1 year						
1 DA[35]	*ICER (cost/unit change in Y-BOCS)* dTMS: $1,647; compared to ADM monotherapy dTMS: $1,002; compared to ADM+AP ADM+CBT: $768 (compared to dTMS)	NA[d]	Imprecise[e]	Direct	Medium[f]	Insufficient[g]

Notes: [a] Downgraded 2 levels for imprecision.
[b] Downgraded 1 level for study limitations: lack of required data to adequately evaluate magnitude and direction of effect.
[c] Downgraded 1 level for imprecision.
[d] Not applicable, single study body of evidence.
[e] No CI on base case estimates; however, study did assess stability and consistency with Monte Carlo simulations.
[f] Based on total modified score of 85 on Quality of Health Economic Study instrument.
[g] Downgraded for imprecision, study limitations, and single study body of evidence.

Abbreviations: ADM = antidepressant medication; AE = adverse event; AP = antipsychotic medication; CBT = cognitive behavioral therapy; CGI-I = Clinical Global Impression Scale-Improvement; CGI-S = Clinical Global Impression–Severity scale; CI = confidence interval; DA = decision analysis; dTMS = deep TMS; ICER = incremental cost-effectiveness ratio; OCD = obsessive-compulsive disorder; posttreatment = end of treatment; RCT = randomized controlled trial; RoB= risk of bias; RR= relative risk; SAE = serious adverse event; SC = some concerns; SOE = strength of evidence; TMS = transcranial magnetic stimulation; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

Remission

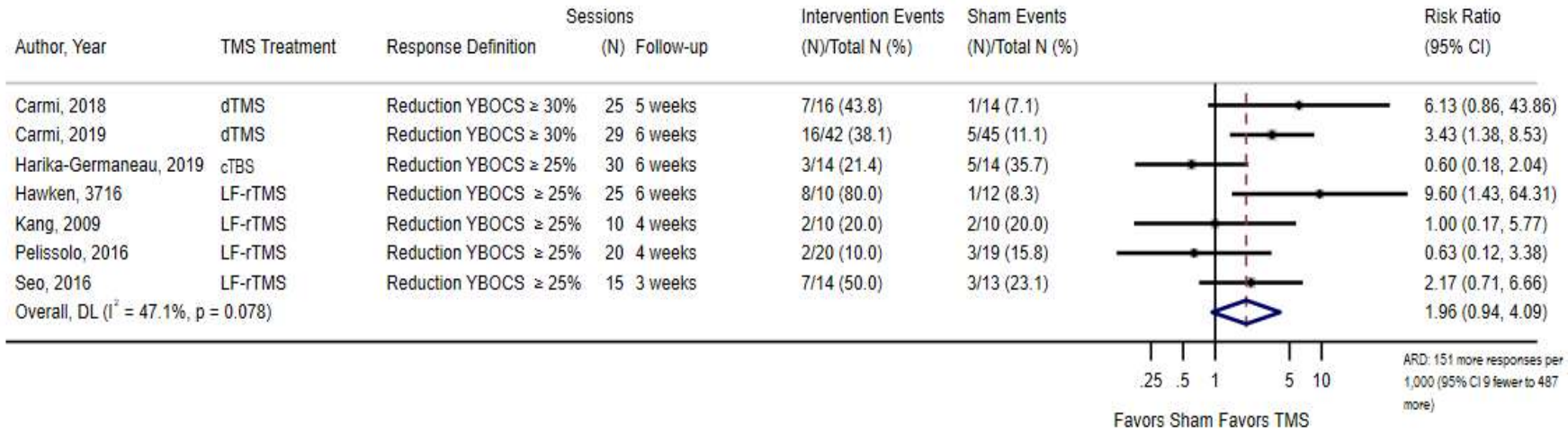
No studies reported remission.

Response

Seven studies reported clinical response.[26-31,34] Most studies defined clinical response as a minimum of a 25% decrease in Y-BOCS score; however, 2 studies used a higher threshold of 30%.[26,27] Four of the 7 studies reported results that favored the intervention at end of treatment;[26,27,30,34] however, differences were only statistically significant in 2 studies.[26,27] In these 2 studies, the rate of response was sustained up to 4 weeks after the end of treatment.[26,27]

A pooled analysis of the 7 RCTs observed a nonsignificant association of higher response in individuals receiving TMS compared to sham (pooled RR, 1.96; 95% CI, 0.94 to 4.09; I^2=47.1%; 281 participants) (***Figure 4***). This is equivalent to an ARD of 155 more clinical responses per 1,000 participants (95% CI from 9 fewer to 487 more). In sensitivity analysis removing the 1 high RoB study,[25] results were comparable (pooled RR, 1.73; 95% CI, 0.79 to 3.78; I^2=50%).

Figure 4. TMS vs. Sham for Outcome of Clinical Response for OCD



Abbreviations: ARD = absolute risk difference; CI = confidence interval; cTBS = continuous theta-burst stimulation; DL = DerSimonian & Laird estimator for pooling estimates; dTMS = deep transcranial magnetic stimulation; LF-rTMS = low frequency repetitive transcranial magnetic stimulation; N = number; TMS = transcranial magnetic stimulation; vs. = versus; YBOC = Yale-Brown Obsessive-Compulsive Scale.

Change in Y-BOCS

All studies used the Y-BOCS to assess change in OCD symptoms, which was the primary endpoint in all but 1 study.[32] Five of the 9 studies reported greater symptom improvements using the Y-BOCS among the TMS-treated group compared to the sham group.[26,27,30,32,34] Study authors for most studies did not provide data necessary for pooling of results, such as variance or follow-up Y-BOC values.

In the largest of the included studies for OCD patients (n=100), the intention-to-treat (ITT) and modified intention-to-treat (mITT) analyses favored the intervention group with an effect size of 0.48 (*P*=0.09) and 0.69 (*P*=0.01), respectively, at the end of the 6-week treatment. The favorable finding persisted and was statistically significant using the mITT at 4 weeks' posttreatment (effect size [ES]=0.62, *P*=0.03).[26] In another study, 6-week treatment with rTMS was associated with significant symptom improvement compared to sham (*P*<0.001) up to 4 weeks' posttreatment.[30] A study of 3 weeks of active rTMS also reported significantly greater improvements in symptom severity for those receiving active treatment compared to those receiving sham (mean change -10.7 [SD 8.2] vs. -3.7 [SD 3.7], *P*=0.005) at the end of treatment.[34] Another study reported that TMS was associated with symptom severity improvement up to 3 months after the end of treatment, but the effect was not statistically significant.[32] A small study (n=41) of dTMS reported that symptom severity improved significantly in the active treatment group compared to the control group; these effects persisted up to 1 week posttreatment but were not sustained 4 weeks after the end of treatment.[27]

Four studies reported no statistically significant differences on symptom severity as measured by the Y-BOCS for TMS compared to sham; the absolute values of follow-up scores were not provided to determine which treatment had a greater effect in 3 studies,[28,31,33] while 1 study favored the sham group.[29]

Clinical Global Impression-Severity

Of 5 studies that reported the CGI-S,[26,28,29,33,34] 2 studies[26,34] reported that results favored TMS at the end of treatment. The favorable result persisted up to 1-week posttreatment; however, the effects of TMS on clinical severity were not sustained at 4 weeks' posttreatment.[26] Two studies reported no difference in CGI-S between the TMS and sham groups at the end of treatment,[28,29,33] while 1 study reported no follow-up values to judge direction of effect.[29] One study, which did not indicate if the outcome reported was the CGI-I or GCI-S, reported no difference between the TMS and sham groups.[30]

Clinical Global Impression-Improvement

Two studies reported that the Clinical Global Impression-Improvement (CGI-I) results favored TMS[26,27] at the end of treatment. The favorable result persisted up to 1-week posttreatment; however, the effects of TMS on clinical severity and improvement were not sustained at 4 weeks' posttreatment.[26,27] One study reported no difference in CGI-I between the TMS and sham groups at the end of treatment (CGI-I 3.6 vs. 3.5).[29]

Global Assessment of Functioning

One study reported no significant difference between groups in change of the Global Assessment of Functioning (GAF) at the end of the 4-week treatment.[29]

Safety Measures

Eight studies reported the incidence of AEs, including any SAEs.[26-29,31-34] Two studies reported any AE. In 1 study (n=99), a high proportion of individuals in both the active and inactive groups reported an AE (73% vs. 69%, *P*=0.639).[26] In a smaller study (n=28), participants reported fewer AEs (all mild headache), but the difference between the active and sham groups was similar (1 participant in the active treatment group and 2 participants from the sham group).[28] Among the 8 studies reporting SAEs, 7 reported no events. The exception was 1 study in which an individual reported significant suicidal thoughts requiring hospitalization before the start of treatment.[26] Headache and localized scalp pain or discomfort were the most commonly reported side effects of treatment.[27-29,31,32,34]

Special Populations

Two studies reported results by subgroup of age or sex.[27,29] In 1 study, there was no significant difference in treatment effect by age.[29] In the other study, male individuals with OCD were more likely to respond to treatment than female individuals with OCD (66% vs. 14%, *P*<0.05).[27]

Cost-Effectiveness

One study based on U.S. data reported cost-effectiveness outcomes.[35] The 1 included study was a decision analysis sponsored by an rTMS device company;[35] we rated it as having some concerns for bias (***Appendix E, Tables E-31, E-32,*** and ***E-33***). Study characteristics are summarized in ***Table 9*** with detailed characteristics in ***Appendix C, Table C-31***. This study, conducted from a payor's perspective, evaluated dTMS in a hypothetical cohort of adults with treatment-refractory OCD and included multiple comparators.[35]

Compared to monotherapy with antidepressant medication, dTMS costs more (incremental cost $6,425) but was more effective (marginal reduction in Y-BOCS score of 3.9 points) for an ICER of $1,647 per unit reduction in Y-BOCS.[35] A similar ratio was observed when compared to treatment with a combination of antidepressant and antipsychotic medication. Antidepressant medication with cognitive behavioral therapy delivered by experts was more effective than dTMS, but also costs more (ICER $768 per unit reduction in Y-BOCS).

Table 9. Study Characteristics and Findings for Studies Reporting Cost-Effectiveness for OCD (CQ1)

Author (Year) Country Risk of Bias Sponsor	Population	Intervention	Comparator	Key Analysis Parameters	Outcomes
Gregory et al. (2022)[35] U.S. Some concerns BrainsWay	Hypothetical cohort of 100,000 adults aged 18 to 64 with treatment-refractory OCD	dTMS	Multiple evaluated including ADM, AP, CBT, PHP, IOP, and PHP with stepdown to IOP	Decision analysis in 2012 to 2015 U.S. dollars; payor perspective; time horizon 1 year; Costs: derived from encounters in Truven Marketscan database	ICER, cost/unit change in Y-BOCS) compared to ADM monotherapy ICER (cost/unit change in Y-BOCS) for dTMS compared to other comparators $1,647; compared to ADM monotherapy $1,002 (compared to ADM+AP) For ADM+CBT trials: $768 compared to dTMS For PHP to IOP: $4,850 compared to dTMS

Abbreviations: ADM = antidepressant medication; AP = antipsychotic medication; CBT = cognitive behavioral therapy; CQ = cost question; dTMS = deep transcranial magnetic stimulation; ICER = incremental cost-effectiveness ratio; IOP = intensive outpatient program; OCD = obsessive compulsive disorder; PHP = partial hospitalization program; Y-BOCS = Yale–Brown Obsessive-Compulsive Scale; U.S. = United States.

3.4 Major Depressive Disorder

We identified 36 RCTs in 40 publications that focused on TMS stimulation compared to sham stimulation for the treatment of MDD. The interventions varied in terms of type of TMS, protocol, number of sessions, duration over which the sessions were provided, and timing of outcome measure at follow-up. In general, few studies had follow-up data beyond the immediate post-treatment period. Key findings are as follows:

- Nineteen RCTs reported on remission, defined by different symptom severity surveys and cut-off points.[36-54] Pooled analyses favored rTMS compared to sham at posttreatment (RR, 1.86; 95% CI, 1.26 to 2.75; 15 RCTs) and TBS compared to sham (RR, 4.68; 95% CI, 1.79 to 12.21; 3 RCTs). Two studies of dTMS also favored active treatment over sham for remission. (SOE: High, favor rTMS; moderate, favor TBS; low, favor dTMS)

- Twenty-six RCTs reported on response, defined by different symptom severity surveys and cut-off points.[36,37,39-62] Pooled analyses favored rTMS and TBS compared to sham at posttreatment (rTMS: RR, 1.90; 95% CI, 1.45 to 2.49; 20 RCTs; TBS: RR, 3.92; 95% CI, 2.28 to 6.73; 5 RCTs). Two studies of dTMS also favored active treatment over sham for MDD response. (SOE: High, favor rTMS; moderate, favor TBS; low, favor dTMS)

- Thirty-six RCTs reported on change in symptom severity score.[36-71] A pooled analysis of change in depression severity score from baseline favored TMS treatment compared to sham at posttreatment (SMD, -0.65; 95% CI, -0.91 to -0.39; 20 rTMS RCTs and 1 dTMS RCT), which was estimated to fall within a minimum clinically important change for the most common measure used (Hamilton Depression Rating Scale-17 item [HAMD17]) to estimate symptom severity. (SOE: Moderate, favor TMS)

- Twenty studies reported on AEs.[37,39,41,42,47,48,51-54,57,58,60-62,64,65,67,68,72] One study reported a greater number of any AEs in the active TMS group compared to sham (41% vs. 29%, no significance testing reported).[53] The remaining studies reported no difference in any AEs between active TMS and sham groups. Most studies reported 0 events for serious AEs. (SOE: Low, no difference)

- Two studies conducted based on U.S. data reported cost-effectiveness outcomes.[73,74] In the base case for both studies, rTMS was the dominant strategy compared to pharmacotherapy, meaning that it cost less and was more effective.[73] In the study using a 1-year time horizon, the cost savings per QALY gained was $746 without productivity costs and was $7,243 when productivity costs were considered.[73,74] In the study using a lifetime horizon, the cost savings per QALY gained ranged from $9,225 to $25,907 depending on the age at diagnosis with more savings accumulating for the younger age groups.[74] (SOE: Low)

The rest of this section provides detailed study characteristics and results.

3.4.1 Study and Population Characteristics

The majority of trials identified were conducted between 1997 and 2021; 13 studies did not report the years they were conducted.[46-48,55,56,58,60-62,67,69-71] We assessed 3 of these trials as having low risk of bias,[38,50,51] 24 as having some concerns for bias,[36,37,39,44,45,47-49,53-60,62,64-66,68-71] and 9 trials as having high risk of bias.[40-43,46,52,61,63,67] Trials were judged as high risk of bias for high attrition;[43,46,63] selective reporting of results;[43,46,130] and absence of an ITT analysis or deviation from intervention,[42,52] measurement domain,[43,67] or randomization domain.[40,41,46,61]

Eight trials were conducted in the United States;[36,38-40,47,49,51,68] 3 trials each were conducted in Canada,[42,43,54] Germany,[48,60,61] Italy,[44,45,67] Netherlands,[41,59,66] and Taiwan[50,52,55] or in multiple countries.[37,53,62] Two trials were conducted in Spain,[69,71] and the remaining trials were conducted in 1 country (Australia, Austria, Belgium, Denmark, France, Greece, South Korea, and the United Kingdom).[46,56-58,63-65,70]

Three trials were fully funded by industry,[36,37,53] and 9 trials were partially funded by industry.[40,42,49,51,54,60,63,65,70] Seven trials did not report on study sponsorship.[41,45,46,59,61,66,67] The rest of the trials were funded by academic institutions, government entities or foundations. ***Table 10*** summarizes the characteristics of included TMS trials; additional details are found in ***Appendix C***, ***Tables C-11, C-12,*** and ***C-13***.

Most studies enrolled participants based on a HAMD score ranging from 15 to 21, which represents moderate to severe disease. For studies that did not require a threshold depression severity, baseline HAMD scores were in the severe range.[41,56,58,62-65,69,71] Most studies were conducted in treatment-resistant study populations, most defining treatment resistance as failure of at least 2 medications. Six studies defined treatment resistance as failure of at least 1 medication,[47,49,50,52,56,65] 1 as at least 3 medications,[67] and 1 as at least 4 medications.[36] Only 1 study enrolled treatment-naive individuals,[46] and 3 studies enrolled both treatment-naive and treatment-resistant individuals.[58,60,62] Seven studies did not specify the treatment history of eligible study participants.[40,45,59,61,63,66,70] Study sample sizes ranged from 25 to 325 participants. The mean age of included populations ranged from 17 to 65 years. All studies included both male and female participants, and 5 studies provided data about participant race.[36-38,40,53] Of those reporting race, all but 1 study included more than 85% White participants.[36-38,53] Eleven studies[36,38,40,42,43,50,51,54,55,57,66] reported on mental health comorbidities, including GAD, OCD, PTSD, panic disorder, attention-deficit hyperactivity disorder, and SUD.

The active intervention in all RCTs was TMS with variation in the type of TMS and protocol used. Most trials studied rTMS (most commonly high-frequency, then low-frequency, and bilateral therapy), 2 trials examined dTMS,[53,54] and 5 trials examined TBS.[50-52,55,56] Studies varied in the number of pulses administered during a single session (range 600 to 6,000) and in the stimulation intensity used (range 80% to 120% MT). The duration of treatment ranged from 2 weeks to 11 weeks. Two trials included maintenance or tapering off of treatment over 3 to 12 weeks.[37,53] Most studies performed 1 session a day. Three studies used more than 1 session per day.[51,56,64] Duration of follow-up ranged from 2 weeks to 28 weeks. The majority of studies followed participants for less than or equal to 6 weeks. Only 5 studies followed patients for longer than 6 weeks.[38,58,65-67]

Most studies included co-interventions with TMS. The majority of trials allowed participants to be treated with medications or psychotherapy as usual, and 7 studies prescribed antidepressant medications per a study protocol.[45,52,60,62,64,65,70] Eight trials required participants to discontinue medications before TMS;[36,37,39,46,47,50,53,56] no studies required discontinuation of psychotherapy.

Table 10. Summary of Study Characteristics of Included Studies of TMS for Treatment of MDD

Author, Year Country RoB	Intervention and Comparator (N Randomized)	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions	Mean Age (SD)	N (%) Female	Comorbidities
Anderson et al. (2007)[58] U.K. Some concerns	HF-rTMS (14) Sham TMS (16)	29	4 to 6 weeks[b] 12 weeks	Medications per treatment as usual	IG1: 48 (8) CG: 46 (12)	Active: 7 (54) Sham: 9 (56)	NR
Avery et al. (2006)[68,131] U.S. Some concerns	HF-rTMS (35) Sham TMS (33)	68	4 weeks[c] 5 weeks	Psychotherapy per treatment as usual; encourage to stop medications before treatment	IG1: 44.3 (10.3) CG: 44.2 (9.7)	37 (54.4)	NR
Blumberger et al. (2016)[42] Canada High	Bilateral rTMS (40) HF-rTMS (40) Sham TMS (41)	121	3 to 6 weeks[d] 6 weeks	Medications per treatment as usual	IG1: 46.4 (12.5) IG2: 46.5 (14.1) CG: 48.1 (12.0)	IG1: 23 (58) IG2: 30 (75) CG: 24 (59)	Anxiety disorder IG1: 3 (8) IG2: 5 (13) CG: 6 (15)
Blumberger et al. (2012)[43] Canada High	Bilateral rTMS (28) HF-rTMS (24) Sham TMS (22)	74	3 to 6 weeks[d] 6 weeks	Medications per treatment as usual	IG1: 58.0 (12.5) IG2: 48.9 (13.4) CG: 45.8 (13.4)	IG1: 14 (54) IG2: 12 (55) CG: 14 (70)	Anxiety: 7%
Bretlau et al. (2008)[65] Denmark Some concerns	HF-rTMS (25) Sham TMS (24)	49	3 weeks[d] 12 weeks	Medication per study protocol	IG: 53.1 (10.1) CG: 57.8 (10.0)	IG: 15 (68) CG: 13 (57)	NR
Chou et al. (2020)[52] Taiwan High	cTBS (30) Sham TMS (30)	60	3 weeks[b] 24 weeks	Medication per study protocol	IG1: 43.6 (16.6) CG: 42.3 (11.1)	IG1: 15 (56) CG: 17 (65)	NR

Author, Year Country RoB	Intervention and Comparator (N Randomized)	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions	Mean Age (SD)	N (%) Female	Comorbidities
Cole et al. (2022)[51] U.S. Low	iTBS (14) Sham TMS (15)	32	1 week[e] 5 weeks	Medication per treatment as usual	IG1: 49 (15) CG: 52 (16)	IG1: 5 (36) CG: 5 (33)	Anxiety IG1: 3 (21) CG: 6 (40) ADHD IG1: 1 (7) CG: 1 (7) PTSD IG1: 1 (7) CG: 1 (7) SUD (in remission) IG1: 0 (0) CG: 3 (20) Eating disorder IG1: 1 (7) CG: 0 (0)
Concerto et al. (2015)[67] Italy High	HF-rTMS (15) Sham TMS (15)	30	4 weeks[d] 28 weeks	Medication per treatment as usual	IG1: 51 (6.5) CG: 53 (6.7)	IG1: 6 (40) CG: 7 (47)	NR
Croarkin et al. (2021)[36] U.S. Some concerns	HF-rTMS (54) Sham TMS (58)	112	6 weeks[d] 6 weeks	Medications discontinued prior to TMS; psychotherapy per treatment as usual	IG1: 17.6 (2.3) CG: 17.1 (2.2)	IG1: 30 (63) CG: 37 (67)	Secondary psychiatric diagnosis IG1: 26 (54) CG: 36 (66)
Duprat et al. (2016)[56,132] Destmyter et al. (2016)[132] Belgium Some concerns	iTBS (47) Sham TMS (47)	50	1 week[f] 4 weeks	Medications discontinued prior to TMS	41.8 (11.8)	33 (70)	NR
Fitzgerald et al. (2012)[57] Australia Some concerns	Bilateral rTMS (22) HF-rTMS (24) Sham TMS (20)	67	3 weeks[d] 3 weeks	Medication per treatment as usual	42.9 (14.4)	31 (46)	Panic disorder: 27% Social phobia: 23% GAD: 30% OCD: 11% PTSD: 11%

Author, Year Country RoB	Intervention and Comparator (N Randomized)	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions	Mean Age (SD)	N (%) Female	Comorbidities
Garcia-Toro et al. (2006)[69] Spain Some concerns	Bilateral rTMS (10) Bilateral rTMS with imaging (10) Sham TMS (10)	30	2 weeks[d] 4 weeks	Medication per treatment as usual	CG: 47.2 (11.8) IG1: 48.5 (13.3) IG2: 51.1 (13.8)	CG: 7 (70) IG1: 4 (40) IG2: 4 (40)	
Garcia-Toro et al. (2001)[71] Spain Some concerns	HF-rTMS (20) Sham TMS (20)	40	2 weeks[d] 4 weeks	Medication per treatment as usual	IG1: 51.5 (15.9) CG: 50 (11)	IG1: 7 (41) CG: 8 (44)	NR
Garcia-Toro et al. (2001)[62] U.S. and Spain Some concerns	HF-rTMS (14) Sham TMS (14)	28	2 weeks[d] 4 weeks	Medication per study protocol	IG1: 43.2 (13.1) CG: 45.0 (18.3)	12 (54.5)	NR
George et al. (2010)[39,133] U.S. Some concerns	HF-rTMS (92) Sham TMS (98)	199	3 weeks[d] 3 weeks	Medications discontinued prior to TMS	47.1 (11.5)	108 (57)	NR
Hausmann et al. (2004)[70] Austria Some concerns	HF-rTMS (13) Bilateral rTMS (14) Sham TMS (14)	41	2 weeks[d] 4 weeks	Medication per study protocol	46.5 (11.9)	23 (60.5)	NR
Herwig et al. (2003)[60] Germany Some concerns	HF-rTMS (13) Sham TMS (12)	25	2 weeks[d] 2 weeks	Medication per study protocol	Mean IG1: 41.6 CG: 47.8	15 (60)	NR
Hoppner et al. (2003)[61] Germany High	HF-rTMS (10) LF-rTMS (10) Sham TMS (10)	30	2 weeks[d] 2 weeks	Medications required to be held at constant dose 2 weeks before TMS	56.4 (11.1)	22 (73)	NR
Januel et al. (2006)[46] France High	LF-rTMS (11) Sham TMS (16)	27	4 weeks[g] 4 weeks	Medications discontinued before TMS	37.78 (11.27)	21 (78)	NR

Author, Year Country RoB	Intervention and Comparator (N Randomized)	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions	Mean Age (SD)	N (%) Female	Comorbidities
Kaster et al. (2018)[54] Canada Some concerns	dTMS (30) Sham TMS (28)	58	4 weeks[d] 4 weeks	Medication per treatment as usual	IG1: 65 (5.5) CG: 65.4 (5.5)	IG1: 8 (32) CG: 12 (44)	Comorbid psychiatric disorder IG1: 17% CG: 30% Comorbid personality disorder IG1: 0% CG: 4%
Kim et al. (2019)[40] U.S. High	LF-rTMS (14) Sham TMS (12)	26	4 weeks[d] 4 weeks	Medication per treatment as usual	28.3 (5.7)	22 (100)	Comorbid anxiety allowed if primary diagnosis was MDD, N (%) IG1: 0 (0) CG: 4 (33)
Koerselman et al. (2004)[66] The Netherlands Some concerns	HF-rTMS (26) Sham TMS (26)	55	2 weeks[d] 14 weeks	Medication per treatment as usual	IG1: 51 (15.4) CG: 52 (13.2)	IG1: 12 (46) CG: 17 (65)	Personality disorder NR by groups IG1: 15 (58) CG: 13 (50)
Lee et al. (2018)[63] Republic of Korea High	HF-rTMS (15) Sham TMS (15)	41	3 weeks[d] 3 weeks	Medication per treatment as usual	35.9 (12.3)	28 (76)	NR
Levkovitz et al. (2015)[53] U.S., Israel, Germany, Canada Some concerns	dTMS (111) Sham TMS (122)	233	4 weeks[d] 5 weeks	Medications discontinued before TMS	IG1: 45.1 (11.7) CG: 47.6 (11.6)	101 (47.6)	NR
Li et al. (2014)[55] Taiwan Some concerns	cTBS (15) iTBS (15) cTBS and iTBS (15) Sham TMS (15)	60	2 weeks[d] 2 weeks	Medication and psychotherapy per treatment as usual	Mean (range) IG1: 49.2 (27–64) IG2: 42.4 (25–61) IG3: 42.5 (23–60) CG: 46.9 (25–58)	IG1: 10 (67) IG2: 8 (53) IG3: 11 (73) CG: 11 (73)	Panic disorder: 12% Social phobia: 2% GAD: 35%

Author, Year Country RoB	Intervention and Comparator (N Randomized)	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions	Mean Age (SD)	N (%) Female	Comorbidities
Li et al. (2020)[50,134] Taiwan Low	iTBS (35) HF-rTMS (35) Sham TMS (35)	105	2 weeks[d] 14 weeks	Medications discontinued before TMS	IG1: 47.1 (14.2) IG2: 47.1 (13.8) CG: 47.1 (12.4)	71 (67.6)	Dysthymia: 22% Panic disorder: 12% Agoraphobia: 17% Social phobia: 5% GAD: 74%
O'Reardon et al. (2007)[37,135] Australia, Canada, U.S. Some concerns	HF-rTMS (165) Sham TMS (160)	325	4 weeks[d] 4 weeks	Medications discontinued before TMS	IG1: 47.9 (11) CG: 48.7 (10.6)	IG1: 86 (55.5) CG: 74 (50.7)	NR
Padberg et al. (2002)[48] Germany Some concerns	HF-rTMS, 100% MT (10) HF-rTMS, 90% MT (10) Sham TMS (10)	31	2 weeks[d] 2 weeks	Medication per treatment as usual	Mean (SEM) IG1: 62.1 (4.6) IG2: 60.3 (4.1) CG: 52.7 (5.7)	IG1: 6 (60) IG2: 7 (70) CG: 8 (80)	NR
Pallanti et al. (2010)[44] Italy Some concerns	Bilateral rTMS (20) LF-rTMS (20) Sham TMS (20)	60	3 weeks[d] 3 weeks	Medication per treatment as usual	IG1: 47.6 (12. 3) IG2: 51.2 (12.5) CG: 47.9 (9.1)	IG1: 11 (55) IG2: 12 (60) CG: 12 (60)	NR
Rossini et al. (2005)[45] Italy Some concerns	HF-rTMS (50) Sham TMS (49)	99	2 weeks[d] 4 weeks	Medication per study protocol	47.4 (12.9)	79 (80)	NR
Schutter et al. (2009)[59] Netherlands Some concerns	HF-rTMS (15) Sham TMS (16)	17	2 weeks[d] 2 weeks	Medication per treatment as usual	IG1: 44.4 (11.8) CG: 43.8 (12.5)	IG1: 10 (59) CG: 7 (41)	NR
Stern et al. (2007)[47] U.S. Some concerns	HF-rTMS (10) LF rTMS, left (10) LF rTMS, right (10) Sham TMS (15)	45	2 weeks[d] 4 weeks	Medications discontinued prior to TMS	IG1: 53.2 (12) IG2: 52.3 (9.4) IG3: 52.8 (9.5) CG: 53.3 (9.0)	28 (62.2)	NR
Taylor et al. (2018)[49] U.S. Some concerns	HF-rTMS (20) Sham TMS (20)	40	4 weeks[d] 4 weeks	Medication per treatment as usual	IG: 46.9 (10.7) CG: 44.1 (11.1)	IG: 11 (69) CG: 10 (63)	NR
Theleritis et al. (2017)[64] Greece Some concern	HF-rTMS, 1/day (27) HF-rTMS, 2/day (27) Sham TMS1 (20) Sham TMS2 (24)	96	3 weeks[h] 5 weeks	Medication per study protocol	IG1: 39.1 (10.1) IG2: 38.9 (13.9) CG1: 38.0 (9.9) CG2: 39.4 (8.9)	IG1: 15 (58) IG2: 11 (42) CG1: 10 (50) CG2: 7 (42)	NR

Author, Year Country RoB	Intervention and Comparator (N Randomized)	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions	Mean Age (SD)	N (%) Female	Comorbidities
van Eijndhoven et al. (2020)[41] Netherlands High	HF-rTMS (15) Sham TMS (16)	31	4 weeks[d] 5 weeks	Medication per treatment as usual	48.6 (11.1)	22 (71)	NR
Yesavage et al. (2018)[38] U.S. Low	HF-rTMS (81) Sham TMS (83)	164	4 to 11[i] weeks 24 weeks	Medication per treatment as usual	55.2 (12.4)	32 (19.5)	PTSD: 81 (49.4) Substance use: 88 (53.7) TBI: 10 (6.1)

Notes: [a] "Last follow-up" indicates last follow-up time point eligible for this HTA (e.g., blinded phase eligible only of a multiphase study with open-label phases). A study may have reported outcomes at follow-up time points that were subsequent to what is reported in this column, although they were not eligible for review (e.g., open-label phase).
[b] 3 sessions/week.
[c] 15 sessions within a 4-week period.
[d] 5 sessions/week.
[e] 10 sessions/day, 5 days/week.
[f] 5 sessions/day, 4 days/week.
[g] 5 sessions/week for 2 weeks, then 3 sessions/week for 2 weeks.
[h] 5 or 10 sessions/week.
[i] 5 sessions over 5 to 12 days.

Abbreviations: ADHD = attention-deficit hyperactivity disorder; CG = control group; cTBS = controlled theta-burst stimulation; dTMS = deep transcranial magnetic stimulation; GAD = generalized anxiety disorder; HF = high frequency; HTA = health technology assessment; IG = intervention group; iTBS = intermittent theta-burst stimulation; LF = low frequency; MDD = major depressive disorder; MT =motor threshold ; N = number; NR = not reported; OCD = obsessive compulsive disorder; PTSD = posttraumatic stress disorder; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; SEM = standard error of the mean; SUD = substance use disorder; TBI =traumatic brain injury; TMS = transcranial magnetic stimulation.

3.4.2 Findings

Detailed findings are provided in ***Appendix C, Tables C-14*** and ***C-15***. A summary of findings and the SOE are provided in ***Table 11***. In general, outcomes of remission, response, and change in symptom severity all favored TMS compared to sham. Few SAEs were reported, although safety outcome data were limited. This section provides detailed results for each category of outcome measure.

Table 11. Summary of Findings and SOE for TMS Compared to Control (Sham Stimulation in RCTs, medication for cost-effectivness) for MDD

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall SOE/ Direction
Remission: rTMS compared to sham at posttreatment to 24 weeks' follow-up						
15 RCTs[36-50]/1,469	Pooled analysis at posttreatment: RR, 1.86 [95% CI, 1.26 to 2.75]. Only 5 studies reported follow-up data, of which 3 showed durable remission at 5 to 24 weeks.	Consistent I^2=38.1%	Precise	Direct	Some concerns (2 low, 8 SC, 5 high)	High Favor TMS
Remission: TBS compared to sham at posttreatment to 12 weeks' follow-up						
3 RCTs[50-52]/197	Pooled analysis at posttreatment: RR, 4.68 (95% CI, 1.79 to 12.21). Two studies reported durable remission at 5 to 12 weeks follow-up though 2 studies did not report statistical testing.	Consistent I^2=0.0%	Imprecise	Direct	Some concerns (1 low, 1 SC, 1 high)	Moderate[a] Favor TBS
Remission: dTMS compared to sham at posttreatment						
2 RCTs[53,54]/269	Two studies reporting remission at posttreatment, calculated RRs 1.89 (95% CI, 1.13 to 3.17) and 2.70 (95% CI, 0.97 to 7.52)	Consistent	Imprecise	Direct	Some concerns (2 SC)	Low[b] Favor dTMS
Response: rTMS compared to sham at posttreatment to 14 weeks						
20 RCTs[36,37,40-51,57-62]/1,386	Pooled analysis at posttreatment: RR, 1.90 (95% CI, 1.45 to 2.49). Mixed results for durability of response in 5 studies at follow-up 2 to 12 weeks	Consistent	Precise	Direct	Some concerns (1 low, 13 SC, 6 high)	High Favor rTMS
Response: TBS compared to sham at posttreatment to 12 weeks						

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall SOE/ Direction
5 RCTs[50-52,55,56]/259	RR, 3.92 (95% CI, 2.28 to 6.73). Two studies reported durability of response, but only 1 performed statistical testing.	Consistent	Imprecise	Direct	Some concerns (1 low, 3 SC, 1 high)	Moderate[a] Favor TBS
Response: Deep TMS compared to sham at posttreatment						
2 RCTs[53,54]/264	Two studies reporting response at post treatment, RRs 1.31 (95% CI, 0.88 to 1.94) and 2.38 (95% CI, 0.96 to 5.88)	Consistent	Imprecise	Direct	Some concerns (2 SC)	Low[b] Favor dTMS
Symptom severity score: TMS compared to sham at posttreatment or last follow-up						
36 RCTs[36-71]/2,615	Pooled analysis of change from baseline to posttreatment: SMD -0.65 (95% CI, -0.91 to -0.39; I^2=81.6%; 21 studies [1,583 participants]). Similar findings were observed by studies that could not be pooled. Mixed results for durability of symptom severity at follow-up ranging from 4 weeks to 24 weeks after the end of treatment.	Inconsistent (I^2=81.6%)	Precise	Direct	Some concerns (2 low, 25 SC, 9 high)	Moderate[c] Favor TMS
CGI-S score: TMS compared to sham at posttreatment and last follow-up						
10 RCTs[36,37,39,40,45,48,58,64,69,71]/ 987	Five studies reported statistically significant improvement favoring TMS compared to sham at posttreatment; 2 studies reported statistically significant improvement favoring TMS at follow-up through 8 weeks. One study reported results favoring TMS at posttreatment and follow-up but did not include significance testing.	Consistent	Precise	Direct	Some concerns (3 low, 6 SC, 1 high)	High Favor TMS

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall SOE/ Direction
Safety (any AEs): TMS compared to sham						
8 RCTs[52,53,61,62,64,65,67,68]/594	Studies reporting a range of any AEs from 0 to 40%. One study reported a greater number of any AEs in the active TMS group compared to sham (41% vs. 29%, no significance testing reported).[53] The remaining studies reported no difference between active TMS and sham groups, though did not report absolute numbers to judge direction of effect.	Consistent	Imprecise	Direct	High (6 SC, 2 high)	Low[a,d] Favor sham
Safety (SAEs): TMS compared to sham						
14 RCTs[37,39,41,42,47,48,51,53,54,57,58,60,67,72]/ 1,266	Two studies reported SAEs in the TMS group and no events in the sham, while 2 studies reported no differences between any SAEs between groups. The remaining studies reported 0 SAEs across groups.	Consistent	Imprecise	Direct	Some concerns (1 low, 9 some concerns, 3 high)	Low No difference[b]
Cost-effectiveness over 1 year						
1 DA[73]	Compared to pharmacotherapy, cost savings per QALY gained: $746 (without productivity costs considered) $7,243 (with productivity costs considered)	NA[e]	Imprecise[f]	Direct	Low	Low[g]
Cost-effectiveness over lifetime						
1 DA[74]	Compared to pharmacotherapy, cost savings per QALY gained was $9,225 to $25,907, depending on age at diagnosis/treatment	NA[e]	Imprecise[h]	Indirect[i]	Low	Low[g]

Notes:
[a] Downgrade 1 level for imprecision

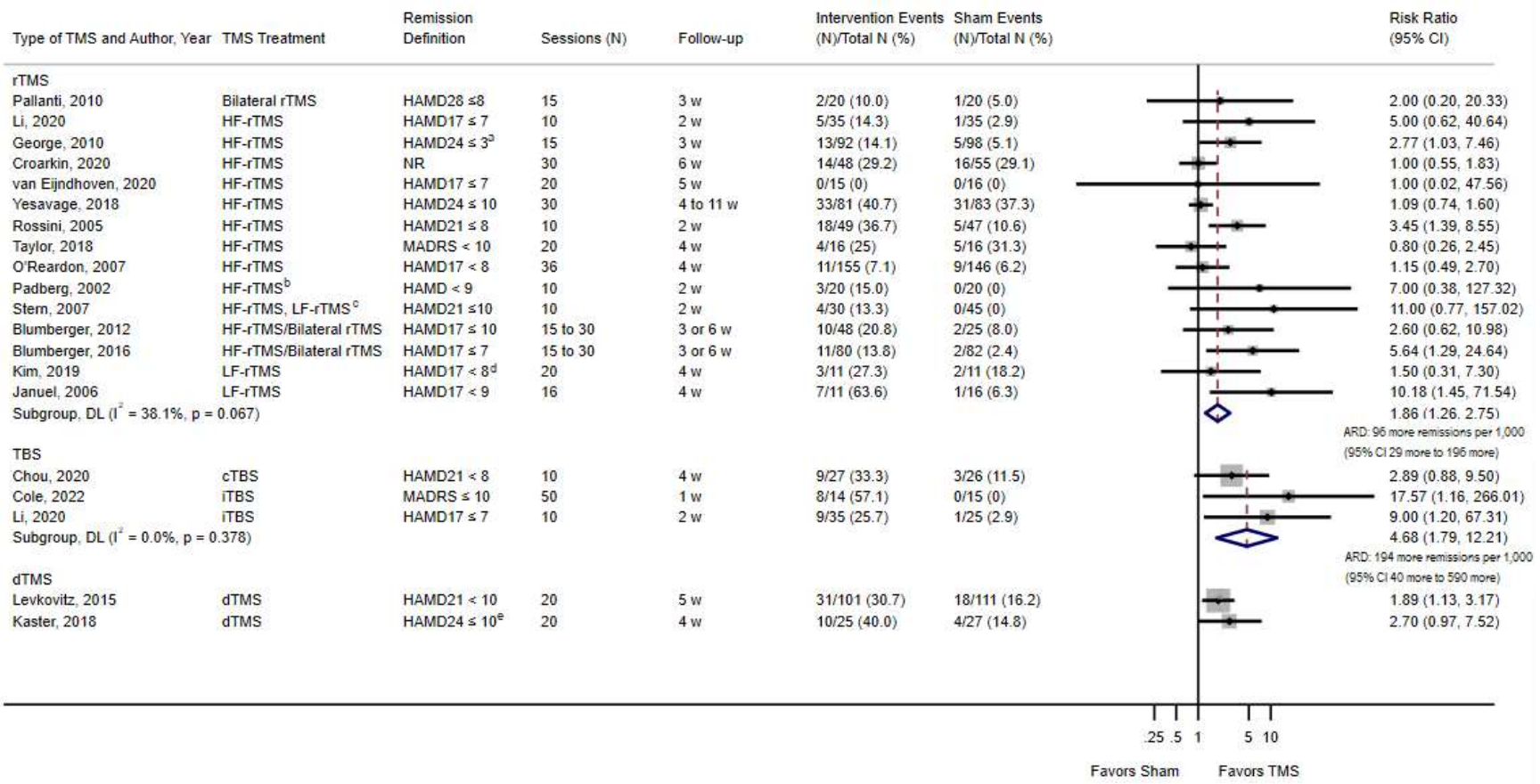
[b] Downgrade 2 levels for imprecision
[c] Downgrade 1 level for inconsistency
[d] Downgrade 1 level for study limitations – lack of required data to adequately evaluate magnitude and direction of effect
[e] Not applicable, single study body of evidence.
[f] Study population contributing inputs was N=465; no CI provided around estimates.
[g] Downgraded 1 level for single study body of evidence and 1 level for imprecision.
[h] No CI on base case estimates; however, did assess stability and consistency with Monte Carlo simulations.
[i] Used a hypothetical cohort with inputs for effectiveness from the literature.

Abbreviations: CI = confidence interval; DA = decision analysis; dTMS = deep transcranial magnetic stimulation, NA = not applicable; QALY = quality-adjusted life-year; RCT = randomized controlled trial; RR = risk ratio; rTMS = repetitive transcranial magnetic stimulation; SAE = serious adverse event; SOE = strength of evidence; TBS = theta-burst stimulation; TMS = transcranial magnetic stimulation.

Remission

Twenty studies reported on remission of MDD using various definitions for remission.[37-54,56,64,68] One study reported remission for the TMS group only and not for the sham group.[56] The remaining trials had data available for pooled analyses of rTMS and TBS at the immediate posttreatment evaluation time point. We report these results in ***Figure 5*** and in the text below, along with results for dTMS and studies with longer durations of follow-up.

Figure 5. Meta-analysis of TMS vs. Sham for Outcome of MDD Remission



Notes: [a] Remission definition=HAMD24 ≤ 3 or 2 consecutive HAMD24 scores <10.
[b] HF-rTMS group includes higher intensity arm of 100% and lower intensity arm of 90%.
[c] LF-rTMS group includes 1 arm targeting right DLPFC and 1 arm targeting left DLPFC.
[d] Remission definition=HAMD17<8 and a CGI-S score≤1.
[e] Remission definition=HAMD24≤10 and ≥60% reduction from baseline on 2 consecutive weeks.

Abbreviations: ARD = absolute risk difference; CGI-S = Clinical Global Inventory-Severity Score; CI = confidence interval; cTBS = continuous theta-burst stimulation; DL = DerSimonian & Laird estimator for pooling estimates; DLPFC = dorsolateral prefrontal cortex; dTMS = deep transcranial magnetic stimulation; HAMD = Hamilton Depression Score; HF-rTMS = high frequency repetitive transcranial magnetic stimulation; iTBS = intermediate theta-burst stimulation; LF-rTMS = low-frequency repetitive transcranial magnetic stimulation; rTMS = repetitive transcranial magnetic stimulation; TBS = theta-burst stimulation; vs. = versus.

rTMS

In a pooled analysis of 15 RCTs (1,469 participants), we observed a higher incidence of remission in the rTMS group compared to sham TMS (RR, 1.86; 95% CI, 1.26 to 2.75; I^2=38.1%) immediately posttreatment[36-50] (***Figure 5***). The ARD was 96 more remissions per 1,000 individuals (95% CI, from 29 more to 196 more). In a sensitivity analysis removing the 5 RCTs we rated as high RoB, the results were comparable (RR, 1.56; 95% CI, 1.04 to 2.35). Five studies reported on remission at some time after the end of treatment;[38,45,47,50,68] all 5 studies found remission at follow-up ranging from 2 to 18 weeks posttreatment, though only 1 study was statistically significant.[68] The remaining 4 studies did not show significant remission at follow-up or report significance testing.[38,45,47,50]

TBS

In a pooled analysis comparing TBS to sham TBS, we observed a higher incidence of remission immediately posttreatment (RR, 4.68; 95% CI, 1.79 to 12.21; I^2=0.0%; 3 RCTs; 197 participants)[50-52] (***Figure 5***). The ARD was 194 more remissions per 1,000 participants (95% CI, from 40 more to 590 more). In terms of longer follow-up, 1 study showed sustained remission in the TBS group at 12 weeks (44.4% vs. 7.7%, P=0.002) but not at 24 weeks (29.6% vs. 11.5%, P=0.10).[52] The other 2 studies reported remission in the TBS group compared to sham at 4 to 12 weeks' posttreatment, although sham data and significance testing were not reported.[50,51]

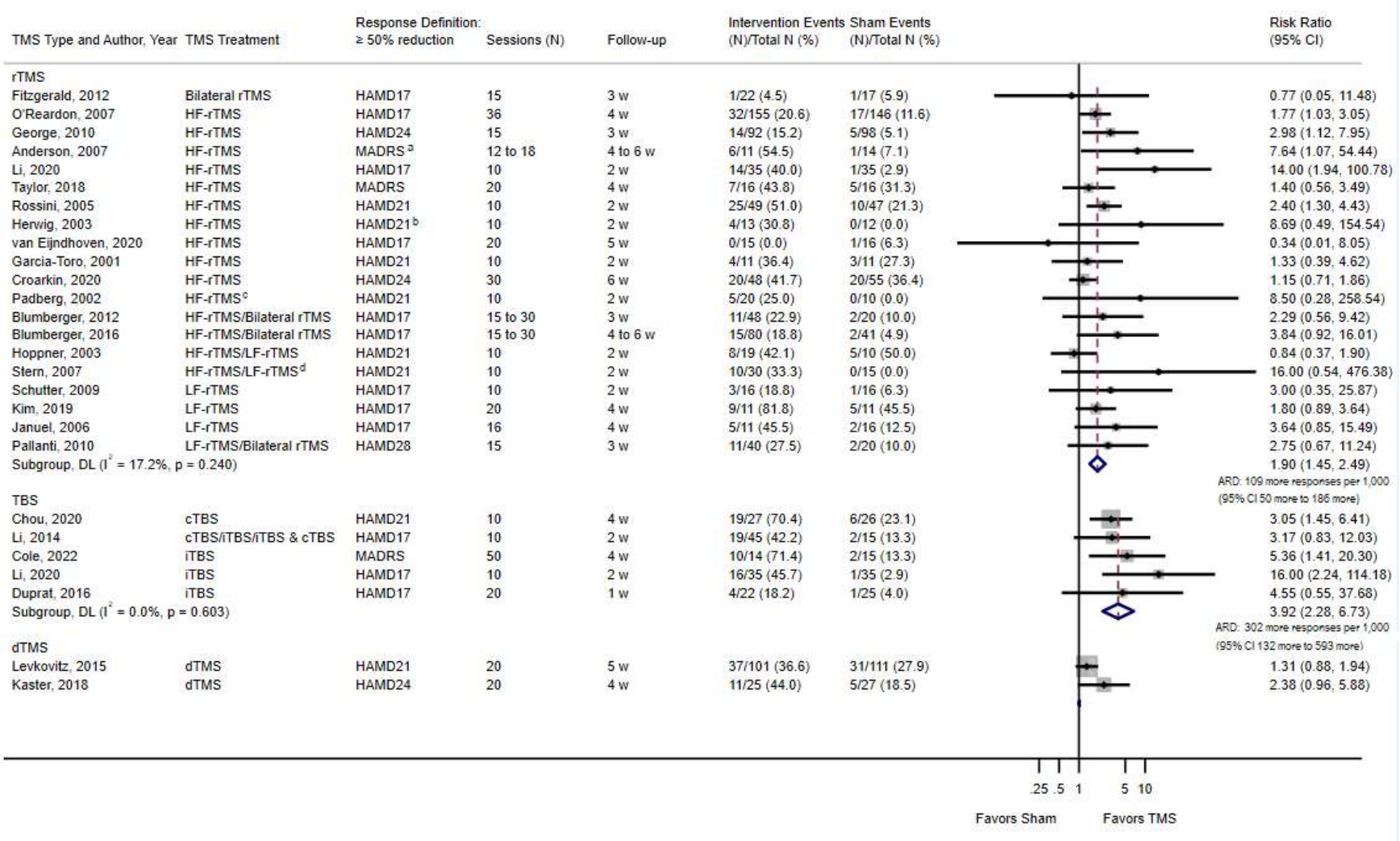
dTMS

Two trials compared dTMS to sham for the outcome of remission. The larger RCT (212 participants) reported that individuals in the dTMS group were more likely to achieve remission posttreatment compared to those in the sham group (calculated RR, 1.89; 95% CI, 1.13 to 3.17).[53] A smaller trial of 52 individuals observed similar results (incidence of remission 40.0% vs. 14.8%; reported P<0.05; calculated RR, 2.70; 95% CI, 0.97 to 7.52).[54]

Response to Treatment

Twenty-six studies including 1,856 participants reported results on response to treatment.[36,37,39-62] In these studies, the definition for response included either a 50% or greater reduction in Montgomery–Åsberg Depression Rating Scale (MADRS) score or a 50% or greater reduction in HAMD score, although the version of HAMD varied from the 17- through 28-item scales. The studies included 3 types of TMS: rTMS, TBS, and dTMS. One study was a 3-arm study comparing rTMS, TBS, and sham treatment.[50] We conducted a meta-analysis of the effects of each type of TMS versus sham treatment on response posttreatment with time points varying overall from 1 week posttreatment to 6 weeks posttreatment. (***Figure 6***). Overall, all types of TMS had a greater effect on response to treatment when compared to sham. Differences in patient populations varied somewhat across studies; however, we did not detect any consistent differences in the patient populations included per type of TMS used.

Figure 6. Meta-analysis of TMS vs. Sham for Outcome of MDD Response



Notes: [a] Response definition: ≥50% reduction MADRS and CGI-I ≥ much improved.
[b] Response definition: ≥ 0% reduction HAMD21 and mean MADRS.
[c] HF-rTMS group includes higher intensity arm of 100% and lower intensity arm of 90%.
[d] LF-rTMS group includes 1 arm targeting right DLPFC and 1 arm targeting left DLPFC

Abbreviations: ARD = absolute risk difference; CGI-I = clinical global inventory-improvement; CI = confidence interval; cTBS = continuous theta-burst stimulation; DL = DerSimonian & Laird estimator for pooling estimates; dTMS = deep transcranial magnetic stimulation; HAMD = Hamilton Depression Score; HF-rTMS = high frequency repetitive transcranial magnetic stimulation; iTBS = intermediate theta-burst stimulation; LF-rTMS = low-frequency repetitive transcranial magnetic stimulation; MADRS= Montgomery-Åsberg Depression Rating Scale; N = number; TBS = theta-burst stimulation; rTMS = repetitive transcranial magnetic stimulation.

rTMS

In a pooled analysis of 20 studies including 1,368 participants, we observed a higher response to rTMS compared to sham (RR, 1.90; 95% CI, 1.45 to 2.49; I^2=17.2%).[36,37,40-51,57-62] Results were reported at the immediate posttreatment time point, the time point for which the most data were available. This RR corresponds to an ARD of 109 more clinical responses per 1,000 individuals (95% CI, from 50 more to 186 more) for rTMS group compared to sham. In a sensitivity analysis removing the 6 RCTs we rated as high RoB, results were similar (RR 2.03; 95% CI, 1.45 to 2.83).

Five studies reported on response at follow-up after posttreatment time points, ranging from 2 to 12 weeks after the end of treatment.[45,50,58,64,68] Response was sustained in 2 studies, both statistically significant at 2 weeks' posttreatment,[64,68] while there was no statistically significant difference between the rTMS and sham groups for 2 studies at 3 to 8 weeks' posttreatment.[45,58] A study with 12 weeks of follow-up after treatment ended showed continued response to treatment but did not report statistical testing.[50]

TBS

In analysis of 5 RCTs (259 participants), we observed a pooled estimate of 3.92 (95% CI, 2.28 to 6.73; I^2=0.0%) comparing TBS to sham at the immediate posttreatment time point.[39,50-52,55,56] This corresponds to an ARD of 302 more clinical responses per 1,000 individuals (95% CI, from 132 more to 593 more) for TBS compared to sham.

Two studies reported follow-up data between 12 and 20 weeks after the end of treatment and reported persistent response to TBS compared to sham.[50,52] One study reported significant response at both 12 weeks (77.8% vs. 23.1%, P<0.001) and 20 weeks follow-up after the end of treatment (81.5% vs. 26.9%, P<0.001).[52] The other study also reported a higher response at 12 weeks' posttreatment for TBS compared to sham but did not report statistical testing.[50]

Deep TMS

Two studies compared dTMS to sham for the outcome of response. The larger RCT (212 participants) reported that individuals in the dTMS group were more likely to achieve response immediately posttreatment compared to those in the sham group (37.0% vs. 27.8%, reported P=0.031; calculated RR, 1.31; 95% CI, 0.88 to 1.94).[53] A smaller trial of 52 individuals observed similar results (44.0% vs. 18.5%, P<0.05; calculated RR, 2.38; 95% CI, 0.96 to 5.88).[54] Neither study reported follow-up beyond the immediate posttreatment period.

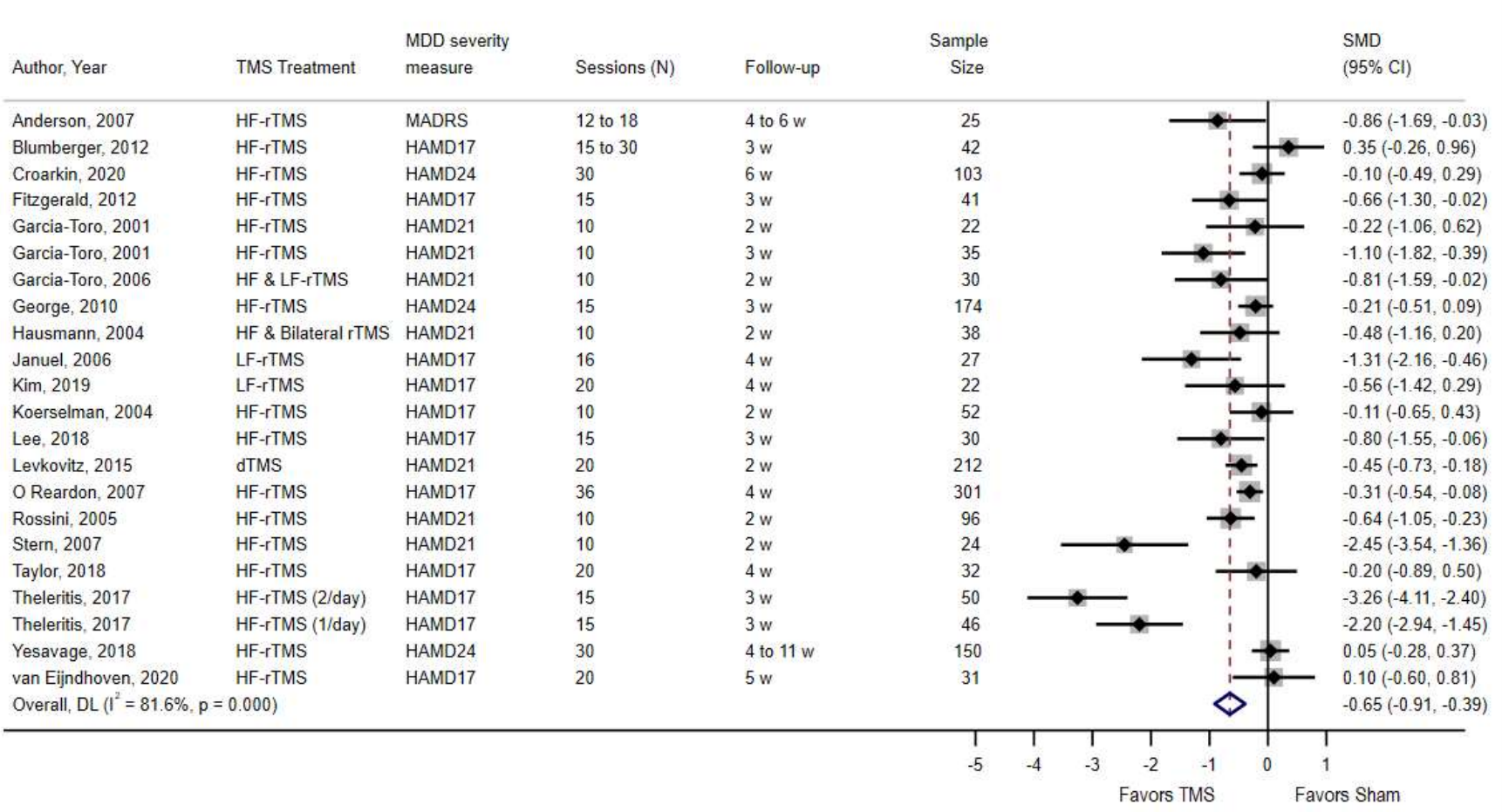
Symptom Severity Measures

Twenty-one RCTs had available data to pool results for the immediate posttreatment evaluation time point.[36-71] MDD severity was measured by several versions of the HAMD, MADRS, and Beck Depression Inventory (BDI). We pooled results using the HAMD (most common measure reported) or the MADRS when the HAMD was not available. There were no TBS studies; the 1 study using dTMS was pooled with rTMS studies.

The pooled SMD in change from baseline immediately posttreatment was -0.65 (95% CI, -0.91 to -0.39; 21 studies; 1,583 participants; I^2=81.6%; ***Figure 7***). This difference translates roughly

to a mean difference on the HAMD17 scale of 3.8 points, which falls within the range considered a minimum clinically important change (MCIC) for this measure (3.9; 95% CI, 3.7 to 4.1).[136] In a sensitivity analysis removing the 4 high RoB RCTs, the results were similar (pooled SMD, -0.72; 95% CI, -1.01 to -0.42). Three study arms from 2 studies had exceedingly large SMDs (range -2.2 to -3.3); however, we could not identify any specific population or intervention characteristics that might explain these findings.[47,64] In a sensitivity analysis dropping these 3 outliers, the SMD was -0.36 (95% CI, -0.52, to -0.20; I^2=45.2%). Studies that did not meet data requirements to be included in the pooled analysis reported similar findings as those that were included.[44,48,50-52,54-56,59-61,65,67,68]

Figure 7. Meta-analysis of TMS vs. Sham for Outcome of MDD Symptom Severity



Note: The pooled SMD (-0.65) is roughly equivalent to a HAMD17 difference of -3.8 points and is equal to the minimum clinically important change established for this measure.

Abbreviations: CI = confidence interval; DL = DerSimonian & Laird estimator for pooling estimates; dTMS = deep transcranial magnetic stimulation; HAMD = Hamilton Depression Score; HF-rTMS = high frequency repetitive transcranial magnetic stimulation; LF-rTMS = low-frequency repetitive transcranial magnetic stimulation; MDD = major depressive disorder; N = number; rTMS = repetitive transcranial magnetic stimulation; SMD = standardized mean difference; TMS = transcranial magnetic stimulation.

The majority of studies did not report extended follow-up, and if they did, there were usually no differences between groups. Only 6 of the 36 studies observed statistically significant differences between groups at follow-up ranging from 4 to 24 weeks' posttreatment.[45,47,50-52,67] Participants in these studies showed improvement immediately posttreatment that persisted at follow-up between 4 and 24 weeks after the end of treatment.

Other Measures

CGI-S

Ten studies reported results based on the CGI-S.[36,37,39,40,45,48,58,64,69,71]

Eight studies reported on CGI-S findings immediately posttreatment.[36,37,39,40,48,58,64,71] Five of these studies[39,40,48,71,137] reported statistically significant improvements in CGI-S scores favoring TMS compared to sham, including 1 study of pregnant women that measured changes in scores between middle of treatment and posttreatment and adjusted for baseline differences (P=0.035).[40] One study reported results favoring the 2 TMS treatment groups compared to the 2 sham groups at 3 weeks' posttreatment but did not report significance testing between groups.[64] Two studies[36,58] reported no statistically significant differences between TMS and sham following treatment; 1 study favored TMS,[58] while the other study did not report absolute values to judge direction of effect.[38]

Four studies reported on CGI-S at posttreatment follow-up up to 8 weeks.[45,58,64,71] Statistically significant improvement in CGI-S scores favoring TMS was reported in 2 studies,[45,71] and 1 study reported improvement in active treatment compared to sham (significance testing not reported).[64] One study[58] reported no statistically significant differences in CGI-S scores at follow-up. Another study[69] reported that the decrease in CGI scores in TMS versus sham treatment was only significant after 1 week of treatment (-0.7 vs. -0.1, P=0.032) but not after 2 weeks of treatment or at 2 weeks' follow-up.

BSI

One study reported on the Beck Scale for Suicide Ideation (BSI).[38] Findings were not statistically significantly different between TMS and sham at posttreatment (adjusted effect estimate, 0.08; 95% CI, -1.46 to 1.62; P=0.91) or through 18 weeks' follow-up (adjusted effect estimate, -0.54; 95% CI, -2.25 to 1.17; P=0.53).[38]

Safety Measures

All RCTs except for 1 study[63] reported on safety outcomes, although the specific ascertainment methods used and outcomes reported varied.

Twenty-two studies reported on SAEs. Among the 14 studies reporting any SAEs, 2 studies reported no differences between any SAE between groups.[37,39,53] Two studies reported some SAEs in the TMS group and no events in the sham group.[42,58] Nine studies reported 0 SAEs in either group.[41,47,48,51,54,57,60,67,72]

Among the 10 studies specifically reporting on seizure as an SAE, 9 reported 0 events across both groups.[38,44,47,50,55,59,64,68,70] Only 1 study reported seizure in 1 participant in the active TMS

group.[58] Six studies specifically reported on suicide ideation, which ranged from 0 to 5% in the 5 studies reporting data by group (absolute numbers ranging from 0 to 4 individuals).[36-38,43,53,66] There was no clear difference in suicide ideation by group across studies reporting this outcome. One study reported a suicide attempt in the control group.[56] No deaths, including suicides, were reported.

Eight studies reported on any AEs:[52,53,61,62,64,65,67,68] studies reported a range from 0 to 40%. One study reported a greater number of AEs in the active TMS group compared to sham (41% vs. 29%, no significance testing reported).[53] The remaining studies reported no difference between active TMS and sham groups. Of those studies reporting specific events, the most frequently reported were headache and application site discomfort, which had higher or similar frequency in the active TMS group compared to sham. In general, these were reported as transient around the time of the treatment and posttreatment period. Other specific AEs reported by multiple studies included dizziness, fatigue, anxiety, nausea, insomnia, and neck or back pain.

Accelerated Protocols

Three studies reported results for protocols that involved more than 1 treatment a day; 2 RCTs were conducted using iTBS[51,56] and 1 with HF-rTMS.[64] Cole et al. administered 10 iTBS treatments a day for 1 week; authors of this study reported a higher RR for remission and response than our pooled RR estimate, though the study estimate had wide CIs.[51] Duprat et al. administered 5 treatments a day for 1 week, in which the response estimate was higher than our pooled estimate, though the CIs were wide and included the null effect.[56] The study by Theleritis et al. of twice a day HF-rTMS had the largest mean difference in symptom severity among all studies included in the meta-analysis.[64]

Special Populations

We identified 3 studies that reported outcomes for subgroups of age, sex, and comorbidity.[38,47,59] There was no difference in clinical response by age[47,59] or sex.[38,47,59] In a study of veterans with MDD, rates of remission were higher for individuals without comorbid PTSD for active TMS groups compared to the sham condition, whereas there was little difference between groups for individuals with comorbid PTSD (P=0.03 for significant difference between subgroups with and without PTSD).[38] We also identified 1 study of individuals who were specifically naïve to treatment,[46] in which TMS had greater magnitude of benefit for measures of remission, response, and reduction of disease severity compared to the pooled estimate, though CIs were very wide for all estimates.

One study each was identified for the following special populations: adolescents,[36] pregnant individuals,[40] and older adults.[54]

The study in adolescents was conducted in individuals aged 12 to 21 years and was funded entirely by industry.[36] Eligible participants had MDD symptoms greater than 4 weeks and less than 3 years and had to report intolerance to at least 4 prior trials of medications. The mean age of participants was 17 years, and over 50% had a secondary psychiatric diagnosis. Medications were stopped before the trial. Participants were randomized to HF-rTMS or sham and treated daily, 5 times a week, for 6 weeks. No differences in remission, response, change in symptom

severity over baseline (as measured by HAMD24 and CGI-S), suicidality, or other SAEs were observed between groups. Specific AEs reported included headache, eye pain, nausea, and facial twitching.[36]

The trial in pregnant individuals was partially funded by industry, enrolled women aged 18 to 39 years and gestational ages 14 to 34 weeks with a primary diagnosis of MDD and treated women with LF-rTMS of the right DLPFC for 4 weeks (daily sessions, 5 sessions/week) compared to most rTMS studies, which used HF-rTMS or bilateral rTMS. There were no differences observed between rTMS and sham for remission and response. Change in severity of symptoms from baseline was not reported, although change in severity at 6 weeks following treatment compared to 4 weeks' posttreatment was reported as statistically significant and favoring TMS for HAMD17 and the Edinburg postnatal depression score. The study did not report on any or serious AEs, but it did report that there were no differences in specific harms (such as headaches, dizziness, and site pain) or infant outcomes.[40]

One partially industry-funded trial studied dTMS compared to sham for the indication of treatment-resistant MDD in individuals aged 60 to 85 years (mean age 65).[54] Outcomes were measured at a posttreatment time point of 4 weeks only. Remission and response, defined by cutoffs of HAMD24 ≤ 10 and ≥ 50% reduction in HAMD24, respectively, were greater in the dTMS group compared to sham, though RRs were not statistically significant when calculated. Although symptom severity improved in both dTMS and sham participants, there was no significant time-by-treatment interaction, nor was there a difference in change from baseline to posttreatment for the Scale for Suicide ideation. There were 0 SAEs reported in either group.[54] The only specific harm that was significantly greater in the TMS group compared to sham was pain at the treatment site (16% vs. 0%, $P<0.05$).[54]

Cost-Effectiveness

Two studies conducted based on U.S. data reported cost-effectiveness outcomes.[73,74] Both studies were decision analyses sponsored by rTMS device companies; we rated both as low risk of bias (***Appendix E, Tables E-31, E-32,*** and ***E-33***). Study characteristics are summarized in ***Table 12*** with detailed characteristic in ***Appendix C, Table C-31***. Both studies considered populations with treatment-resistant MDD and evaluated rTMS.[73,74] One study was conducted over a 1-year time horizon using data from participants in 3 clinical trials of rTMS; costs were obtained from the trials and from Medicaid billing data.[73] The other study was conducted over a lifetime horizon with a hypothetical cohort of adults aged 20 to 50 years with inputs for effectiveness culled from the literature and costs based on Medicare reimbursement rates.[74]

One study reported findings over a 1-year horizon and focused only on active treatment phases, while the other reported findings over a lifetime and included both active and maintenance treatment. In the base case for both studies, rTMS was the dominant strategy compared to pharmacotherapy, meaning that it cost less and was more effective.[73,74] In the study using a 1-year time horizon, the cost savings per QALY gained was $746 without productivity costs and was $7,243 when productivity costs were considered.[73] This study also reported findings compared to sham treatment; active treatment was more effective but also cost more whether productivity costs were included or not (***Table 12***).[73] In the study using a lifetime horizon, the

cost savings per QALY gained ranged from $9,225 to $25,907 depending on the age at diagnosis; more savings accumulated for younger age groups (***Table 12***).[74]

Table 12. Study Characteristics and Findings for Studies Reporting Cost-Effectiveness for MDD (CQ 1)

Author (Year) Country Risk of Bias Sponsor	Population	Intervention	Comparator	Key Analysis Parameters	Outcomes
Simpson et al. (2009)[73] U.S. Low Neuronetics, Inc.	Data from participants in trials; unipolar depression with moderate to severe treatment resistance, mean age 48 years	rTMS for 6 weeks followed by 3-week taper and transition to single-drug antidepressant	Two comparators; sham treatment or pharmacotherapy	Decision analysis in 2006 U.S. dollars Payer and societal perspective Time horizon 1 year Costs: clinical trial and Medicaid 2004 billing data	*Sham comparator:* ICER with and without productivity costs/QALY: $3,544/$36,551 *Pharmacotherapy comparator:* ICER with and without productivity costs/QALY: -$7,243/-$746 (both cost saving)
Voigt et al. (2017)[74] U.S. Low Magstim	Hypothetical cohort of adults aged 20s to 50s with MDD and single failed medication trial	rTMS (up to 4 courses of treatment) with maintenance for responders,[a] ECT for nonresponders	Pharmacotherapy for active treatment and maintenance for responders,[a] ECT for nonresponders	Decision analysis 2016 U.S. dollars Payor perspective Time horizon: lifetime Costs: Medicare 2016 reimbursement rates	rTMS cost less and was more effective for all age groups ICER 20s: -$25,907 30s: -$20,407/QALY 40s: -$14,865/QALY 50s: -$9,225/QALY In sensitivity analysis, ICERs between $29,000 and $56,000 assuming maximum number of rTMS sessions or lowest costs for pharmacotherapy

Notes: [a] Maintenance could include rTMS and pharmacotherapy for intervention and psychotherapy for both intervention and comparator.

Abbreviations: CQ = cost question; ECT = electroconvulsive therapy; ICER = incremental cost-effectiveness ratio; MDD = major depressive disorder; NR = not reported; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; rTMS = repetitive transcranial magnetic stimulation; U.S. = United States.

3.5 Posttraumatic Stress Disorder

We identified 4 parallel-assignment RCTs that focused on TMS[75-77] or TBS[78] compared to sham stimulation for the indication of PTSD. The interventions varied in terms of protocol, number of sessions, duration over which the sessions were provided, and timing of outcome measure follow-up. Key findings are as follows:

- One RCT[75] reported on remission and response. The study reported very low remission rates that did not statistically differ between groups. Likewise, for response to treatment, defined as at least a 50% decrease in the Clinician Administered PTSD Scale (CAPS), results were not statistically significant. (SOE: Insufficient for remission and response)

- Four RCTs[75-78] reported on the change from baseline in the CAPS score to either end of treatment or last follow-up. Two studies using LF-rTMS showed improvement in CAPS scores for TMS vs. sham, but the improvement was only statistically significant in the larger study (n=103).[76] One study of iTBS showed no difference from sham, and 1 study favored sham over dTMS though the results were not statistically significant. (SOE: Low, favors TMS)

- Three RCTs[75,76,78] reported on safety outcomes. One study reported no difference in AEs across groups, 1 study reported no serious AEs, and another reported 2 SAEs in the TMS group. Headache and treatment site discomfort were the most common specific AEs reported. (SOE for AE: Low, no difference; SOE for SAE: Insufficient)

The rest of this section provides detailed study characteristics and results.

3.5.1 Study and Population Characteristics

Three[75,76,78] of the 4 trials were conducted from 2011 to 2020; 1 study did not report the years it was conducted.[77] We assessed 1 of these trials as low risk of bias;[78] 2 studies as having some risk of bias due to lack of blinding of some participants, high attrition, and incomplete outcome data;[75,76] and 1 study as having high risk of bias arising from the randomization process and selective outcome reporting.[77]

Three trials[76-78] were conducted in the United States, and 1 trial was conducted in the United States, Israel, Canada, and Europe.[75] Three studies reported no industry support,[76-78] and 1 study was entirely funded by industry.[75] ***Table 13*** summarizes the characteristics of included TMS trials; additional details are found in ***Appendix C***, ***Tables C-16, C-17,*** and ***C-18***.

Table 13. Summary of Study Characteristics of Included Studies of TMS for Treatment of PTSD

Author (Year) Country RoB	Intervention and Comparator (N Randomized)	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions; Exposure Therapy (Y/N)	Mean Age (SD)	N (%) Female	N (%) Race-Ethnicity
Isserles et al. (2021)[75] U.S., Israel, Canada, Europe Some concerns	dTMS (60) Sham dTMS (65)	134	4 weeks;[c] 9 weeks	Medication and psychotherapy per usual treatment; Yes	TMS: 44.8 (13.2) Sham: 43.7 (12.3)	TMS: 39 (65) Sham: 44 (68)	Caucasian: TMS: 54 (90) Sham: 53 (82) African American: TMS: 3 (5) Sham: 4 (6) Hispanic: TMS: 4 (6) Sham: 3 (5) Other: TMS: 1 (2) Sham: 5 (8)

Author (Year) Country RoB	Intervention and Comparator (N Randomized)	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions; Exposure Therapy (Y/N)	Mean Age (SD)	N (%) Female	N (%) Race-Ethnicity
Kozel et al. (2018)[76] U.S. Some concerns	LF-rTMS+CPT (54) Sham rTMS+CPT (49)	103	12 weeks;[d] 6 months posttreatment	CPT per study protocol; No	TMS: 34.1 (7.6) Sham: 32.9 (6.0)	NR[e]	White: TMS: 42 (78) Sham: 42 (86) Black: TMS: 7 (13) Sham: 6 (12) Other: TMS: 5 (9) Sham: 1 (2)
Philip et al. (2019)[78] U.S. Low	iTBS (25) Sham iTBS (25)	50	2 weeks;[b] 2 weeks	Medication and psychotherapy per usual treatment; No	TBS: 48 (13) Sham: 53 (12)	TBS: 5 (20) Sham: 3 (12)	White: TBS: 22 (88) Sham: 20 (80) African American: TBS: 0 (0) Sham: 2 (8) American Indian/Alaska Native: TBS: 1 (4) Sham: 0 (0) Multiracial: TBS: 2 (8) Sham: 1 (4)
Watts et al. (2012)[77] U.S. High	LF-rTMS (10) Sham rTMS (10)	20	2 weeks;[b] 2 weeks	Medication and psychotherapy per usual treatment; No	TMS: 54.0 (12.3) Sham: 57.8 (11.8)	TMS: 1 (10) Sham: 1 (10)	White: TMS: 10 (100) Sham: 10 (100)

Notes: [a] "Last follow-up" indicates last follow-up time point eligible for this HTA (e.g., blinded phase eligible only of a multiphase study with open-label phases). A study may have reported outcomes at follow-up time points that were subsequent to what is reported in this column though were not eligible for review (e.g., open-label phase).
[b] 5 sessions/week.
[c] 3 sessions/week; with 1 booster treatment given at weeks 5 and 9 during the follow-up period.
[d] 1 session/week; up to 3 additional sessions of CPT allowed.
[e] Study report states "participants were predominantly male."

Abbreviations: CPT = cognitive processing therapy; dTMS = deep TMS; HF = high frequency; HTA = health technology assessment; iTBS = intermittent theta-burst stimulation; LF = low frequency; N = number; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; TMS = transcranial magnetic stimulation; U.S. = United States.

Two studies enrolled participants based on threshold values of CAPS score of 25[75] and 50;[77] the remaining 2 studies did not require minimum CAPS scores, although baseline scores corresponded to moderate[78] and severe[76] disease. One study[77] included only treatment-resistant participants defined as being on a stable dose of medication, 1 study[76,78] included both treatment-naive and treatment-resistant participants, and 2 studies[75,82] did not specify treatment history of the study populations. The study sample sizes ranged from 20 to 134 participants. The mean age of included populations ranged from 32.9 to 57.8 years. All studies included both male and female participants, and all studies included participants of more than 1 race or ethnicity, except

1 study[77] that included only White participants. Three studies included only military veterans.[76-78] All studies except 1[75] reported on mental health comorbidities, and the most prevalent comorbidity was SUD.

There was variation in the protocols across all 4 studies. The active intervention in 2 RCTs was low-frequency rTMS of the RDLPFC.[76,77] One study[78] used iTBS of the RDLPFC, and 1 study used dTMS to bilaterally stimulate the medial prefrontal cortex and ACC.[75] Studies also varied in the number of pulses administered during a single session (range 400 to 2,880) and in the stimulation intensity used (range 80 to 110% MT). Two studies[77,78] provided active or sham treatment over 2 weeks with 5 sessions per week; 1 study[75] provided 4 weeks of treatment with 3 sessions per week and a booster treatments at weeks 5 and 9; while 1 study provided 1 session per week for 12 weeks.[76] Duration of follow-up ranged from 2 weeks to 6 months posttreatment. One study[76] included cognitive processing therapy (CPT) to all participants as a co-intervention, while 3 studies[75,77,78] allowed ongoing medication and psychotherapy per usual treatment. One study included exposure therapy aimed to amplify the participants' symptoms before each TMS session.[75] The studies included a variety of sham TMS controls.

3.5.2 Findings

Detailed findings are provided in ***Appendix C, Tables C-19*** and ***C-20***. A summary of findings and the SOE are provided in ***Table 14***. The included studies showed mixed results across different clinical outcomes and measurement time points. Data on safety outcomes were limited and may show little to no difference between TMS and sham, although the strength of the evidence is low. The following section provides detailed results for each category of outcome measure.

Table 14. Summary of Findings and SOE for TMS Compared to Sham Stimulation for PTSD

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall SOE/ Direction
Remission of PTSD symptoms at last follow-up						
1 RCT[75]/134	dTMS; reported remission rates were very low and did not statistically differ between groups.	Unknown (Single study)	Imprecise	Direct	Some (1 SC RoB)	Insufficient[a,b]
Clinical response (decrease in symptoms of at least 50% reported in CAPS score) end of treatment and 4 weeks' posttreatment						
1 RCT[75]/134	dTMS; participants in the sham group were more likely to have a response to treatment at both time points, although results were not statistically significant.	Unknown (Single study)	Imprecise	Direct	Some (1 SC RoB)	Insufficient[a,b]

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall SOE/ Direction
Change in CAPS score from baseline (various time points from 2 to 7 weeks)						
4 RCTs[75-78]/307	Two studies using LF-rTMS showed improvement in CAPS scores for rTMS vs. sham, statistically significant in the larger study (n=103). One study of iTBS showed no difference from sham, and 1 study favored sham over dTMS though the results were not statistically significant.	Consistent	Imprecise	Direct	Some (1 low, 2 SC, 1 high RoB)	Low[b] Favor TMS
Change in PCL score from baseline (various time points)						
3 RCTs[76-78]/173	1 study (n=20) with high RoB favored rTMS, while a second study (n=50) with low RoB showed both the iTBS and sham groups improved, but the difference in improvement between the 2 groups was not statistically significant. Another study (n=103) with some RoB concerns measured change in score from baseline to last follow-up at 6 months' posttreatment and found the rTMS group showed statistically significant improvement in PCL score compared to sham.	Consistent	Imprecise	Direct	Some (1 low, 1 SC, 1 high RoB)	Low[b] Favor TMS
Safety (any AEs) up to 9 weeks						
1 RCT[75]/134	1 study reported a similar number of any AEs occurring in both the dTMS and sham groups (77% vs. 63%, *P*=0.099).	Unknown (Single study)	Imprecise	Direct	Some (1 SC RoB)	Low[a,c] No difference

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall SOE/ Direction
Safety (serious AEs)						
3 RCTs[75,76,78]/ 287	One study reported no SAEs and 1 study reported 2 SAE (1 emergent homicidal ideation; 1 hospitalization for suicidality) in the sham group only. A third study reported on specific AEs, noting similar numbers of moderate or severe anxiety across groups and 2 reports of suicidal ideation in the TMS group, none in the sham group.	Inconsistent	Imprecise	Direct	Some (1 low, 2 SC RoB)	Insufficient[b,d]

Notes:
[a] Downgraded 1 level for inconsistency—single study.
[b] Downgraded 2 levels for imprecision.
[c] Downgraded 1 level for imprecision—wide CI with range in clinical meaning.
[d] Downgraded 1 level for inconsistency—studies showed different directions of effect.

Abbreviations: AE = adverse event; CAPS = Clinician Administered PTSD Scale; CI = confidence interval; dTMS = deep transcranial magnetic stimulation; iTBS = intermittent theta-burst transcranial magnetic stimulation; NA= not applicable; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; RoB = risk of bias; rTMS = repetitive transcranial magnetic stimulation; SAE = serious adverse events; SC = some concerns; SMD = standardized mean difference; SOE = strength of evidence; TMS = transcranial magnetic stimulation.

Remission

One RCT reported that remission rates were very low and did differ statistically in both the TMS and sham groups; however, the authors did not define remission nor present numerical findings.[75]

Response to Treatment

One RCT reported on response to treatment, defined as at least a 50% decrease from baseline in CAPS-5 score, indicating improvement.[75] Authors found that participants in the sham group were more likely to have a response to treatment (55%) than those in the dTMS group posttreatment (43%); however, the results were not statistically significant *(P*>0.05).[75] Response to treatment improved across both groups at 4 weeks' posttreatment with the sham group still more likely to have a response to treatment (68%) than those in the dTMS group (54%); the difference between groups remained not statistically significant (*P*>0.05).

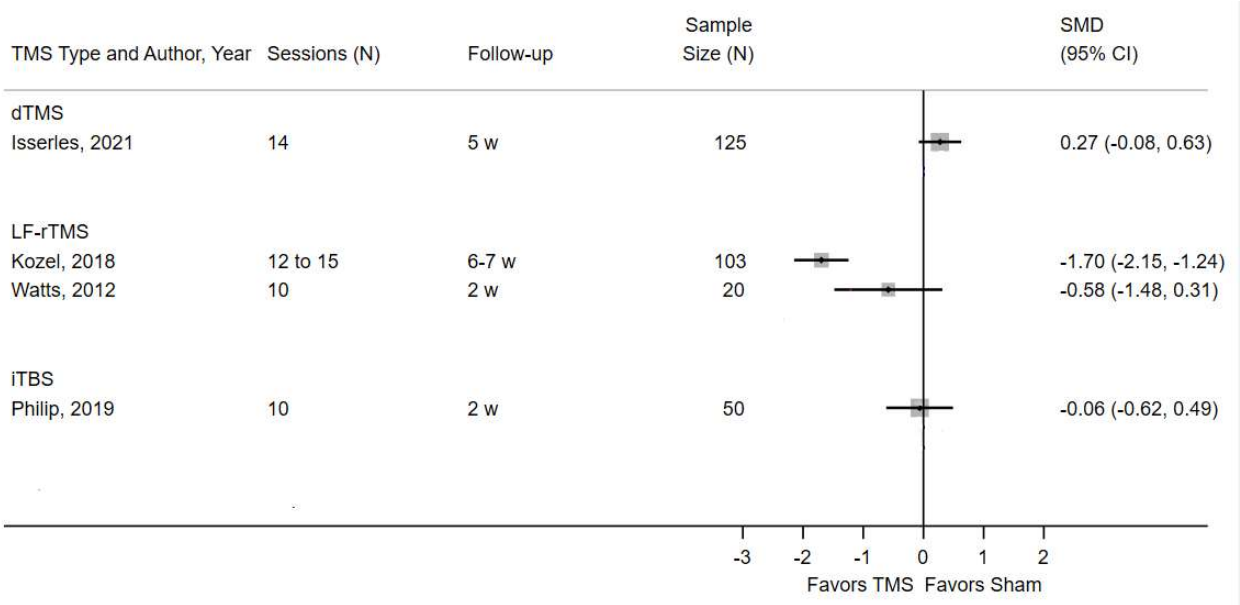
Symptom Severity Measures

CAPS

All 4 RCTs[75-78] reported on the change in CAPS score from baseline: 3 studies[75,76,78] used the CAPS-5 and 1 study[77] used the CAPS-1 scale (***Figure 8***). Both LF-rTMS studies[76,77] showed favorable impacts for rTMS, although findings were only statistically significant in 1 of the studies.[76] The study using iTBS[78] did not show a statistically significant difference between

treatments, and the study of dTMS[75] showed the sham group had a greater effect than the dTMS group, although not statistically significant. Heterogeneity of effects is likely due to differences in enrolled populations, TMS type and target, and presence or absence of various co-treatments.

Figure 8. PTSD: TMS vs. Sham for Outcome of PTSD Symptom Severity



Note: Symptom severity as measured by the CAPS-5 or CAPS 1 outcome.

Abbreviations: CAPS = Clinician Administered PTSD Scale; CI = confidence interval; dTMS = deep transcranial magnetic stimulation; iTBS = intermittent theta-burst stimulation; LF-rTMS = low frequency repetitive transcranial magnetic stimulation; N = number; PTSD = posttraumatic stress disorder; SMD=standardized mean difference; TMS = transcranial magnetic stimulation.

PTSD Checklist

Three RCTs[76-78] reported on change in PTSD Checklist (PCL) score from baseline. Two studies[77,78] reported on the change from baseline to posttreatment. One study (n=20) with high RoB found a statistically significant change from baseline favoring the rTMS group compared to sham.[77] The other study[78] (n=50) with low RoB found that although the iTBS improved more over the sham group, the difference in improvement between the 2 groups was not statistically significant (*P*=0.31).

One study[76] reported on the change from baseline to 6 months' posttreatment follow-up and found the rTMS group showed statistically significant improvement in PCL score compared to sham (actual values not reported, *P*<0.05).

Mississippi Scale for Combat Related PTSD

One RCT[76] reported on the change in M-PTSD score from baseline to 6 months' posttreatment follow-up and found the rTMS group showed statistically significant improvement in M-PTSD score compared to sham (actual values not reported, *P*<0.05).

Modified PTSD Symptom Scale, Self-Report

One RCT[75] reported on a change in the Modified PTSD Symptom Scale (MPSS) score from

baseline to end of treatment (mean difference [MD], 4.6; 95% CI, 1.7 to 7.5) and to 4 weeks' posttreatment (MD, 5.65; 95% CI, 2.1 to 9.2) and found at both time points that the sham group showed a statistically significant improvement in MPSS score compared to the dTMS group ($P<0.05$).

Safety Measures

Four RCTs[75-78] reported on safety outcomes, although the specific outcomes reported varied. Two studies reported on SAEs; 1 study[76] found no SAEs in either group, while another study[78] reported 2 SAEs (1 emergent homicidal ideation; 1 hospitalization for suicidality) in the sham group only. Another study[75] reported on specific SAEs, including a similar frequency of moderate or severe anxiety in both the dTMS and sham groups (5% vs. 6%) and 2 incidences of suicidal ideation in the dTMS group (3%) and none occurring in the sham group. One study[75] reported on any AEs: a similar percentage of participants experienced AEs in the dTMS group compared to sham (77% vs. 63%, $P=0.099$). Of those studies reporting specific AEs, the most frequently reported were headache and treatment site discomfort. One study reported 24% of participants in the TBS group experienced treatment site discomfort, while the sham group did not report any discomfort.[78]

3.6 Smoking Cessation

We identified 5 parallel-assignment RCTs in 5 publications that focused on rTMS stimulation compared to sham stimulation for the indication of smoking cessation.[79-83] The interventions varied in terms of protocol, number of sessions, duration over which the sessions were provided, and timing of outcome measure follow-up. Key findings are as follows:

- Five RCTs[79-83] reported on remission. Although various measures of abstinence from smoking generally favored TMS over sham, findings were statistically significant in only 3 studies at the posttreatment time point and durable beyond posttreatment for 1 study. (SOE: Low, favors TMS)

- Two RCTs[80,83] reported lower nicotine use as measured by self-report or nicotine biomarkers, statistically significant posttreatment for both studies and at follow-up for 1 study. (SOE: Low, favors TMS) One of these studies also reported a 50% decrease in number of cigarettes smoked for TMS compared to sham; however the study was small and had a high RoB. (SOE: Insufficient)[80] Both studies also reported measures of nicotine dependence, which improved in the TMS group compared to sham, statistically significant in 1 study. (SOE: Low, favor TMS)

- Four RCTs[79-81,83] reported on safety outcomes. One study reported no AEs, 2 studies reported no difference in AEs across groups, and the largest trial found more AEs in the TMS group compared to sham. Headache was the most common specific AE reported. (SOE: Low, favors sham)

The rest of this section provides detailed study characteristics and results.

3.6.1 Study and Population Characteristics

Four of the 5 trials were conducted from 2011 to 2019; 1 study did not report the years it was conducted.[82] We assessed 1 of these trials as low risk of bias,[83] 1 study as having some risk of bias in randomization and selective reporting domains,[79] and 3 studies as high risk of bias, primarily for high attrition and absence of an ITT analysis.[80-82]

Two trials[79,80] were conducted in the United States, 1 trial[82] in Germany, and 1 trial in the United States and Israel.[83] Three studies reported no industry support;[79,81,82] 1 grant-funded study accepted equipment donation from industry,[80] and 1 study was entirely funded by industry.[83] ***Table 15*** summarizes the characteristics of included rTMS trials; additional details are found in ***Appendix C***, ***Tables C-21, C-22,*** and ***C-23***.

Of the included studies, the eligible study sample sizes ranged from 29 to 262 participants. The mean age of included participants ranged from 41.2 to 49.6 years. All studies included both male and female participants, and only 1 study[79] provided data about participant race. No studies reported on mental health comorbidities. Disease severity was reported in a variety of ways, including number of cigarettes smoked[80,83] and nicotine dependence as measured by the FTND score.[80,83] Only 1 study specified the treatment history of the study population, specifically a history of at least 2 unsuccessful quit attempts.[81]

The active intervention in all RCTs was rTMS, although there was variation in the rTMS protocol used across the 5 studies. Two studies were conducted using high-frequency rTMS of the left dorsolateral prefrontal cortex (LDLPFC),[79,80] and 1 study each of low-frequency rTMS of the right dorsolateral prefrontal cortex (RDLPFC),[81] iTBS of the RDLPFC,[82] and dTMS of the bilateral insula and prefrontal cortex.[83] Studies also varied in the number of pulses administered during a single session (range 360 to 3000) and in the stimulation intensity used (range 80 to 120% MT). Four studies[79-82] provided active or sham treatment over 2 weeks (number of sessions ranging from 2 to 5 sessions per week), while 1 study provided 6 weeks of treatment.[83] Duration of follow-up ranged from 12 weeks to 12 months. Four of the 5 studies included co-interventions, 1 study used nicotine replacement therapy,[81] 1 study provided psychotherapy,[82] 1 study distributed evidence-based self-help materials,[79] and 1 study provided a motivational talk.[83] The studies included a variety of sham rTMS controls.

Table 15. Summary of Study Characteristics of Included Studies of TMS for Treatment of Smoking Cessation

Author, Year Country RoB	Intervention and Comparator (N Randomized)	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions; Exposure Therapy (Y/N)	Mean Age (SD)	N (%) Female	N (%) Race-Ethnicity
Dieler (2014)[82] Germany High	iTBS (38) Sham TMS (36)	74	4 days; 12 months	Psychotherapy; No	45.5 (10.6)	34 (46)	NR
Li (2020)[80] U.S. High	HF-rTMS (22) Sham TMS (20)	42	2 weeks;[d] 12 weeks	None; Yes	TMS: 41.2 (11.8) Sham: 44.1 (9.1)	TMS: 12 (57) Sham: 9 (53)	NR
Sheffer (2018)[79] U.S. Some concerns	HF-rTMS (16) Sham TMS (13)	29	2 weeks;[b] 12 weeks	Self-help materials; No	49.6 (8.3)	12 (41)	White: 3 (10) Black: 21 (72) Other[c]: 5 (17)
Trojak (2015)[81] France High	LF-rTMS (19) Sham TMS (19)	37	2 weeks;[d] 12 weeks	Nicotine replacement; therapy No	TMS: 47.6 (13.5) Sham: 42.3 (12.1)	TMS: 8 (22) Sham: 9 (24)	NR
Zangen (2021)[83] U.S., Israel Low	dTMS (123) Sham TMS (139)	262	6 weeks;[e] 12 weeks	Motivational talk; Yes	TMS: 45 (13.0) Sham: 44.8 (13.4)	TMS: 60 (49) Sham: 66 (48)	NR

Notes: [a] "Last follow-up" indicates last follow-up time point eligible for this HTA (e.g., blinded phase eligible only of a multiphase study with open-label phases). A study may have reported outcomes at follow-up time points that were subsequent to what is reported in this column though were not eligible for review (e.g., open-label phase).
[b] 4 sessions/week.
[c] Other = Asian/Pacific Islander, American Indian/Alaska Native/multi-ethnic (more than 1).
[d] 5 sessions/week.
[e] 5 sessions/week for 3 weeks, then 1 session/week for 3 weeks.

Abbreviations: dTMS = deep transcranial magnetic stimulation HF = high frequency; HTA = health technology assessment; iTBS = intermittent theta-burst stimulation; LF = low frequency; N = number; RoB= risk of bias; rTMS = repetitive transcranial magnetic stimulation; TMS = transcranial magnetic stimulation; U.S. = United States.

3.6.2 Findings

Detailed findings are provided in ***Appendix C, Tables C-24*** and ***C-25***. A summary of findings and the SOE are provided in ***Table 16***. Most studies showed differences in remission, response, nicotine use, and relapse favoring the active TMS group, although most statistically significant results were for immediate posttreatment measurement time points only. Mixed results were observed for nicotine dependence and safety outcomes. This section provides detailed results for each category of outcome measure.

Table 16. Summary of Findings and SOE for TMS Compared to Sham Stimulation for Smoking Cessation

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Direct-ness	Study Limitations	Overall SOE/ Direction
Cessation of tobacco smoking (various time points)						
5 RCTs[79-83]/444	Various measures reported (quit on target quit date, continuous abstinence, continuous quit rate, self-reported or self-report verified with urine cotinine or exhaled CO) Three studies reported statistically significant differences favoring TMS immediately after treatment (range 1 to 6 weeks), but these results were only durable at subsequent time points in 1 study. Two studies reported abstinence measures favoring TMS, but differences were not statistically significant for any reported follow-up time points.	Consistent	Imprecise	Direct	High (1 low, 1 SC, 3 high RoB)	Low[a,b] Favor TMS
Decrease in smoking of at least 50% at 2 weeks						
1 RCT[80]/42	Statistically significantly higher in participants allocated to active TMS compared to sham TMS immediately posttreatment (adjusted OR, 10.0; 95% CI, 2.1 to 48.0).	Unknown (Single study)	Imprecise	Direct	High (1 high RoB)	Insufficient[a,b,d]
Nicotine use up to 1 month posttreatment						
2 RCTs[80,83]/ 304	Various measures reported (self-reported number of cigarettes smoked, biomarkers of exhaled CO, urine cotinine). Majority of participants from 1 RCT (n=262). Both studies reported lower number cigarettes smoked by participants in TMS group compared to sham. One study additionally reported lower CO and cotinine levels for TMS compared to sham group.	Consistent	Imprecise	Direct	High (1 low, 1 high RoB)	Low[a,b] Favor TMS

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Direct-ness	Study Limitations	Overall SOE/ Direction
Nicotine dependence (measured by the Fagerstrom Test of Nicotine Dependence) up to 3 months						
2 RCTs[80,83]/ 304	2 studies reported lower nicotine dependence in the TMS group at post-treatment, statistically significant in 1 small high RoB study and not significant in 1 large low RoB study, which also reported no difference in nicotine dependence posttreatment and at 3 month follow-up	Consistent	Imprecise	Direct	High (1 low, 1 high RoB)	Low[a,b] Favor TMS
Smoking relapse up to 3 months						
1 RCT[79]/29	Measures included risk of relapse (RR, 0.29; 95% CI, 0.10 to 0.76) for TMS compared to sham	Unknown (Single study)	Imprecise	Direct	Some (1 SC RoB)	Low[a,d] Favors TMS
Safety (any AEs) up to 3 months						
3 RCTs[79-81,83]/370	1 study reported no AEs in either group, 2 studies reported higher incidence of AEs in the active TMS group compared to sham, statistically significant for 1 study only.	Consistent	Imprecise	Direct	High (1 low, 1 SC, 2 high RoB)	Low[a,b] Favor sham
Safety (SAEs)						
2 RCTs[81,83]/ 299	One study reported no SAEs and 1 study reported only 1 SAE (tinnitus).	Consistent	Imprecise	Direct	High (1 low, 1 high RoB)	Insufficient[b,c]

Notes:
[a] Downgraded 1 level for imprecision.
[b] Downgraded 1 level for study limitations.
[c] Downgraded 2 levels for imprecision.
[d] Downgraded 1 level for single study body of evidence.

Abbreviations: AE = adverse event; CI = confidence interval; CO = carbon monoxide; OR = odds ratio; RCT = randomized controlled trial; RoB= risk of bias; RR = relative risk; rTMS = repetitive transcranial magnetic stimulation; serious adverse event; SC = some concerns, SOE = strength of evidence; TMS = transcranial magnetic stimulation.

Remission (Cessation of Smoking)

Five RCTs[79-83] reported on remission defined as self-reported abstinence with or without biomarker confirmation, quit on target date, or continuous quit rate (CQR). Three studies[81-83] reported increased remission in the TMS group immediately posttreatment ($P<0.05$), although these results remained durable at the 12-week and 18-week follow-ups for only 1 study[83] that reported relatively low CQR for both times points (18% and 19%, respectively). Remission measures for the remaining 2 studies also favored rTMS immediately posttreatment, although 1 study approached but did not achieve statistical significance[79] and 1 study showed statistically significance, although reported at the 90% CI.[80]

Response to Treatment (Decrease in smoking)

One RCT reported on response to treatment, defined as at least a 50% reduction in the number of cigarettes smoked.[80] Authors found that participants in the rTMS group were more likely to have a response to treatment (72%) than those in the sham group posttreatment (30%; adjusted OR, 10.0; 95% CI, 2.1 to 48.0). Response to treatment was not measured at follow-up time points.

Other Measures

Nicotine Use

Two RCTs[80,83] reported on nicotine use, measured by self-reported number of cigarettes smoked and biomarkers of exhaled carbon monoxide and urine cotinine. Both studies reported decreased number of cigarettes smoked in the rTMS group compared to the sham group, posttreatment ($P<0.05$). One study also reported 1-month follow-up measures of continued decreased cigarette consumption favoring the TMS group, as measured by number of cigarettes smoked ($P<0.001$) and lower urine cotinine levels ($P=0.024$) compared to sham.[80]

Nicotine Dependence

Two RCTs reported lower nicotine dependence using the Fagerstrom Test of Nicotine Dependence (FTND).[80,83] One small (n=42) study with high RoB found lower mean FTND scores at 1 month posttreatment in the active compared to sham TMS group, which was statistically significant. A larger (n=262) study with low RoB found larger improvements in FTND scores posttreatment (6 weeks) for participants allocated to rTMS; however, these were not statistically significant compared to sham rTMS at either 6 weeks' or 12 weeks' posttreatment.[83]

Smoking Relapse

One RCT reported on smoking relapse at 10 weeks' posttreatment.[79] Participants in the rTMS group were approximately a third less likely to relapse than those in the sham group (RR, 0.29; 95% CI, 0.10 to 0.76), and the median time to relapse was longer in the rTMS group compared to sham (36 days vs. 8 days).

Safety Measures

Four RCTs[79-81,83] reported on safety outcomes, although the specific outcomes reported varied. Two studies reported on SAEs; 1 study[81] found no SAEs in either group, while another study[83] reported 1 SAE (tinnitus) in the rTMS group only. Results were mixed for the 3 studies[80,81,83] reporting on any AEs: 1 study reported no AEs, 1 study reported no difference in any AEs between groups but did not report absolute numbers of events, and 1 study reported significantly more AEs in the rTMS group compared to sham (54% vs. 36%; $P=0.004$). Of those studies reporting specific AEs, the most frequently reported was headache. One study found the only significant difference between the TMS and sham groups was application site discomfort ($P=0.004$).[83]

3.7 Substance Use Disorder

We identified 6 parallel-assignment RCTs in 6 publications that focused on rTMS or deep TMS stimulation compared to sham stimulation for the treatment of alcohol use disorder (AUD) and cocaine use. The interventions varied in terms of protocol, number of sessions, duration over

which the sessions were provided, and timing of outcome measure follow-up. Key findings are as follows:

- Two RCTs reported on abstinence, 1 for AUD at 12 months' posttreatment[84] and 1 for cocaine use disorder at 3 months' posttreatment.[85] In the AUD study,[84] the difference in total number of abstinent days was statistically significant between rTMS and sham (*P*=0.004), but there was no difference in percentage abstinence (*P*=0.126). Findings were not statistically significant for differences between TMS and sham in the cocaine use disorder study, but the direction of effect favored TMS.[85] (SOE: Insufficient)

- Four RCTs reported on substance use based on results of urine or blood tests, 2 for AUD[86,87] and 2 for cocaine use disorder.[85,88] Both AUD studies showed no statistically significant differences between TMS and sham treatment, although 1 study favored TMS for percentage of positive urine ethyl glucuronide samples at 12 weeks' posttreatment (*P*=0.069, actual values NR).[86] The other AUD study showed no differences in biomarkers during treatment at weeks 1, 2, and 3 (*P*=0.6) and favored TMS posttreatment at 2, 4, 8, and 12 weeks' follow-up (*P*=0.8).[87] Differences in positive tests favored TMS in both cocaine use disorder studies but were not statistically significant (SOE: Low, favor TMS)

- Six RCTs reported on safety outcomes, 4 for alcohol use[84,86,87,89] and 2 for cocaine use.[85,88] Among the 3 studies that reported on SAEs,[84-86] no SAEs occurred. (SOE: Insufficient)

The rest of this section provides detailed study characteristics and results.

3.7.1 Study and Population Characteristics

The 6 trials were conducted between 2015 and 2020. We assessed 4 of these trials as having some risk of bias, primarily for missing outcomes data, deviations from intended interventions, and selective reporting of results,[86-89] and 2 studies as high risk of bias for high attrition, selective reporting of results, and absence of an ITT analysis.[84,85]

Two trials[84,89,138-141] were conducted in the Netherlands, 2 trials[85,88] in Italy, 1 trial[86] in Israel, and 1 trial[87] in Sweden. No trial reported receiving industry funding. ***Table 17*** summarizes the characteristics of included TMS trials; additional details are found in ***Appendix C***, ***Tables C-26, C-27,*** and ***C-28***.

Of the included studies, the study sample sizes ranged from 34 to 82 participants. The mean age of included populations ranged from 37 to 53.5 years. All studies included both male and female participants, and males comprised 65% or more of the study population. No study provided data about participant race. Three studies[84,85,89] reported on mental health comorbidities, including OCD, depression, PTSD, and other substance use. Two studies recruited participants with moderate to severe substance use disorder based on clinical diagnosis,[85,86] while others did not

indicate severity of disease. Only 1 studied specified that both treatment-naive and treatment-resistant participants were eligible,[84,85] while the others did not specify treatment history.

The active intervention was rTMS in 4 RCTs[84,85,88,89] and deep TMS in 2 RCTs;[86,87] there was variation in the TMS protocol used across the 6 studies. Two studies on persons with AUD were conducted using rTMS of the RDLPFC,[84,89] and 2 studies on cocaine use disorder were conducted using rTMS of the LDLPFC.[85,88] Two studies on AUD were conducted with deep TMS, 1 of the insular cortex and overlaying regions[87] and 1 of the midline frontocortical areas (ACC and medial prefrontal cortex).[86] Studies also varied in the number of pulses administered during a single session (range 60 to 3,000) and in the stimulation intensity used (range 100 to 120% MT). Three studies[86-88] provided active or sham treatment over 15 days (1 session/day), 2 studies[84,89] provided treatment over 10 days (1 session/day), and 1 study[85] provided 44 treatment sessions over 34 days. Duration of follow-up ranged from 2 weeks to 12 months. Five of the 6 studies included co-interventions: 4 studies, including both cocaine use studies, used medication and psychotherapy per treatment as usual,[84,85,88,89] and 1 study used medication per treatment as usual.[87] Three studies included an exposure before treatment: 2 AUD studies[86,87] had participants hold and smell alcoholic beverages, and 1 cocaine use study[85] had participants view a video containing cocaine-related images. The studies included a variety of sham TMS controls.

Table 17. Summary of Study Characteristics of Included Studies of TMS for Treatment of SUD

Author, Year Country RoB	Intervention and Comparator (N Randomized) Condition	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions; Exposure Therapy (Y/N)	Mean Age (SD)	N (%) Female	N (%) Race-Ethnicity
Belgers (2022)[84] Netherlands High	HF-rTMS (16) Sham TMS (18) Alcohol use disorder	34	10 days;[b] 12 months	Medication and psychotherapy per treatment as usual; No	47.4 (8.9)	2 (6)	NR
Harel (2021)[86] Israel Some concerns	Deep TMS (27) Sham TMS (24) Alcohol use disorder	51	15 days;[b] 12 weeks	None; Yes	TMS: 43.7 (8.7) Sham: 42.5 (9.8)	TMS: 8 (35) Sham: 8 (35)	NR
Lolli (2021)[88] Italy Some concerns	HF-rTMS (32) Sham TMS (30) Stimulant use (cocaine)	62	15 days;[b] 8 weeks	Medication and psychotherapy per treatment as usual; No	40.7 (9)	11 (18)	NR
Martinotti (2022)[85] Italy High	HF-rTMS (42) Sham TMS (33) Stimulant use (cocaine)	75	34 days;[c] 12 weeks	Medication and psychotherapy per treatment as usual; No	37 (7.4)	9 (12)	NR
Perini (2020)[87] Sweden Some concerns	Deep TMS (29) Sham TMS (27) Alcohol use disorder	56	15 days;[b] 12 weeks	Medication per treatment as usual; Yes	TMS: 50.6 (10.4) Sham: 53.5 (7.5)	TMS: 4 (17) Sham: 4 (18)	NR

Author, Year Country RoB	Intervention and Comparator (N Randomized) Condition	Total Sample Size	Treatment Duration; Last Follow-Up[a]	Co-interventions; Exposure Therapy (Y/N)	Mean Age (SD)	N (%) Female	N (%) Race-Ethnicity
Schluter, 2019[89] Netherlands Some concerns	HF-rTMS (41) Sham TMS (41) Alcohol use disorder	82	10 days;[b] 2 weeks	Medication and psychotherapy per treatment as usual; No	TMS: 44.95 (10.03) Sham: 43.75 (11.41)	TMS: 11 (28) Sham: 9 (23)	NR

Notes: [a] "Last follow-up" indicates last follow-up time point eligible for this HTA (e.g., blinded phase eligible only of a multiphase study with open-label phases). A study may have reported outcomes at follow-up time points that were subsequent to what is reported in this column though were not eligible for review (e.g., open-label phase).
[b] 1 session/day. [c] Active phase: 2 sessions/day, 5 days/week, 2 weeks; maintenance phase: 1 session/day, 2 day/week, 12 weeks.

Abbreviations: HF = high frequency; HTA = health technology assessment; NR = not reported; RoB= risk of bias; SD = standard deviation; SUD = substance use disorder; TMS = transcranial magnetic stimulation.

3.7.2 Findings

Detailed findings are provided in ***Appendix C, Tables C-29*** and ***C-30***. A summary of findings and the strength of evidence are provided in ***Table 18***. Studies did not show statically significant results for abstinence, substance use as measured by urine or blood tests, or relapse. There were mixed findings for self-reported substance use. No SAEs were reported, although safety outcome data were limited. This section provides detailed results for each category of outcome measure.

Table 18. Summary of Findings and SOE for TMS Compared to Sham Stimulation for SUD

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall SOE/ Direction
Abstinence up to 12 months' posttreatment						
2 RCTs[84,85]/114	One study in AUD showed statistically significant difference in total number of abstinent days favoring TMS but not in percentage abstinent; 1 study in cocaine use disorder showed no significant differences but direction favored TMS.	Consistent	Imprecise	Direct	High (2 high RoB)	Insufficient[a,b]
Substance use up to 12 months' posttreatment						
5 RCTs[84-88]/283	Various measures reported (self-reported days of use and heavy drinking days, biomarkers in urine or blood). Three studies reported statistically significant differences in substance use favoring TMS at 8 weeks', 12 weeks', and 12 months' posttreatment. Two studies reported no differences in substance use during TMS treatment and through 12 weeks' posttreatment.	Consistent	Imprecise	Direct	High (3 SC, 2 high RoB)	Low[b,c] Favor TMS
Relapse at 12 months' posttreatment						
1 RCT[84]/34	1 study on AUD reported mean days to relapse favoring TMS but differences were not statistically significant.	Unknown (Single study)	Imprecise	Direct	High (1 high RoB)	Insufficient[b,c,d]
Safety (Total AEs)						
6 RCTs[84-89]	Studies did not report total AEs by group. Specific harms reported included headache and discomfort at the stimulation site and were present in both groups.	NA	NA	NA	NA	NA
Safety (SAEs)						
3 RCTs[84-86]/165	Three studies reported no SAEs in any groups.	Consistent	Imprecise	Direct	High (1 SC, 2 high RoB)	Insufficient[a,b]

Notes: [a] Downgraded 2 levels for imprecision.
[b] Downgraded 1 level for study limitations.
[c] Downgraded 1 level for imprecision.
[d] Downgraded 1 level for single study body of evidence.

Abbreviations: AE = adverse event; AUD = alcohol use disorder; NA = not applicable; RCT = randomized controlled trial; RoB = risk of bias; SAE = serious adverse events; SC = some concerns; SOE = strength of evidence; SUD = substance use disorder; TMS = transcranial magnetic stimulation.

Abstinence

Two RCTs reported on abstinence, 1 for AUD[84] and 1 for cocaine use disorder.[85] In the AUD study,[84] total number of abstinent days and percentage abstinence were measured at the 12 months' follow-up. Difference in total number of abstinent days was statistically significant between rTMS and sham (70.07 for TMS vs. 29.63 for sham, *P*=0.00), while there was no difference in percentage abstinence (14% vs. 0.0%, *P*=0.126). In the cocaine use disorder study,[85] TMS was favored but the results were not statistically significant for the end of TMS treatment for longest period of cocaine abstinence (in days) (60.1 vs. 52.9) and 3-month follow-up (73.3 vs. 55.2) (test for trend *P*=0.09).

Response to Treatment

No studies reported on response to treatment for SUD.

Other Measures

Substance Use: Urine or Blood Tests

Four RCTs[85-88] reported on substance use measured by urine or blood drug tests. There were no significant differences between groups.

In 2 AUD studies,[86,87] authors measured biomarkers of use (ethyl glucuronide in urine or phosphatidylethanol in blood). Both studies showed no statistically significant differences between TMS and sham treatment, although 1 study favored TMS for percentage of positive urine ethyl glucuronide samples at 12 week's posttreatment (*P*=0.069, actual values NR).[86] The other AUD study showed no differences in biomarkers during treatment at weeks 1, 2, and 3 (P=0.6) and favored TMS posttreatment at 2, 4, 8, and 12 weeks' follow-up (*P*=0.8).[87]

Authors of 1 cocaine use disorder study reported urine negativity (2 consecutive negative drug urine tests) and average time to negativization of urine drug screen at 8 weeks' posttreatment.[88] Ten rTMS patients (33%) tested negative for cocaine in urine as compared to 4 (14%) sham patients (OR, 2.88;95% CI 0.9 to 10; *P*=0.18). Average time to negativization or urine drug screen was 61 days (95% CI, 40 to 83) in rTMS patients and 90 days (95% CI, 69 to 112) in sham patients (*P*=0.20). Another cocaine use disorder study[85] reported the proportion of positive urine testing; differences between TMS and sham treatment favored TMS but were not statistically significant different at end of intensive TMS treatment (*P*=0.6) or end of all TMS treatment (*P*=0.4).

Substance Use: Self-reported Use

Five RCTs (3 for AUD[84,86,87] and 2 for cocaine use disorder[85,88]) reported findings for self-reported substance use.

Among AUD studies, 2 RCTs[84,86] found statistically significant improvements in self-reported alcohol use at 12 weeks' and 12 months' posttreatment. At 12 weeks' posttreatment, 1 study[86] showed that the percentage of heavy drinking days (HDD) was lower in the TMS group

compared to sham (2.9 vs. 10.6; *P*=0.037), and the mean difference in weekly alcohol consumption was statistically significant favoring TMS (*P*=0.02). In the other study,[84] similar results were found at 12 months' posttreatment: total number of HDD and alcohol use per day in mg were lower in the TMS group compared to sham (25.36 vs. 47.25; *P*=0.018 and 31.27 vs. 57.94; *P*=0.03, respectively). In the third AUD study,[87] no significant differences in self-reported alcohol use were reported during treatment (*P*>0.4) or at 2, 4, 8, or 12 weeks' posttreatment (*P*>0.4).

Among cocaine use disorder studies, the percentage of days of cocaine use was lower in the treatment group (35%) compared to the sham group (52%) at 8 weeks' posttreatment (OR, 3.4; 95% CI, 1.1 to 10, *P*<0.03) in 1 study.[88] In the other study,[85] no statistically significant differences were found between treatment and sham in days of cocaine use per week at the end of the intensive TMS treatment (0.3 vs. 0.3; *P*=0.8), end of all TMS treatment (0.1 vs. 0.1; *P*=0.9), or at 3 months' posttreatment (0.3 vs. 0.1; *P*=0.6).

Relapse

One RCT on AUD reported time to relapse at 12 months' posttreatment.[84] Participants in the rTMS group had a mean 256.4 days to relapse compared to 115.1 days in the sham group; this difference favored the active treatment but did not reach the level of statistical significance (*P*=0.010).

Safety Measures

Six RCTs[84-89] reported on safety outcomes. Four of these studies were on use for AUD[84,86,87,89] and 2 were on use for cocaine use disorder.[85,88] There were no SAEs among the 3 studies that reported on SAEs.[84-86] Of the studies on alcohol use, one[84] reported that some participants experienced the treatment as uncomfortable due to muscle twitches around the eye, and 2 others reported no difference in moderate to severe headache after the TMS session[87] and at 12 weeks' post treatment.[86] The fourth AUD study[89] reported greater incidence of headache after stimulation in the sham TMS group (1.9% vs. 4.6%, *P*=0.034) and greater incidence of an unpleasant sensation at the stimulation site in the TMS group (2.4% vs. 0.6%, *P*=0.036). It also reported no differences between groups in pain, beep in ear, or tiredness after stimulation. One cocaine use disorder study[85] reported specific AEs, the most common of which were headache and mood alterations: a similar number of participants experienced these events in both the TMS and sham groups. The other cocaine use disorder study[88] reported a minor treatment-related adverse event, mild and transient paresthesia in a single patient undergoing 1 sham treatment session.

Special Populations

One study on cocaine use disorder[85] reported a statistically significant difference favoring TMS for days of cocaine use (*P*<0.05) among the subgroup of participants with higher depression levels (MADRS score >20). This study found no other correlations between demographic or clinical variables and treatment outcomes.

4. Discussion

4.1 Summary of the Evidence

The SOE ratings for the effectiveness of TMS for the conditions included in this HTA ranged from insufficient to high. A summary of the SOE ratings is provided in ***Table 19***; detailed ratings are provided in the respective report sections for each condition.

Table 19. Summary of SOE Ratings for TMS for Indications Included in This HTA

Condition	Outcome	No. Studies (No. Participants)	Strength of Evidence[a]	Direction
GAD	Remission	2 RCTs (76)	●○○○	Unable to determine
	Response	2 RCTs (76)	●○○○	Unable to determine
	Symptom severity	2 RCTs (76)	●●○○	Favor TMS
	Any SAEs	2 RCTs (76)	●○○○	Unable to determine
OCD	Response	7 RCTs (281)	●●○○	Favor TMS
	Symptom severity	9 RCTs (337)	●●○○	Favor TMS
	Any AEs	8 RCTs (315)	●●○○	No difference
	Any SAEs	8 RCTs (315)	●●○○	No difference
	Cost-effectiveness	1 DA (NA)	●○○○	NA
MDD	Remission (rTMS)	15 RCTs (1,469)	●●●●	Favor TMS
	Remission (TBS)	3 RCTs (197)	●●●○	Favor TMS
	Remission (dTMS)	2 RCTs (269)	●●○○	Favors TMS
	Response (rTMS)	20 RCTs (1,386)	●●●●	Favor TMS
	Response (TBS)	5 RCTs (259)	●●●○	Favor TMS
	Response (dTMS)	2 RCTs (264)	●●○○	Favor TMS
	Symptom severity	36 RTCs (2,615)	●●●○	Favor TMS
	Any AEs	8 RCTs (594)	●●○○	Favor sham
	Any SAEs	14 RCTs (1,266)	●●○○	No difference
	Cost-effectiveness	2 DAs (NA)	●●○○	NA
PTSD	Remission	1 RCT (134)	●○○○	Unable to determine
	Response	1 RCT (134)	●○○○	Unable to determine
	Symptom severity	4 RCTs (307)	●●○○	Favor TMS
	Any AEs	1 RCT (134)	●●○○	No difference
	Any SAEs	3 RCTs (287)	●○○○	Unable to determine
Smoking cessation	Remission (smoking cessation)	5 RCTs (444)	●●○○	Favor TMS
	Response	1 RCT (42)	●○○○	Unable to determine
	Symptom severity (nicotine use)	2 RCTs (304)	●●○○	Favor TMS
	Any AEs	3 RCTs (370)	●●○○	Favor sham
	Any SAEs	2 RCTs (299)	●○○○	Unable to determine
Substance abuse	Remission (abstinence)	2 RCTs (114)	●○○○	Unable to determine
	Symptom severity (substance use)	5 RCTs (283)	●●○○	Favor TMS
	Any SAEs	3 RCTs (165)	●○○○	Unable to determine

Notes: [a] SOE ratings: ●○○○ Insufficient, ●●○○ Low, ●●●○ Moderate, ●●●● High

Abbreviations: AE = adverse event; DA = decision analysis; dTMS = deep TMS; GAD = generalized anxiety disorder; MDD = major depressive disorder; NA = not applicable; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SAE = serious adverse event; SOE = strength of evidence; TBS = theta-burst stimulation TMS; TMS = transcranial magnetic stimulation.

The largest body of evidence was for MDD, and nearly all of these studies enrolled patients with moderate to severe depression with treatment resistant to medications. Although many trials

enrolled small numbers of participants, our pooled results for remission, response, and change in severity of symptoms suggested high SOE for benefit of TMS by the end of a course of treatment. In the 1 study of individuals who were specifically naïve to treatment,[46] TMS had greater magnitude of benefit for measures of remission, response, and reduction of disease severity compared to the pooled estimate, though CIs were very wide for all estimates, precluding conclusions about the benefit of TMS is non-treatment-resistant populations. The 3 RCTs examining accelerated protocols suggested that more than 1 treatment a day may be associated with more favorable results, although study samples were small and effect estimates imprecise. We also found few studies examining special populations such as children, elderly persons, or pregnant persons or subgroups based on sex or race/ethnicity.

The remaining conditions had much smaller evidence bases, ranging from 2 to 9 studies each and with SOE ratings of low or insufficient for all outcomes we evaluated. Compared to the studies evaluating MDD, studies evaluating other conditions were more varied with respect to TMS protocol used, including brain location target, numbers of sessions per treatment course, numbers of pulses per session, durations of treatment, types of TMS used, and co-treatments.

Evidence was also limited with respect to longer term follow-up across all conditions. The durability of TMS benefits was mixed among the handful of studies reporting at time points beyond the end of a course of treatment, which ranged from 2 to 24 weeks posttreatment. For each condition, we found only 1 to 2 studies with follow-up of 3 months or longer. In general results were durable at 3 months for this handful of studies with respect to remission, response, or reduction in symptom severity for GAD,[25] OCD,[32] MDD,[52,67] and SUD.[84,86] One study of smoking cessation found abstinence rates were durable at 18 weeks, though absolute rates of remission were < 20%.[83] Only 2 RCTs evaluated outcomes at 20 weeks and 24 weeks; these studies examined changes in symptom severity in MDD and found results were durable for 1 study,[52] and statistical testing was not reported for the other study.[67]

For each condition, harms were graded as low (no difference or favor sham) or insufficient, often because of imprecision or study limitations related to deficiencies in how harms were ascertained and reported, which was highly variable within and across conditions, limiting our ability to pool these data. We have no biologic reason to believe that harms from TMS would be condition specific, and at this time, we interpret the evidence as suggesting a low risk of AEs or SAEs for TMS as a procedure. More robust and systematic ascertainment of harms in future studies would facilitate pooling across conditions and would likely increase the SOE ratings that could be assigned to harm outcomes.

Depression findings are largely consistent with findings from other systematic reviews of TMS for the treatment of depression. An HTA authored by Ontario Health found similar remission and response benefits, and another systematic review observed a similar safety profile for TMS.[90,91] Systematic reviews of TMS for GAD, OCD, and PTSD have generally found greater benefit in symptom severity from baseline than our HTA; however, these reviews often included study designs that were ineligible for this HTA, including comparative effectiveness research, open-label studies, uncontrolled studies, or sample sizes fewer than 10 per study arm.[49,92,93] Systematic

reviews of substance abuse often included only TMS among other nonpharmacologic treatments or reported on intermediate outcome of craving as the primary outcome.[94,95]

4.2 Limitations of the Evidence Base

This HTA included many RCTs with high risk of bias and studies with small sample sizes, resulting in imprecise effect estimates, particularly for nondepression indications for TMS. The trials included in this HTA infrequently reported on race or ethnicity, and further understanding of how TMS performs in populations defined by race or ethnicity is unavailable. Similarly, a minority of studies reported on variation in treatment effect by other psychiatric comorbidities, and few studies performed subgroup analyses for comorbid conditions that commonly present in patients (e.g., GAD and MDD). For nondepression indications, there was a broader range of protocols for TMS, including several different brain targets, suggesting that further research into the neural networks underlying these diseases is needed to determine optimal treatment parameters. For studies of participants with tobacco use disorder and SUD, disease severity was defined in variables ways, and prior treatment trials were rarely documented. Measuring and reporting these population characteristics will clarify which individuals may gain greater benefits from this treatment. Finally, a limited number of studies reported outcomes at a follow-up time point beyond a few weeks after the end of treatment. Understanding of the durability of TMS therapy would help guide clinical decision making on the use of this therapy.

4.3 Clinical Practice Guidelines

Clinical practice guidelines and recommendations for the use of TMS for selected behavioral disorders are found in ***Tables 20, 21,*** and ***22***. We rated the quality of each guideline using the Appraisal of Guidelines for Research & Evaluation II (AGREE-II) instrument.[142,143] With this instrument 6 domains are assessed and an overall score of 1 (lowest quality) to 7 (best quality) is assigned. In addition to the interventions included within the scope of the HTA, some of the guidelines we identified also included interventions outside of the scope of this HTA, notably medications, herbal supplements, and invasive treatments. Our summary focuses only on TMS interventions.

The largest number of guidelines with recommendations for the use of TMS was for depression (***Table 20***), although these guidelines ranged from general to specific about when and how to use TMS for treatment. Canadian guidelines offered the most detailed recommendations for TMS protocols for depression,[144] while others made more general statements about safety and possible uses.

Table 20. Clinical Practice Guidelines including Recommendations on the Use of TMS: Depression

Title	Year	AGREE Rating	Summary of Treatment Recommendation(s)
Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) (European Expert Panel)[145,b]	2020	5	Definite antidepressant efficacy of deep HF-rTMS over the left DLPFC in major depression. (Level A[b]) Probable antidepressant efficacy of: LF-rTMS of the right DLPFC in major depression; bilateral right-sided LF-rTMS and left-sided HF-rTMS of the DLPFC in major depression (Level B[b]); and bilateral right-sided cTBS and left-sided iTBS of the DLPFC in major unipolar depression, while unilateral right-sided cTBS is possibly ineffective. (Level C[b]) Possibly no differential antidepressant efficacy between right LF-rTMS and left HF-rTMS, bilateral and unilateral rTMS of the DLPFC, and rTMS performed alone and combined with antidepressants. (Level C[b])
Clinical guidelines for the management of treatment-resistant depression French Recommendations from experts, the French Association for Biological Psychiatry and Neuropsychopharmacology and the foundation FondaMental[146]	2019	4	TMS is never recommended as a first-line treatment for initial major depressive episode, irrespective of the clinical severity or clinical features. Brain stimulation techniques should be reserved for situations of treatment resistance and recommended only from the fourth line of treatment (after the failure of 3 adequately conducted antidepressant therapies).
National Network of Depression Centers rTMS Task Group and the American Psychiatric Association Council on Research Task Force on Novel Biomarkers and Treatments Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation in the Treatment of Depression[147]	2018	5	The expert opinion is that rTMS is appropriate as a treatment in patients with MDD even if the patient is medication resistant or has significant comorbid anxiety. However, patients who have comorbid psychotic symptoms or acute suicidal ideation should be considered for other antidepressant treatments with established efficacy such as electroconvulsive therapy. There is insufficient evidence to support routine clinical rTMS use in children, adolescents, and pregnant women. At this time, there is no one recommended maintenance antidepressant strategy for patients after beneficial rTMS acute course. Further research is needed to systematically develop evidenced-based antidepressant maintenance strategies following acute clinical benefits with rTMS.
Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder[144]	2016	5	rTMS is a first-line recommendation for patients with MDD who have failed at least 1 antidepressant (Level 1[a] Evidence for Acute Efficacy, Safety and Tolerability; Level 3[a] Evidence for Maintenance Efficacy). Summary of treatment parameters for rTMS: • Intensity, frequency, and site • Stimulate at 110%–120% of resting motor threshold (70%–80% for theta-burst stimulation) (Level 1[a]) • Select stimulation frequency and site: High frequency rTMS to left DLPFC or low frequency rTMS to right DLPFC (first-line, Level 1[a]) Treatment course ▪ Perform stimulation 5 times weekly (Level 1[a]) ▪ Deliver initial course until symptom remission is achieved, up to 20 sessions (Level 1[a]) ▪ Extend course to 30 sessions (6 weeks) in responders who have not achieved symptom remission (Level 3[a]) Maintenance course: Use rTMS as needed to maintain response (Level 3[a])

Title	Year	AGREE Rating	Summary of Treatment Recommendation(s)
National Institute of Health and Care Excellence (NICE) Repetitive transcranial magnetic stimulation for depression[148]	2015	6	1.1 The evidence on repetitive TMS for depression shows no major safety concerns. The evidence on its efficacy in the short term is adequate, although the clinical response is variable. Repetitive transcranial magnetic stimulation for depression may be used with normal arrangements for clinical governance and audit. 1.2 During the consent process, clinicians should, in particular, inform patients about the other treatment options available and make sure that patients understand the possibility the procedure may not give them benefit.

Notes: [a] Level 1 evidence: Meta-analysis with narrow CI or 2 or more RCTs with adequate sample size, preferably placebo controlled. Level 3 evidence: Small-sample RCTs or nonrandomized, controlled prospective studies or case series or high-quality retrospective studies.
[b] Level of evidence:
A: (''definitely effective or ineffective") required at least 2 Class I studies or 1 Class I study and at least 2 Class II studies.
B: (''probably effective or ineffective") required at least 2 Class II studies or the combination of 1 Class I or II study and at least 2 Class III studies.
C: (''possibly effective or ineffective") required at least 2 Class III studies or any combination of 2 studies of different Classes I, II or III: Class I study: randomized, sham-controlled clinical trial including 25 or more patients receiving real stimulation therapy with clearly reported primary outcome, exclusion/inclusion criteria, randomization/blinding procedure, and statistical analyses, and taking into account study bias. Class II: randomized, placebo-controlled trial of between 10 and 25 patients receiving real stimulation therapy with the same high levels of methodological quality as a Class I study or a study with a larger sample but not filling all the aforementioned criteria of high methodological quality. Class III: all other controlled trials with lower methodological quality, but only studies with at least 10 patients receiving real stimulation therapy were taken into account in making these recommendations. Class IV studies: uncontrolled studies or case series.

Abbreviations: AGREE = Appraisal of Guidelines for Research & Evaluation II instrument; CI = confidence interval; cTBS = controlled theta-burst stimulation; DLPFC = dorsal lateral prefrontal cortex; HF = high frequency; iTBS LF = low frequency; MDD = major depressive disorder; RCT = randomized controlled trials; rTMS = repetitive transcranial magnetic stimulation; TMS = transcranial magnetic stimulation.

Guidelines for OCD made similar general statements, and few guidelines were found for GAD, PTSD, and SUD (***Table 21*** and ***Table 22***). Smoking cessation guidelines or recommendations from the American Heart Association, American College of Cardiology, American Association of Chest Physicians, the American Thoracic Society, and the U.S. Preventive Services Task Force were reviewed, and none included TMS in treatment recommendations. Likewise, the American Society of Addiction Medicine did not include TMS in its 2020 National Practice Guideline Update.[149]

Table 21. Clinical Practice Guidelines Including Recommendations on the Use of TMS: OCD

Title	Year	AGREE Rating	Summary of Treatment Recommendation(s)
National Institute of Health and Care Excellence (NICE): Repetitive transcranial magnetic stimulation for obsessive-compulsive disorder[150]	2020	6	1.1 Evidence on the safety of TMS for OCD raises no major safety concerns. However, evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. 1.2 Research should ideally be in the form of preregistered, adequately powered, RCTs. It should report details of patient selection, including the use of concurrent therapies, type, duration and frequency of stimulation, and the intended target in the brain. Outcomes should include improvement in symptoms, quality of life, and duration of effect.
Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) (European Expert Panel)[145]	2020	5	Possible efficacy of LF-rTMS of the right DLPFC in OCD. (Level C[b])
Canadian Clinical Practice Guideline for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders[151]	2014	4	Biological therapies may be useful in patients with OCD who have not responded to CBT and multiple medication trials. Open trials have suggested that rTMS may be a promising adjunctive therapy in patients with treatment-refractory OCD. However, results of sham-controlled trials are conflicting: some trials found significant improvements and others concluded that rTMS was ineffective for treatment-resistant OCD. (Level 1[c], conflicting)

Notes: [a] Criteria for treatment-refractory OCD in adults: 3 adequate SSRI trials and at least 2 of the following medications for at least 1 month: antipsychotic, clonazepam, lithium, buspirone and adequate CBT with at least 20 sessions of exposure and response prevention therapy.
[b] Level of evidence:
A: (‘‘definitely effective or ineffective”) required at least 2 Class I studies or 1 Class I study and at least 2 Class II studies.
B: (‘‘probably effective or ineffective”) required at least 2 Class II studies or the combination of 1 Class I or II study and at least 2 Class III studies.
C: (‘‘possibly effective or ineffective”) required at least 2 Class III studies or any combination of 2 studies of different Classes I, II or III: Class I study: randomized, sham-controlled clinical trial including 25 or more patients receiving real stimulation therapy with clearly reported primary outcome, exclusion/inclusion criteria, randomization/blinding procedure, and statistical analyses, and taking into account study bias. Class II: randomized, placebo-controlled trial of between 10 and 25 patients receiving real stimulation therapy with the same high levels of methodological quality as a Class I study or a study with a larger sample but not filling all the aforementioned criteria of high methodological quality. Class III: all other controlled trials with lower methodological quality, but only studies with at least 10 patients receiving real stimulation therapy were taken into account in making these recommendations. Class IV studies: uncontrolled studies or case series.
[c] Level 1 evidence: Meta-analysis or at least 2 RCTs that included a placebo condition.

Abbreviations: AGREE = Appraisal of Guidelines for Research & Evaluation II instrument; CBT = cognitive behavioral therapy; DLPFC = dorsal lateral prefrontal cortex; LF = low frequency; OCD = obsessive-compulsive disorder; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SSRI = selective serotonin reuptake inhibitor; TMS = transcranial magnetic stimulation; U.S. = United States; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Table 22. Clinical Practice Guidelines Including Recommendations on the Use of TMS: GAD, PTSD, and SUD

Title	Condition	Year	AGREE Rating	Summary of Treatment Recommendation(s)
Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) (European Expert Panel)[145,a]	GAD	2020	5	Because of the absence of sufficient data, no recommendations could be made for the use of rTMS protocols to treat GAD, given the heterogeneity in targets and stimulation frequencies.
	PTSD			Probable efficacy of HF-rTMS of the right DLPFC in PTSD. (Level B[b])
	SUD			Possible efficacy of HF-rTMS of the left DLPFC on cigarette craving and consumption. (Level C[b])
Canadian Clinical Practice Guideline for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders[151]	GAD	2014	4	Biologic therapies, including rTMS, may be useful for some patients; however, more data are needed. In a small open trial, rTMS was effective as monotherapy or as an adjunct to SSRIs in patients with GAD, and improvements were largely maintained 6 months after treatment. (Level 3[b])

[a] Level of evidence:
A: (''definitely effective or ineffective") required at least 2 Class I studies or 1 Class I study and at least 2 Class II studies
B: (''probably effective or ineffective") required at least 2 Class II studies or the combination of 1 Class I or II study and at least 2 Class III studies.
C: (''possibly effective or ineffective") required at least 2 Class III studies or any combination of 2 studies of different Classes I, II or III: Class I study: randomized, sham-controlled clinical trial including 25 or more patients receiving real stimulation therapy with clearly reported primary outcome, exclusion/inclusion criteria, randomization/blinding procedure, and statistical analyses, and taking into account study bias. Class II: randomized, placebo-controlled trial of between 10 and 25 patients receiving real stimulation therapy with the same high levels of methodological quality as a Class I study or a study with a larger sample but not filling all the aforementioned criteria of high methodological quality. Class III: all other controlled trials with lower methodological quality, but only studies with at least 10 patients receiving real stimulation therapy were taken into account in making these recommendations. Class IV studies: uncontrolled studies or case series.
[b] Level 3 evidence: Uncontrolled trial with at least 10 subjects

Abbreviations: AGREE = Appraisal of Guidelines for Research & Evaluation II instrument; DLPFC = dorsal lateral prefrontal cortex; GAD = generalized anxiety disorder; HF = high frequency; PTSD = posttraumatic stress disorder; rTMS = repetitive transcranial magnetic stimulation; SSRI = serotonin selective reuptake inhibitor; SUD = substance abuse disorder; TMS = transcranial magnetic stimulation.

4.4 Selected Payer Coverage Policies

No Medicare national coverage determination for TMS exists, but we did identify local coverage determinations for some Medicare contractors. We also conducted a scan of commercial payor coverage documents for TMS (***Table 23***). Two payors cover TMS for OCD, and all payors cover TMS for depression; however, clinical criteria for coverage varies (***Table 24***). Coverage policies often required multiple criteria, most commonly 2 to 4 medication trials from at least 2 classes or adjunctive treatment with psychotherapy, additional medications, or both. Inability to tolerate ECT and prior favorable clinical response to TMS were also indications for TMS for some payors.

Table 23. Select Overview of Payer Coverage Policies for TMS

Condition	Medicare[152]	Cigna[153]	Kaiser Permanente[154,155]	Premera Blue Cross[156]	Regence BlueShield[157]	UnitedHealth[158]
Depression	LCD only (no NCD)	✓	✓	✓	✓	✓
OCD	X	✓	X	✓	X	X
Smoking cessation	X	X	X	X	X	X
PTSD	X	X	X	X	X	X
GAD	X	X	X	X	X	X
Substance abuse	X	X	X	X	X	X

Notes: ✓ = covered; X = not covered; — = no policy identified.

Abbreviations: GAD = generalized anxiety disorder; LCD = local coverage determinations through Medicare contractors; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; TMS = transcranial magnetic stimulation.

Table 24. TMS Coverage Policy for Selected Commercial Payers

Payer (Effective Date)	Coverage Policy
Cigna[153] (9/15/2022)	**MDD:** An initial regimen (i.e., 30-36 treatments) of transcranial magnetic stimulation administered in an outpatient office setting using an FDA-approved device is considered medically necessary for MDD when an individual meets ALL of the following criteria: (1) Age 18 or older (2) Diagnosis of MDD (unipolar), moderate to severe, single or recurrent episode or acute relapse, without psychosis, as defined by the most recent edition of DSM (3) During the current episode of depression all of the following criteria are met: • Failure of 2 or more t**rials of antidepressant medications from 2 separate classes. Failed trial defined as either use of an antidepressant medication at adequate therapeutic doses for at least 4 weeks with no significant reduction in depressive symptoms OR use of an antidepressant medication with documented intolerance/medical contraindication** • **An adequate trial of an evidence-based psychotherapy known to be effective in the treatment of MDD, without significant improvement in depressive symptoms** • **Validated depression monitoring scales are administered at the beginning and at the end of the initial and each subsequent course of TMS** Repeat transcranial magnetic stimulation (TMS) (i.e., 30-36 treatments) administered in an outpatient office setting for a recurrence or an acute relapse of MDD is considered medically necessary when ALL of the following criteria are met: (1) All of the above criteria for initial TMS therapy were met prior to the initial course of TMS (2) Individual had more than a 50% improvement as evidenced by 1 or more standard rating scales for depression (3) Improvement has been maintained for at least 2 months after initial course of TMS

Payer (Effective Date)	Coverage Policy
Cigna[153] (9/15/2022) (continued)	**OCD:** An initial regimen (i.e., 30-36 treatments) of TMS administered in an outpatient office setting using an FDA-approved device for OCD is considered medically necessary for OCD when an individual meets ALL of the following criteria: (1) Age 18 or older (2) Diagnosis of OCD as defined by the most recent edition of DSM (3) Failure of 2 or more trials of psychopharmacologic medications for the treatment of OCD. A failed trial is defined as either use of a psychopharmacologic medication at adequate therapeutic doses for at least 8 weeks with no significant reduction in OCD symptoms OR use of a psychopharmacologic medication with documented intolerance/medical contraindication (4) An adequate trial of an evidence-based psychotherapy known to be effective in the treatment of OCD without significant improvement in OCD symptoms Repeat TMS (i.e., 30-36 treatments) administered in an outpatient office setting for a recurrence or an acute relapse of OCD is considered medically necessary when ALL of the following criteria are met: (1) All of the above criteria for initial TMS therapy were met prior to the initial course of TMS (2) Individual had more than a 30% improvement as evidenced by Y-BOCS (3) Improvement has been maintained for at least 2 months after initial course of TMS
Kaiser Permanente[154] (3/3/2022)	**Treatment-resistant depression:** Following criteria in the Milliman Care Guidelines. Unable to access specific criteria, as their care guidelines are proprietary. **Other diagnoses:** Require Medical Director review
Medicare LCD (L34641)[152]	**MDD** TMS may be covered if prescribed and administered by a licensed physician who is knowledgeable in the use of repetitive transcranial magnetic stimulation. Outpatient rTMS may be indicated for patients with DSM-IV defined Major Depressive Disorder who have failed to benefit from initial treatment of their depression. Initial Treatment Left Prefrontal rTMS of the brain is considered medically necessary for use in an adult who has a confirmed diagnosis of severe major depressive disorder (MDD) single or recurrent episode; and One or more of the following: • Resistance to treatment with psychopharmacologic agents as evidenced by a lack of a clinically significant response to 1 trial of psychopharmacologic agents in the current depressive episode from at least 2 different agent classes. Each agent in the treatment trial must have been administered at an adequate course of mono- or poly-drug therapy; or • Inability to tolerate psychopharmacologic agents as evidenced by 2 trials of psychopharmacologic agents from at least 2 different agent classes, with distinct side effects; or • History of response to rTMS in a previous depressive episode; or • If patient is currently receiving electro-convulsive therapy, rTMS may be considered reasonable and necessary as a less invasive treatment option. AND A trial of an evidence-based psychotherapy known to be effective in the treatment of MDD of an adequate frequency and duration without significant improvement in depressive symptoms as documented by standardized rating scales that reliably measure depressive symptoms. AND The order for treatment (or retreatment) is written by a psychiatrist (MD or DO) who has examined the patient and reviewed the record. The physician will have experience in administering TMS therapy. The treatment shall be given under direct supervision of this physician (physician present in the area but does not necessarily personally provide the treatment).

Payer (Effective Date)	Coverage Policy
Premera Blue Cross[156] (2/3/2023)	**MDD (unipolar depression):** The following types of TMS may be considered medically necessary for the treatment of MDD (unipolar depression) when policy criteria are met: • dTMS of the brain • Standard/conventional rTMS of the brain • TBS of the brain with the exceptions of accelerated TBS and the SNT/SAINT protocol TMS of the brain may be considered medically necessary for the treatment of MDD (unipolar depression) without psychotic features when: (1) The individual is at least 15 years old (2) The individual is experiencing a current episode of moderate to severe depression as demonstrated by documentation of the individual's symptoms and their severity or by 1 or more standardized depression rating scales (3) One of the following criteria are met: • Failure of at least 3 different antidepressant medications from at least 2 different classes, in separate trials OR • Failure of at least 2 different antidepressant medications from at least 2 different classes, in separate trials, plus failure with the addition of an augmenting agent to at least 1 of the failed antidepressants • A positive clinical response to a previous course of treatment with TMS for MDD **Major depression as a component of bipolar disorder (bipolar depression):** The following types of TMS may be considered medically necessary when policy criteria are met: • dTMS of the brain • Standard/conventional rTMS of the brain TMS of the brain may be considered medically necessary for the treatment of bipolar depression (major depression as a component of Bipolar disorder) without psychotic or manic features when: (1) The individual is at least 18 years old (2) The individual is experiencing a current episode of moderate to severe depression as demonstrated by documentation of the individual's symptoms and their severity or by 1 or more standardized depression rating scales (3) One of the following criteria are met: • Failure of separate trials of at least 3 of the following medications: cariprazine/Vraylar; lamotrigine/Lamictal; lithium; lumateperone/Caplyta; lurasidone/Latuda; olanzapine-fluoxetine combination/Symbyax; quetiapine regular (immediate release) or XR/Seroquel; valproate/Depakote • A positive clinical response to a previous course of treatment with TMS for bipolar depression **OCD:** The following types of TMS may be considered medically necessary when policy criteria are met: • dTMS of the brain • Standard/conventional rTMS of the brain TMS of the brain may be considered medically necessary for the treatment of OCD when: (1) The individual is at least 18 years old (2) The individual has an OCD that is currently moderate to severe as demonstrated by documentation of the individual's symptoms and their severity or by a standardized rating scale (3) One of the following criteria are met: • Failure of separate trials of at least 3 of the following medications: clomipramine/Anafranil; all SSRIs • A positive clinical response to a previous course of treatment with TMS for OCD

Payer (Effective Date)	Coverage Policy
Regence Blue Shield[157] (5/1/2022)	**MDD:** TMS of the brain may be considered medically necessary as a treatment of MDD when either of the following criteria are met: A. As initial treatment of a depressive episode (up to 36 treatment sessions, including tapering) when all of the following criteria are met: (1) Confirmed diagnosis of severe MDD (single or recurrent) confirmed by a standardized rating scale that reliably measures depressive symptoms, including documentation of the scale used and the score (2) Patient is 18 years or older (3) One of the following conditions is present: • Symptoms are ongoing despite treatment with at least 3 psychopharmacologic regimens, and each has been ineffective, not tolerated (as evidenced by distinct side effects), or is contraindicated • History of response to TMS in a previous depressive episode (at least 3 months since the prior episode) • Patient is a candidate for ECT; and patient does not have psychosis, acute suicidal risk, catatonia, significantly impaired essential function, or other condition for which ECT would be clinically superior to TMS. (4) Failure of a trial of a psychotherapy known to be effective in the treatment of MDD with documentation that psychotherapy was conducted for minimum duration of 6 weeks at least 1 time per week, and no significant improvement in depressive symptoms has occurred, as documented by standardized rating scales that reliably measure depressive symptoms B. Extension of initial therapy when both of the following criteria are met: (1) The TMS is demonstrating meaningful improvements as documented by standardized rating scales that reliably measure depressive symptoms in the member's clinical status (2) There is reasonable expectation that continued treatment will produce improvement
United Health[158] (10/18/2022)	**MDD** TMS (see below for TBS) is proven and medically necessary for the treatment of individuals 18 years of age or older with a confirmed diagnosis of MDD when all of the following conditions are met: (1) One of the following scenarios applies: • Resistance to treatment with psychopharmacologic agents (evidence-based depression treatment regimen) as evidenced by a lack of a clinically significant response to 4 trials of psychopharmacologic agents (evidence-based depression treatment regimen) in the current depressive episode from at least 2 different agent classes. The individual's medication dose during the failed trials should have been above the minimal effective dose and duration in the current episode. • Inability to tolerate psychopharmacologic agents (same as above) • A documented history of response to TMS in a previous depressive episode, as evidenced by a greater than 50% improvement on a standardized rating scale for depression symptoms (2) Trial of an evidence-based psychotherapy known to be effective in the treatment of MDD of an adequate frequency and duration has been attempted without significant improvement as documented on a standardized rating scale for depression symptoms (3) The individual's current baseline depression measurement score has been documented using an evidence-based validated rating scale (e.g., BDI; HAM-D; MADRS) (3) Ordered and supervised by a psychiatrist who has experience in administering rTMS therapy (4) Performed on an FDA-approved device (5) TMS is considered reasonable and necessary for up to 30 treatment sessions, followed by 6 tapered treatments Accelerated and/or theta-burst stimulation is currently unproven and being investigated as a newer type of TMS.

Abbreviations: BDI = ; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; dTMS = deep transcranial magnetic stimulation; ECT = electroconvulsive therapy; FDA = Food and Drug Administration; HAM-D = Hamilton Depression Score; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; OCD = obsessive-compulsive

disorder; OR = odds ratio; rTMS = repetitive transcranial magnetic stimulation; SAINT = Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression; SNT = Stanford Neuromodulation Therapy; TBS = theta-burst stimulation; TMS = transcranial magnetic stimulation; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

4.5 Limitations of This HTA

This HTA was limited to peer-reviewed studies published in English. We did not include data or results presented solely in conference abstracts. Our research questions did not include comparative effectiveness of various TMS types or comparison between TMS and other treatment options (e.g., ECT, medication). For practical reasons, we abstracted only symptom severity scores for the primary indication for TMS (e.g., depression scores for MDD studies); other mental health or quality-of-life outcomes reported but not abstracted are listed in ***Appendix C, Table C-32***. TMS may have also affected symptoms associated with comorbid conditions (e.g., anxiety in persons with MDD), but we did not capture the impact on comorbid conditions unless there was a formal subgroup analysis. Additionally, we did not abstract neurocognitive outcomes that may have been reported, but these are listed in ***Appendix C, Table C-33***.

We ultimately included only trial study designs, which generally have a short follow-up and cannot offer evidence concerning the durability of TMS on longer term clinical benefits or adverse effects. A comprehensive assessment of longer term benefits and harms may require a broader evidence base that includes observational or registry-based studies. Additionally, for harms, we did not use data from the FDA Manufacturer and User Facility Device Experience (MAUDE) database to assess safety because passive surveillance systems such as MAUDE include incomplete, inaccurate, untimely, and unverified data.[96] Studies conducted in countries other than *very high* on the United Nations Human Development Index were also excluded from this review.

4.6 Ongoing and Future Research

We identified 744 clinical trials registered in clinicaltrials.gov that are relevant to this HTA. ***Table 25*** summarizes these trials by study status and intervention category. Depression and SUD were the conditions most frequently found to have active trials.

Table 25. Clinical Trials of TMS by Status and Behavioral Health Condition

Condition	Not Yet Recruiting	Active or Recruiting[a]	Completed	Stopped or Unknown[b]	Total by Condition
Depression	26	104	137	92	359
OCD	2	12	20	10	44
Smoking cessation	6	29	48	32	115
PTSD	3	11	21	8	43
GAD	0	1	4	2	7
Substance abuse	16	57	56	47	176
Total by Study Status	**53**	**214**	**286**	**191**	**744**

Notes: [a] Includes active, not recruiting; enrolling by invitation; and recruiting.
[b] Includes terminated, withdrawn, and unknown status.

Abbreviations: GAD = generalized anxiety disorder; OCD = obsessive compulsive disorder; PTSD = posttraumatic stress disorder; TMS = transcranial magnetic stimulation.

The evidence base for TMS is more mature for MDD compared to the other conditions included in this HTA. Research on conditions other than depression may require additional work to determine the optimal brain target and TMS treatment parameters that can then be evaluated in larger, sham-controlled effectiveness trials. Future effectiveness trials should seek to address limitations of the current evidence base, including adequately powered designs with robust execution to minimize risk of bias from attrition, outcome assessment, deviations from protocol, and post hoc analyses. For all conditions, trials should include longer term outcomes to evaluate the durability of treatment effect and to identify harms that may only emerge later to elucidate the role of TMS among treatment options. Additionally, all trials should include a measure of disease severity and treatment resistance to support clinical decision making on when to use TMS compared to another therapy, such as further medication management or ECT. The role of co-treatment, with cognitive therapies or medication therapies, particularly for nondepression conditions such as tobacco use disorder or SUD, remains an area where further research could elucidate the role of TMS in treatment. Another future focus of research is to determine regimens for maintenance therapy after an initial course of TMS treatment. Lastly, trials that enroll diverse racial and ethnic populations or that are specifically designed to evaluate the effect of psychiatric comorbidities on treatment effect would advance our understanding of the applicability of this evidence to broader populations.

5. Conclusion

This HTA examined the efficacy, safety, and cost-effectiveness of active TMS compared to sham TMS for selected behavioral health conditions. TMS has moderate to high SOE for benefit in MDD and low SOE for benefit in OCD at posttreatment. Evidence for benefit for the other conditions (GAD, PTSD, smoking cessation, SUD) ranges from insufficient to low for benefit depending on the outcome assessed. Data on the efficacy of TMS at longer follow-up assessment are lacking across all conditions. There was less robust evidence for safety outcomes, although studies generally reported fewer AEs for sham TMS; few SAEs were reported for either active or sham TMS. Evidence is lacking with respect to cost-effectiveness outcomes.

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Appendix A. State of Washington Health Care Authority Utilization Data

The State of Washington Health Care Authority provided this data and analysis for inclusion in this Health Technology Assessment (HTA).

Populations

Administrative claims and encounter data for transcranial magnetic stimulation (TMS) for treatment of selected conditions from the following Washington State health programs were assessed: the Public Employees Benefit Board (PEBB) and School Employees Benefit Board (SEBB) Uniform Medical Plan (UMP), Medicaid managed care (MC) and fee-for-service (FFS), and the Department of Labor and Industries (L&I) Workers' Compensation Plan.

The assessment includes final paid and adjudicated claims and encounters for all ages. Denied claims or rejected encounters are excluded. Individuals that were dually eligible for both Medicare and Medicaid are excluded from the Medicaid program analysis. The PEBB/SEBB UMP experience includes claims for non-Medicare services.

TMS Procedures

The assessment includes only procedures and services specific to TMS with a date of service between January 1, 2018, and December 31, 2021.

Claims and encounters with qualifying procedures or services according to current procedural terminology (CPT) codes during the period were extracted for analysis. Qualifying CPT codes included 90867, 90868, and 90869.

The following tables provide utilization counts, age, and cost by CPT code for TMS (***Tables A-1, A-2,*** and ***A-3***).

Table A-1. Utilization of TMS and Related Procedures and Services by Washington State Health Program (2018–2021)

Program	2018	2019	2020	2021	Total (Unique)
Medicaid fee for service (FFS)					
Individuals with at least 1 TMS-related procedure/service	NR	NR	NR	NR	NR
Medicaid managed care (MC)					
Individuals with at least 1 TMS-related procedure/service	24	92	142	361	548
Female, count	14	59	97	250	371
Male, count	10	33	44	111	177
Number of encounters with TMS	567	2,268	3,241	10,119	16,195
Average encounters with TMS/individual	24	25	23	28	30

Program	2018	2019	2020	2021	Total (Unique)
Amount paid, TMS	$74,099	$360,195	$499,445	$1,325,173	$2,258,911
Average payments per individual	$3,087	$3,915	$3,517	$3,671	$4,122
Public Employees Benefit Board/School Employees Benefit Board Uniform Medical Plan (PEBB/SEBB UMP)					
Individuals with at least 1 TMS-related procedure/service	48	138	223	314	591
Female, count	NR	98	167	218	NR
Male, count	NR	40	56	96	NR
Number of encounters with TMS	1,586	4,441	7,230	9,984	23,241
Average encounters with TMS/individual	33	32	32	32	39
Amount paid, TMS	$349,353	$970,764	$1,489,632	$2,069,633	$4,879,382
Average payments per individual	$7,278	$7,035	$6,680	$6,591	$8,256
Department of Labor and Industries (L&I)					
Individuals with at least 1 TMS-related procedure/service	12	14	16	17	48
Female, count	NR	NR	NR	NR	NR
Male, count	NR	NR	NR	NR	NR
Number of encounters with TMS	572	314	627	903	2,416
Average encounters with TMS/individual	48	22	39	53	50
Amount paid, TMS	$198,198	$182,479	$262,984	$458,039	$1,101,699
Average payments per individual	$16,516	$13,034	$16,437	$26,943	$22,952
Combined Total (Medicaid, PEBB/SEBB UMP, L&I)					
Individuals with at least 1 TMS-related procedure/service	84	244	381	692	1,187
Female, count	NR	NR	NR	NR	NR
Male, count	NR	NR	NR	NR	NR
Number of encounters with TMS	2,725	7,023	11,098	21,006	41,852
Amount paid, TMS	$621,649	$1,513,438	$2,252,061	$3,852,845	$8,239,993
Utilization, Depression Diagnosis					
Number of encounters with TMS	2,418	6,818	10,869	20,090	40,195
Amount paid, TMS	$516,003	$1,458,598	$2,197,273	$3,587,917	$7,759,791

Data notes: Small numbers suppressed to protect patient privacy. Claimant sex was not always reported. Annual members for Medicaid excludes members that are dually eligible for Medicaid and Medicare. Amount paid reflects all claims submitted for the procedure codes specified. Managed care amount paid reflects an estimate of the amount paid for the procedure. UMP data does not reflect patient cost share. Individuals who had a procedure in more than 1 year are only counted once in the "Total" summary. Amounts paid of $0 were excluded from amount paid table value calculations. Depression diagnoses included ICD-10 codes in categories F32 and F33.

Abbreviations: FFS = fee for service; ICD-10 = 10th revision of the International Statistical Classification of Diseases and Related Health Problems; L&I = labor and industries; MC = managed care; NR = not reported; PEBB = Public Employees Benefit Board; SEBB = School Employees Benefit Board; TMS = transcranial magnetic stimulation; UMP = Uniform Medical Plan.

Table A-2. Demographics of Medicaid and UMP Beneficiaries With at Least 1 TMS Procedure, Washington State, State Fiscal Year 2018–2021

Age	Total (Count)
<18 years	26
18–64 years	1,053
65 years or older	66
Total	1,145

Abbreviations: TMS = transcranial magnetic stimulation; UMP = Uniform Medical Plan.

Table A-3. Codes and Cost by HCPCS/CPT Code (Maximum Allowable), by State Health Program and Setting, Washington State

Code	Description	Medicaid FFS		L&I	
CPT		Non-facility	Facility	Nonfacility	Facility
90867	Therapeutic repetitive transcranial magnetic stimulation treatment; initial, including cortical mapping, motor threshold determination, delivery and management	$218.89	$218.89	BR	BR
90868	Therapeutic repetitive transcranial magnetic stimulation treatment; subsequent delivery and management, per session	$117.45	$117.45	$431.66	$431.66
90869	Therapeutic repetitive transcranial magnetic stimulation treatment; subsequent motor threshold re-determination with delivery and management	$203.88	$203.88	BR	BR

Data notes: Medicaid FFS from October 1, 2021 Physician-Related Services Fee Schedule and Mental Health Services Fee Schedule (accessed December 1, 2022; webpage). L&I from 2021 provider fee schedule (accessed December 1, 2022). PEBB/UMP fees are confidential and not publicly available (proprietary).

Abbreviations: BR = by report; CPT = current procedural terminology; FFS = fee for service; HCPCS = healthcare common procedure coding system; L&I = labor and industries; MC = managed care; NR = not reported; PEBB = Public Employees Benefit Board; UMP = Uniform Medical Plan.

Appendix B. Search Strategy

May 24, 2022

TMS Search Strategy_5-24-2022

Databases: PubMed, Cochrane Library, PsycInfo

Language: English

Study Type: humans, research studies

PubMed

Intervention

#1 "Transcranial Magnetic Stimulation"[Mesh] OR "transcranial magnetic stimulation"[tiab] OR "TMS"[tiab] OR "rTMS"[tiab] OR "sTMS"[tiab] Filters: English 24,727

Conditions

#2 "Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR depress*[tiab] OR "Obsessive-Compulsive Disorder"[Mesh] OR "Obsessive-Compulsive Disorder"[tiab] OR "OCD"[tiab] OR "Smoking Cessation"[Mesh] OR "smoking cessation"[tiab] OR "Tobacco Use Disorder"[Mesh] OR "tobacco"[tiab] OR cigarette*[tiab] OR "smoking"[tiab] OR "nicotine"[tiab] OR craving*[tiab] OR "consumption"[tiab] OR "addiction"[tiab] OR "dependence"[tiab] OR "abstinence"[tiab] OR "Stress Disorders, Post-Traumatic"[Mesh] OR "PTSD"[tiab] OR "posttraumatic stress disorder"[tiab] OR "post-traumatic stress disorder"[tiab] OR "post traumatic stress disorder"[tiab] OR (("generalized anxiety disorder*"[tiab] OR "GAD"[tiab]) NOT ("Obsessive-Compulsive Disorder"[Mesh] OR "Anxiety, Separation"[Mesh] OR "Neurocirculatory Asthenia"[Mesh] OR "Neurotic Disorders"[Mesh] OR "obsessive-compulsive disorder*"[tiab] OR "separation anxiety"[tiab] OR "neurocirculatory asthenia"[tiab] OR "neurotic disorder*"[tiab])) OR "Substance-Related Disorders"[Mesh] OR "substance dependence"[tiab] OR "substance-related disorder*"[tiab] OR "substance use disorder*"[tiab] OR "substance addiction"[tiab] OR "substance abuse"[tiab] OR "addiction"[tiab] OR craving*[tiab] OR alcohol*[tiab] OR "ethanol"[tiab] OR "psychostimulant drug*"[tiab] OR "psychoactive drug*"[tiab] OR "cocaine"[tiab] OR "cannabis"[tiab] OR "marijuana"[tiab] OR "heroin"[tiab] OR "morphine"[tiab] OR opioid*[tiab] OR amphetamine*[tiab] Filters: English 1,958,284

#3 #1 AND #2 Filters: English 4,320

Humans

#4 #3 NOT (("Animals"[Mesh] NOT "Humans"[Mesh]) OR "rat"[tw] OR "rats"[tw] OR "cow"[tw] OR "cows"[tw] OR chicken*[tw] OR "horse"[tw] OR "horses"[tw] OR "mice"[tw] OR "mouse"[tw] OR "bovine"[tw] OR "sheep"[tw] OR "ovine"[tw] OR "murinae"[tw]) Filters: English 4,093

Research Publications

#5 #4 NOT ("Address"[Publication Type] OR "Autobiography"[Publication Type] OR "Bibliography"[Publication Type] OR "Biography"[Publication Type] OR "Case Reports"[Publication Type] OR "Comment"[Publication Type] OR "Congress"[Publication Type] OR "Dictionary"[Publication Type] OR "Directory"[Publication Type] OR "Editorial"[Publication Type] OR "Festschrift"[Publication Type] OR "Government Publication"[Publication Type] OR "Historical Article"[Publication Type] OR "Interview"[Publication Type] OR "Lecture"[Publication Type] OR "Legal Case"[Publication Type] OR "Legislation"[Publication Type] OR "Letter"[Publication Type] OR "News"[Publication Type] OR "Newspaper Article"[Publication Type] OR "Patient Education Handout"[Publication Type] OR "Periodical Index"[Publication Type]) Filters: English 3,604

Trials

#6 #5 AND ("Controlled Clinical Trial"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type] OR "Clinical Trial, Phase III"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "Comparative Study"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh] OR "Pragmatic Clinical Trial"[Publication Type] OR "Clinical Trial"[Publication Type] OR "randomized"[tiab] OR trial*[tiab]) Filters: English 1,623

Systematic Reviews

#7 #5 AND ("Systematic Review"[Publication Type] OR "Systematic Reviews as Topic"[Mesh] OR ("Review"[Publication Type] AND "systematic"[tiab]) OR "systematic review*"[All Fields] OR ("Review Literature as Topic"[Mesh] AND "systematic"[tiab]) OR "Meta-analysis"[Publication Type] OR "Meta-analysis as Topic"[Mesh] OR "meta-analysis"[All Fields]) Filters: English 370

Observational

#8 #5 AND ("Observational Study"[Publication Type] OR "Comparative Study"[Publication Type] OR "Epidemiologic Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Cohort Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "observational"[tiab]) Filters: English 489

Cochrane Library

Intervention

#1 [mh "Transcranial Magnetic Stimulation"] OR ("transcranial magnetic stimulation" OR "TMS" OR "rTMS" OR "sTMS"):ti,ab 6,606

Conditions

#2 [mh "Depression"] OR [mh "Depressive Disorder"] OR [mh "Obsessive-Compulsive Disorder"] OR [mh "Smoking Cessation"] OR [mh "Tobacco Use Disorder"] OR [mh "Stress Disorders, Post-Traumatic"] OR [mh "Substance-Related Disorders"] OR (depress* OR "Obsessive-Compulsive Disorder" OR "OCD" OR "smoking cessation" OR "tobacco" OR cigarette* OR "smoking" OR "nicotine" OR craving* OR "consumption" OR "addiction" OR "dependence" OR "abstinence" OR "PTSD" OR "posttraumatic stress disorder" OR "post-traumatic stress disorder" OR "post traumatic stress disorder" OR "substance dependence" OR "substance-related" NEXT disorder* OR "substance use" NEXT disorder* OR "substance addiction" OR "substance abuse" OR "addiction" OR craving* OR alcohol* OR "ethanol" OR psychostimulant NEXT drug* OR psychoactive NEXT drug* OR "cocaine" OR "cannabis" OR "marijuana" OR "heroin" OR "morphine" OR opioid* OR amphetamine*):ti,ab 226,404

#3 ("generalized anxiety" NEXT disorder* OR "GAD"):ti,ab 3,628

#4 [mh "Obsessive-Compulsive Disorder"] OR [mh "Anxiety, Separation"] OR [mh "Neurocirculatory Asthenia"] OR [mh "Neurotic Disorders"] OR ("obsessive-compulsive" NEXT disorder* OR "separation anxiety" OR "neurocirculatory asthenia" OR neurotic NEXT disorder*):ti,ab 3,160

#5 #3 NOT #4 3,435

Trials

#6 #1 AND (#2 OR #5) 2,338

#7 #6 in Cochrane Database of Systematic Reviews 10

PsycInfo

Intervention

S1 DE "Transcranial Magnetic Stimulation" OR TI "transcranial magnetic stimulation" OR TI "TMS" OR TI "rTMS" OR TI "sTMS" OR AB "transcranial magnetic stimulation" OR AB "TMS" OR AB "rTMS" OR AB "sTMS" Limiters – English 12,349

Conditions

S2 DE "Depression (Emotion)" OR DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR TI depress* OR AB depress* OR DE "Obsessive Compulsive Disorder" OR DE "Obsessive Compulsive Personality Disorder" OR TI "Obsessive-Compulsive Disorder" OR TI "OCD" OR AB "Obsessive-Compulsive Disorder" OR AB "OCD" OR DE "Smoking Cessation" OR TI "smoking cessation" OR AB "smoking cessation" OR DE "Tobacco Use Disorder" OR TI "tobacco" OR TI cigarette* OR TI "smoking" OR TI "nicotine" OR TI craving* OR TI "consumption" OR TI "addiction" OR TI "dependence" OR TI "abstinence" OR AB "tobacco" OR AB cigarette* OR AB "smoking" OR AB "nicotine" OR AB craving* OR AB "consumption" OR AB "addiction" OR AB "dependence" OR AB "abstinence" OR DE "Posttraumatic Stress Disorder" OR DE "Complex PTSD" OR DE "DESNOS" OR TI "PTSD" OR TI "posttraumatic stress disorder" OR TI "post-traumatic stress disorder" OR TI "post traumatic stress disorder" OR AB "PTSD" OR AB "posttraumatic stress disorder" OR AB "post-traumatic stress disorder" OR AB "post traumatic stress disorder" OR ((DE "Generalized Anxiety Disorder" OR TI "generalized anxiety disorder*" OR TI "GAD" OR AB "generalized anxiety disorder*" OR AB "GAD") NOT (DE "Obsessive Compulsive Disorder" OR DE "Obsessive Compulsive Personality Disorder" OR DE "Separation Anxiety" OR DE "Separation Anxiety Disorder" OR DE "Asthenia" OR DE "Neurosis" OR TI "obsessive-compulsive disorder*" OR TI "separation anxiety" OR TI "neurocirculatory asthenia" OR TI "neurotic disorder*" OR AB "obsessive-compulsive disorder*" OR AB "separation anxiety" OR AB "neurocirculatory asthenia" OR AB "neurotic disorder*")) OR DE "Substance Use Disorder" OR DE "Addiction" OR DE "Alcohol Use Disorder" OR DE "Cannabis Use Disorder" OR DE "Drug Abuse" OR DE "Drug Dependency" OR DE "Inhalant Abuse" OR DE "Opioid Use Disorder" OR DE "Tobacco Use Disorder" OR TI "substance dependence" OR TI "substance-related disorder*" OR TI "substance use disorder*" OR TI "substance addiction" OR TI "substance abuse" OR TI "addiction" OR TI craving* OR TI alcohol* OR TI "ethanol" OR TI "psychostimulant drug*" OR TI "psychoactive drug*" OR TI "cocaine" OR TI "cannabis" OR TI "marijuana" OR TI "heroin" OR TI "morphine" OR TI opioid* OR TI amphetamine* OR AB "substance dependence" OR AB "substance-related disorder*" OR AB "substance use disorder*" OR AB "substance addiction" OR AB "substance abuse" OR AB "addiction" OR AB craving* OR AB alcohol* OR AB "ethanol" OR AB "psychostimulant drug*" OR AB "psychoactive drug*" OR AB "cocaine" OR AB "cannabis" OR AB "marijuana" OR AB "heroin" OR AB "morphine" OR AB opioid* OR AB amphetamine* Limiters – English 693,459

S3 S1 AND S2 Limiters – English 2,918

Humans

S4 S3 NOT ((ZP "animal" NOT ZP "human") OR "rat" OR "rats" OR "cow" OR "cows" OR chicken* OR "horse" OR "horses" OR "mice" OR "mouse" OR "bovine" OR "sheep" OR "ovine" OR "murinae") Limiters – English 2,803

Research Publications

S5 S4 NOT (ZZ "bibliography" OR ZC "clinical case study" OR ZC "nonclinical case study" OR DE "Case Report" OR ZZ "comment/reply" OR ZZ "editorial" OR ZZ "interview" OR ZZ "letter") Limiters – English 2,325

Trials

S6 S5 AND (DE "Randomized Controlled Trials" OR DE "Randomized Clinical Trials" OR DE "Clinical Trials" OR DE "Meta Analysis" OR ZC "meta analysis" OR ZC "clinical trial" OR TI "randomized" OR TI trial* OR AB "randomized" OR AB trial*) Limiters – English 951

Systematic Reviews

S7 S5 AND (DE "Systematic Review" OR ZC "systematic review" OR (ZC "literature review" AND "systematic") OR "systematic review*" OR (DE "Literature Review" AND "systematic") OR DE "Meta Analysis" OR ZC "meta analysis" OR "meta-analysis") Limiters – English 238

Observational

S8 S5 AND (ZC "followup study" OR DE "Followup Studies" OR TI "observational" OR AB "observational") Limiters – English 79

	Total before Study Design Filters	+Trials	+SRs	+Obs	
PubMed	3,604	1,623	370	489	
Cochrane	10	----	10	---	
PsycInfo	2,325	951	238	79	
Total (de-dup – ENDB numbers)		1,892	97	151	2,140

Cost Addendum Search

June 29, 2022

TMS Search Strategy_Cost Addendum_6-29-2022

Databases: PubMed, Cochrane Database of Systematic Reviews, PsycInfo

Language: English

Study Type: humans, research studies

PubMed

Intervention

#1 "Transcranial Magnetic Stimulation"[Mesh] OR "transcranial magnetic stimulation"[tiab] OR "TMS"[tiab] OR "rTMS"[tiab] OR "sTMS"[tiab] Filters: English 24,950

Conditions

#2 "Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR depress*[tiab] OR "Obsessive-Compulsive Disorder"[Mesh] OR "Obsessive-Compulsive Disorder"[tiab] OR "OCD"[tiab] OR "Smoking Cessation"[Mesh] OR "smoking cessation"[tiab] OR "Tobacco Use Disorder"[Mesh] OR "tobacco"[tiab] OR cigarette*[tiab] OR "smoking"[tiab] OR "nicotine"[tiab] OR craving*[tiab] OR "consumption"[tiab] OR "addiction"[tiab] OR "dependence"[tiab] OR "abstinence"[tiab] OR "Stress Disorders, Post-Traumatic"[Mesh] OR "PTSD"[tiab] OR "posttraumatic stress disorder"[tiab] OR "post-traumatic stress disorder"[tiab] OR "post traumatic stress disorder"[tiab] OR (("generalized anxiety disorder*"[tiab] OR "GAD"[tiab]) NOT ("Obsessive-Compulsive Disorder"[Mesh] OR "Anxiety, Separation"[Mesh] OR "Neurocirculatory Asthenia"[Mesh] OR "Neurotic Disorders"[Mesh] OR "obsessive-compulsive disorder*"[tiab] OR "separation anxiety"[tiab] OR "neurocirculatory asthenia"[tiab] OR "neurotic disorder*"[tiab])) OR "Substance-Related Disorders"[Mesh] OR "substance dependence"[tiab] OR "substance-related disorder*"[tiab] OR "substance use disorder*"[tiab] OR "substance addiction"[tiab] OR "substance abuse"[tiab] OR "addiction"[tiab] OR craving*[tiab] OR alcohol*[tiab] OR "ethanol"[tiab] OR "psychostimulant drug*"[tiab] OR "psychoactive drug*"[tiab] OR "cocaine"[tiab] OR "cannabis"[tiab] OR "marijuana"[tiab] OR "heroin"[tiab] OR "morphine"[tiab] OR opioid*[tiab] OR amphetamine*[tiab] Filters: English 1,970,240

#3 #1 AND #2 Filters: English 4,380

Humans

#4 #3 NOT (("Animals"[Mesh] NOT "Humans"[Mesh]) OR "rat"[tw] OR "rats"[tw] OR "cow"[tw] OR "cows"[tw] OR chicken*[tw] OR "horse"[tw] OR "horses"[tw] OR "mice"[tw] OR "mouse"[tw] OR "bovine"[tw] OR "sheep"[tw] OR "ovine"[tw] OR "murinae"[tw]) Filters: English 4,152

Research Publications

#5 #4 NOT ("Address"[Publication Type] OR "Autobiography"[Publication Type] OR "Bibliography"[Publication Type] OR "Biography"[Publication Type] OR "Case Reports"[Publication Type] OR "Comment"[Publication Type] OR "Congress"[Publication Type] OR "Dictionary"[Publication Type] OR "Directory"[Publication Type] OR "Editorial"[Publication Type] OR "Festschrift"[Publication Type] OR "Government Publication"[Publication Type] OR "Historical Article"[Publication Type] OR "Interview"[Publication Type] OR "Lecture"[Publication Type] OR "Legal Case"[Publication Type] OR "Legislation"[Publication Type] OR "Letter"[Publication Type] OR "News"[Publication Type] OR "Newspaper Article"[Publication Type] OR "Patient Education Handout"[Publication Type] OR "Periodical Index"[Publication Type]) Filters: English 3,660

Cost Studies

#6 #5 AND ("Costs and Cost Analysis"[Mesh] OR "cost-benefit*"[tiab] OR "cost benefit*"[tiab] OR "cost-effective*"[tiab] OR "cost effective*"[tiab] OR "cost-utility"[tiab] OR "cost utility"[tiab] OR "cost-utilities"[tiab] OR "cost utilities"[tiab] OR "Insurance, Health, Reimbursement"[Mesh] OR "Prospective Payment System"[Mesh] OR cost*[tiab] OR "costs"[tiab]) Filters: English 103

Cochrane Library

Intervention

#1 [mh "Transcranial Magnetic Stimulation"] OR ("transcranial magnetic stimulation" OR "TMS" OR "rTMS" OR "sTMS"):ti,ab 6,640

Conditions

#2 [mh "Depression"] OR [mh "Depressive Disorder"] OR [mh "Obsessive-Compulsive Disorder"] OR [mh "Smoking Cessation"] OR [mh "Tobacco Use Disorder"] OR [mh "Stress Disorders, Post-Traumatic"] OR [mh "Substance-Related Disorders"] OR (depress* OR "Obsessive-Compulsive Disorder" OR "OCD" OR "smoking cessation" OR "tobacco" OR cigarette* OR "smoking" OR "nicotine" OR craving* OR "consumption" OR "addiction" OR "dependence" OR "abstinence" OR "PTSD" OR "posttraumatic stress disorder" OR "post-traumatic stress disorder" OR "post traumatic stress disorder" OR "substance dependence" OR "substance-related" NEXT disorder* OR "substance use" NEXT disorder* OR "substance addiction" OR "substance abuse" OR "addiction" OR craving* OR alcohol* OR "ethanol" OR psychostimulant NEXT drug* OR psychoactive NEXT drug* OR "cocaine" OR "cannabis" OR "marijuana" OR "heroin" OR "morphine" OR opioid* OR amphetamine*):ti,ab 227,343

#3 ("generalized anxiety" NEXT disorder* OR "GAD"):ti,ab 3,645

#4 [mh "Obsessive-Compulsive Disorder"] OR [mh "Anxiety, Separation"] OR [mh "Neurocirculatory Asthenia"] OR [mh "Neurotic Disorders"] OR ("obsessive-compulsive"

NEXT disorder* OR "separation anxiety" OR "neurocirculatory asthenia" OR neurotic NEXT disorder*):ti,ab 3,171

#5 #3 NOT #4 3,452

#6 #1 AND (#2 OR #5) 2,352

Cost Studies

#7 [mh "Costs and Cost Analysis"] OR [mh "Insurance, Health, Reimbursement"] OR [mh "Prospective Payment System"] OR (cost NEXT benefit* OR cost NEXT effective* OR "cost-utility" OR "cost utility" OR "cost-utilities" OR "cost utilities" OR cost* OR "costs"):ti,ab 76,426

#8 #6 AND #7 79

#9 #8 in Cochrane Database of Systematic Reviews 0

PsycInfo

Intervention

S1 DE "Transcranial Magnetic Stimulation" OR TI "transcranial magnetic stimulation" OR TI "TMS" OR TI "rTMS" OR TI "sTMS" OR AB "transcranial magnetic stimulation" OR AB "TMS" OR AB "rTMS" OR AB "sTMS" Limiters – English 12,393

Conditions

S2 DE "Depression (Emotion)" OR DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR TI depress* OR AB depress* OR DE "Obsessive Compulsive Disorder" OR DE "Obsessive Compulsive Personality Disorder" OR TI "Obsessive-Compulsive Disorder" OR TI "OCD" OR AB "Obsessive-Compulsive Disorder" OR AB "OCD" OR DE "Smoking Cessation" OR TI "smoking cessation" OR AB "smoking cessation" OR DE "Tobacco Use Disorder" OR TI "tobacco" OR TI cigarette* OR TI "smoking" OR TI "nicotine" OR TI craving* OR TI "consumption" OR TI "addiction" OR TI "dependence" OR TI "abstinence" OR AB "tobacco" OR AB cigarette* OR AB "smoking" OR AB "nicotine" OR AB craving* OR AB "consumption" OR AB "addiction" OR AB "dependence" OR AB "abstinence" OR DE "Posttraumatic Stress Disorder" OR DE "Complex PTSD" OR DE "DESNOS" OR TI "PTSD" OR TI "posttraumatic stress disorder" OR TI "post-traumatic stress disorder" OR TI "post traumatic stress disorder" OR AB "PTSD" OR AB "posttraumatic stress disorder" OR AB "post-traumatic stress disorder" OR AB "post traumatic stress disorder" OR ((DE "Generalized Anxiety Disorder" OR TI "generalized anxiety disorder*" OR TI "GAD" OR AB "generalized anxiety disorder*" OR AB "GAD") NOT (DE "Obsessive Compulsive Disorder" OR DE "Obsessive Compulsive Personality Disorder" OR DE "Separation Anxiety" OR DE "Separation

Anxiety Disorder" OR DE "Asthenia" OR DE "Neurosis" OR TI "obsessive-compulsive disorder*" OR TI "separation anxiety" OR TI "neurocirculatory asthenia" OR TI "neurotic disorder*" OR AB "obsessive-compulsive disorder*" OR AB "separation anxiety" OR AB "neurocirculatory asthenia" OR AB "neurotic disorder*")) OR DE "Substance Use Disorder" OR DE "Addiction" OR DE "Alcohol Use Disorder" OR DE "Cannabis Use Disorder" OR DE "Drug Abuse" OR DE "Drug Dependency" OR DE "Inhalant Abuse" OR DE "Opioid Use Disorder" OR DE "Tobacco Use Disorder" OR TI "substance dependence" OR TI "substance-related disorder*" OR TI "substance use disorder*" OR TI "substance addiction" OR TI "substance abuse" OR TI "addiction" OR TI craving* OR TI alcohol* OR TI "ethanol" OR TI "psychostimulant drug*" OR TI "psychoactive drug*" OR TI "cocaine" OR TI "cannabis" OR TI "marijuana" OR TI "heroin" OR TI "morphine" OR TI opioid* OR TI amphetamine* OR AB "substance dependence" OR AB "substance-related disorder*" OR AB "substance use disorder*" OR AB "substance addiction" OR AB "substance abuse" OR AB "addiction" OR AB craving* OR AB alcohol* OR AB "ethanol" OR AB "psychostimulant drug*" OR AB "psychoactive drug*" OR AB "cocaine" OR AB "cannabis" OR AB "marijuana" OR AB "heroin" OR AB "morphine" OR AB opioid* OR AB amphetamine* Limiters – English 696,360

S3 S1 AND S2 Limiters – English 2,934

Humans

S4 S3 NOT ((ZP "animal" NOT ZP "human") OR "rat" OR "rats" OR "cow" OR "cows" OR chicken* OR "horse" OR "horses" OR "mice" OR "mouse" OR "bovine" OR "sheep" OR "ovine" OR "murinae") Limiters – English 2,819

Research Publications

S5 S4 NOT (ZZ "bibliography" OR ZC "clinical case study" OR ZC "nonclinical case study" OR DE "Case Report" OR ZZ "comment/reply" OR ZZ "editorial" OR ZZ "interview" OR ZZ "letter") Limiters – English 2,339

Cost Studies

S6 S5 AND (DE "Costs and Cost Analysis" OR DE "Budgets" OR DE "Cost Containment" OR DE "Health Care Costs" OR DE "Money" OR DE "Health Care Reimbursement" OR TI "cost-benefit*" OR TI "cost benefit*" OR TI "cost-effective*" OR TI "cost effective*" OR TI "cost-utility" OR TI "cost utility" OR TI "cost-utilities" OR TI "cost utilities" OR TI "prospective payment system*" OR TI cost* OR TI "costs" OR AB "cost-benefit*" OR AB "cost benefit*" OR AB "cost-effective*" OR AB "cost effective*" OR AB "cost-utility" OR AB "cost utility" OR AB "cost-utilities" OR AB "cost utilities" OR AB "prospective payment system*" OR AB cost* OR AB "costs") Limiters – English 56

Appendix C. Evidence Tables

Table C-1. Study Characteristics for Included Repetitive TMS Interventions for GAD

Author (Year) Country Registry #	Study Design Years Conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
Diefenbach et al. (2016)[25] U.S. NCT01659736	Parallel RCT 2012 to 2014	Hartford HealthCare Research Funding Initiative; Neuronetics provided material support and reviewed draft report prior to submission	Yes, partially	Age 18 or older diagnosed with at least moderate severity GAD (CGI-S score of at least 4) as principal or coprincipal disorder, HARS score of at least 18 and HAMD score of at maximum 17	History of bipolar, psychotic, developmental or OCD, or SUD within the past 6 months; current PTSD; brain trauma or disorder; serious or unstable medical illness; any contraindication for MRI or rTMS; concurrent psychotherapy
Dilkov et al. (2017)[24] Canada, Bulgaria NCT00616447	Parallel RCT 2008 to 2012	NR	Sponsorship not reported	Ages 18 to 65 years meeting MINI criteria for primary GAD without GAD pharmacotherapy for a least 2 weeks prior to the start of the study or who had 6 weeks of stable pharmacotherapy treatment or were enrolled in individual or group supportive psychotherapy	Diagnoses of schizophrenia, other psychotic disorders, bipolar I disorder, current major depressive episodes, or substance and alcohol dependence within the last 6 months; diagnoses/history of severe Axis II disorder, severe or unstable medical conditions, epilepsy, neurological disorders leading to increased intracranial pressure, and severe cardiac disorder; having metallic implant in the cranium (except mouth), ECT treatment within the last 3 months or TMS treatment in the past 6 months; suicidal

Abbreviations: CGI-S = Clinical Global Impression-Severity; ECT = electroconvulsive therapy; GAD = generalized anxiety disorder; HAMD = Hamilton Rating Scale for Depression; HARS = Hamilton Anxiety Rating Scale; MINI = Mini International Neuropsychiatric Interview; MRI = magnetic resonance imaging; NR = not rated; OCD = obsessive compulsive disorder; PTSD = posttraumatic stress disorder; RCT = randomized, controlled trial; rTMS = repetitive transcranial magnetic stimulation; SUD = substance use disorder; TMS = transcranial magnetic stimulation.

Table C-2. Intervention Characteristics for Included Repetitive TMS Interventions for GAD

First Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
Diefenbach et al. (2016)[25]	Sham rTMS (12) Sham type: Sham coil, not specified	Active rTMS (14) Target location: Right DLPFC Localization technique: Image -guided Frequency: 1 Hz Intensity: 90 Number of pulses: 900	Treatment days: 30 (5 days per week for 6 weeks) Treatment sessions total: 30	Medication per treatment as usual	None
Dilkov et al. (2017)[24]	Sham rTMS (25) Sham type: Angle wand away from scalp	rTMS (25) Target location: Right DLPFC Localization technique: Manual measurement Frequency: 20 Hz Intensity: 110 Number of pulses: 3,600	Treatment days: 25 total (5 sessions per week for 4 weeks, then 3 sessions/week for 1 week, then 2 sessions/week for final week) Treatment sessions total: 25	Medication per treatment as usual, psychotherapy per treatment as ususal	None

Abbreviations: cTBS = controlled theta-burst stimulation, a variation of rTMS; DLPFC = dorsolateral prefrontal cortex; GAD = generalized anxiety disorder; Hz = electromagnetic wavelength frequency; rTMS = repetitive transcranial magnetic stimulation; TMS = transcranial magnetic stimulation.

Table C-3. Population Characteristics for Included Repetitive TMS Interventions for GAD

Author (Year)	Sample Size (Total)	Treatment History	Mean Age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
Diefenbach et al. (2016)[25]	26	Unspecified treatment naive or resistance	IG1: 44.0 (12.0) CG: 44.6 (14.8)	IG1: 11 (84.6) CG: 8 (66.7)	White IG1: 12 (92) CG: 12 (100)	Comorbid anxiety disorder IG1: 39% CG: 33% Comorbid depressive disorder IG1: 62% CG: 25%
Dilkov et al. (2017)[24]	50	Unspecified treatment naive or resistance	Active: 34 (7) Sham: 38 (10)	Active: 6 (15) Sham: 13 (33)	NR	NR

Abbreviations: CG = control group; GAD = generalized anxiety disorder; IG = intervention group; N = number; NR = not rated; TMS = transcranial magnetic stimulation.

Table C-4. Efficacy Outcomes for Included Repetitive TMS Interventions for GAD

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Diefenbach et al. (2016)[25] Active rTMS (14) Sham rTMS (12)	**Remission**: HARS score less than 8 and CGI-I score of 1 (very much improved) or 2 (much improved)	Remission, posttreatment (6 weeks); mITT (IG1=13; CG=12); N (%) IG1: 4 (30.8) CG: 1 (8.3) *P*=0.161 Remission, 6 weeks after end of treatment (12 weeks); mITT (IG1=13; CG=12); N (%) IG1: 7 (53.8) CG: 0 (0) *P*=0.003
	Response: At least 50% HARS improvement	Response based on HARS, posttreatment (6 weeks); mITT (IG1=13; CG=12); N (%) IG1: 8 (61.5) CG: 2 (16.7) *P*=0.022 Response based on HARS, 6 weeks post-treatment (12 weeks); mITT (IG1=13, CG=12), N (%) IG1: 8(61.5) CG: 0 (0) *P*=0.001
	Continuous outcomes: HARS	HARS score, baseline (0 weeks), mITT (IG1=13, CG=12), mean (SD) IG1: 25.3 (5.2) CG: 20.8 (3. 7) HARS score, posttreatment (6 weeks); mITT (IG1=13; CG=12); mean (SD) IG1: 12.1 (5.8) CG: 14.4 (4.8) HARS score, 6 weeks after end of treatment (12 weeks); mITT (IG1=13; CG=12); mean (SD) IG1: 10.4 (7.9) CG: 18.0 (7.5) Group × Time interaction: *P*<0.001
	Subgroup analyses: No subgroups of interest reported	NR

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Dilkov et al. (2017)[24] rTMS (25) Sham rTMS (25)	**Remission**: HARS score less than 10	Remission, end of treatment (6 weeks); ITT (IG1=15; CG=25); N (%) IG1: 12 (80) CG: NR Remission, 6 weeks after end of treatment (12 weeks); ITT (IG1=15; CG=25); N (%) IG1: 15 (100) CG: NR
	Response: At least 50% improvement on HARS scores from baseline to end of treatment	Response, end of treatment (6 weeks); ITT (IG1=15; CG=25); N (%) IG1: 15 (100) CG: 3 (12) Response, 6 weeks after end of treatment (12 weeks); ITT (IG1=15, CG=25), N (%) IG1: 15 (100) CG: 3 (12)
	Continuous outcomes • HARS • CGI-S	HARS change in score from baseline to end of treatment (6 weeks); ITT (IG1=15; CG=25); mean (SD) IG1: 25 (4) CG: NR Hedge's g: 2.1 *P*<0.001 CGI-S, posttreatment (6 weeks); ITT (IG1=15; CG=25); mean (SD) IG1: 3 (0.5) CG: 5 (1) *P*<0.001 CGI-S, 6 weeks' posttreatment (12 weeks); ITT (IG1=15; CG=25); mean (SD) IG1: 2 (0.5) CG: 5 (1) *P*<0.001
	Subgroup analyses: No subgroups of interest reported	NR

Abbreviations: CG = control group; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; GAD = generalized anxiety disorder; HARS = Hamilton Anxiety Rating Scale; IG = intervention group; ITT = intention to treat; mITT = modified intention-to-treat; NR = not rated; rTMS = repetitive transcranial magnetic stimulation; TMS = transcranial magnetic stimulation.

Table C-5. Safety Outcomes for Included Repetitive TMS Interventions for GAD

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
Diefenbach et al. (2016)[25] Active rTMS (14) Sham rTMS (12)	**Any Adverse Event**	NR
	Serious Adverse Event	Any SAE, 6 weeks posttreatment (12 weeks); mITT (IG1=13, CG=12); N (%) IG1: 1 (8) (chest pain determined to be unrelated to the study intervention) CG: 0 (0)
	Other Harms	All presumed to be reported between baseline and 6 weeks after end of treatment (12 weeks) Pinprick sensation mITT (IG1=13; CG=12); N (%) IG1: 9 (69) CG: 10 (83) Pain at stimulation site; mITT (IG1=13, CG=12); N (%) IG1: 11 (85) CG: 8 (67) *P*=NS Facial pain including eye pain; mITT (IG1=13; CG=12); N (%) IG1: 3 (23) CG: 1 (8) *P*=NS Headache; mITT (IG1=13; CG=12); N (%) IG1: 6 (46) CG: 3 (25) *P*=NS Toothache; mITT (IG1=13; CG=12); N (%) IG1: 3 (23) CG: 0 (0) *P*=NS Lightheadedness or dizziness; mITT (IG1=13; CG=12); N (%) IG1: 0 (0) CG: 2 (17) *P*=NS Facial twitch; mITT (IG1=13; CG=12); N (%) IG1: 6 (46) CG: 0 (0) *P*<0.01

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
Dilkov et al. (2017)[24] rTMS (25) Sham rTMS (25)	**Any Adverse Event**	NR
	Serious Adverse Events	Generalized tonic-clonic seizure; ITT (IG1=15; CG=25); N (%) IG1: 1 (7) CG: 0 (0)
	Other Harms	All patients reported twitching of facial muscles during RMT determinations. Transient dizziness in 3 patients (not reported by group)

Abbreviations: CG = control group; GAD = generalized anxiety disorder; IG = intervention group; ITT = intention to treat; mITT = modified intention-to-treat; NR = not rated; NS = not significant; RMT = resting motor threshold; TMS = transcranial magnetic stimulation.

Table C-6. Study Characteristics for Included Repetitive TMS Interventions for OCD

Author (Year) Country Registry #	Study Design Years Conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
Carmi et al. (2018)[27] Israel NCT01343732	Parallel RCT 2012 to 2014	Brainsway (partial support), other support NR	Yes, partially	Age 18 to 65 years; meeting DSM-IV criteria for OCD; failure of 2 SRI trials plus CBT; baseline Y-BOCS score of ≥20; with stable CBT or SSRI medication in maintenance	Any other Axis I pathology or current depressive episode
Carmi et al. (2019)[26] U.S., Israel, Canada NCT02229903	Parallel RCT 2014 to 2017	Brainsway	Yes, entirely	Age 22 to 68; receiving treatment in outpatient setting; Y-BOCS score 20 or greater; limited response to prior treatment defined as (1) maintenance treatment with SRI for at least 2 months or (2) CBT maintenance therapy and failed at least 1 past trial of SRI	Primary Axis I diagnosis other than OCD; severe neurological impairment; condition associated with increased risk of seizures
Harika-Germaneau et al. (2019)[28] France	Parallel RCT 2013 to 2016	NR	Sponsorship not reported	Outpatients age 18 to 65 years with Y-BOCS score of 20 or more; minimum 2-year duration of OCD meeting DSM-IV-TR criteria; at least 2 failed SRI treatments	Diagnosis of schizophrenia; current MDD; psychotic disorder; bipolar I disorder; substance and alcohol dependence; suicidal; metallic implant in the cranium (except teeth); severe or unstable medical condition; history of TMS, epilepsy, or neurological disorders leading to increased intracranial pressure; severe cardiac disorder, intracardiac lines; cardiac pacemaker or contraindication to MRI; abnormal finding on brain MRI
Hawken et al. (2016)[30] Turkey; Bulgaria NCT00616486	Parallel RCT NR	NR in study publication; CT.gov registry indicates: Queen's University, Military Medical Academy, Dokuz Eylul University	No	Age 18 to 65 years; DSM-IV primary diagnosis of OCD; 8 weeks of adequate treatment; 4 weeks of a stable dose SSRI; treatment refractory; score of ≥20 on the Y-BOCS	Schizophrenia; current MDD (HAMD17 > 18); psychotic disorders; bipolar I disorder; substance and alcohol dependence within prior 6 months; severe Axis II disorder; suicidal; metallic implant in the cranium (except mouth); severe or unstable medical conditions; failure to respond to ECT; TMS in prior 6 months; history of epilepsy; neurological disorders leading to increased

Author (Year) Country Registry #	Study Design Years Conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
					ICP; severe cardiac disorder; intracardiac line or cardiac pacemaker
Kang et al. (2009)[31] Republic of Korea NCT00932204	Parallel RCT February 2007 and January 2008	Authors declared no funding or support	No	DSM-IV diagnosed patients with OCD who failed a minimum 8 weeks of treatment of at least 2 serotonin reuptake inhibitors and behavior therapy	Movement disorder other than a tic; psychotic symptoms other anxiety disorder; mental retardation; alcohol or other substance abuse in prior 6 months; history of psychosurgery, encephalitis or significant head trauma
Meek et al. (2021)[32] Canada NCT02018185	Parallel RCT 2014 to 2018	University of Manitoba Start-Up Fund; St. Boniface Hospital Foundation	No	Adults meeting DSM-5 criteria for OCD	History of a psychotic episode; neurological illness; head injury; active substance use disorder; seizure disorder; current pregnancy; general rTMS contraindications; prior rTMS treatment; receiving CBT at time of study; currently taking more than 1 SSRI or SNRI
Pelissolo et al. (2016)[29] France	Parallel RCT NR	Grant from Programme Hospitalier de la Recherche Clinique; Assistance Publique-Hopitaux de Paris	No	DSM-IV OCD diagnosis; Y-BOCS score of ≥15; disease duration of 2 years or more; 2 prior failed 8-week SSRI treatment sequences	Previous TMS exposure
Prasko et al. (2006)[33] Czech Republic	Parallel RCT NR	Internal Grand Agency of Ministry of Health	No	Age 18 to 45 years, DSM-IV diagnosed OCD and ICD-10 research criteria for OCD, nonresponders to SRIs (after 8 weeks of treatment)	MDD; suicidality; score of 16 or higher on the HAMD17; organic psychiatric disorder; history of psychotic disorder; alcohol or drug abuse; serious somatic disease; use of nonprescribed medication; pregnant or nursing; epilepsy or pathological EEG; implant or pacemaker
Seo et al. (2016)[34] Republic of Korea	Parallel RCT NR	Grant from Seoul R&BD Program; CR Tech (now REMED Inc.)	Yes, partially	Right-handed adults age 18 to 60 years; primary DSM-IV diagnosis of OCD with residual symptoms and Y-BOCS score of 16 or higher; 2 failed anti-OCD medications	Comorbid psychiatric disorder other than depression; history of epilepsy, drug abuse, significant head injury, or any neurosurgical procedure; metal implant; pacemaker; ECT in prior 6 months

Abbreviations: CBT = cognitive behavioral therapy; DSM-IV = Diagnostic Manual of Mental Disorders, 4th edition; DSM-IV-TR = Diagnostic Manual of Mental Disorders, 4th edition (Text Revision); ECT = electroconvulsive therapy; EEG = electroencephalogram; HAMD17 = Hamilton Depression Rating Scale (17 item); ICP = increased intracranial pressure; MDD = major depressive disorder; MRI = magnetic resonance imaging; NR = not reported; OCD = obsessive compulsive disorder; RCT = randomized, controlled trial; rTMS = repetitive transcranial magnetic stimulation; SRI = serotonin reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TMS = transcranial magnetic stimulation; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Table C-7. Intervention Characteristics for Included Repetitive TMS Interventions for OCD

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
Carmi et al. (2019)[26]	Sham treatment (47) Sham type: Sham coil, not specified	dTMS (47) Target location: Dorsal mPFC and ACC Localization technique: Manual measurement Frequency: 20 Intensity: 100 Number of pulses: 2,000	Treatment days: 29 Treatment sessions total: 29	Medication per treatment as usual	Personalized OCD symptom provocations
Carmi et al. (2018)[27]	Sham (15) Sham type: Sham coil, not specified	High frequency dTMS (18) Target location: mPFC and ACC Localization technique: Manual measurement Frequency: 20 Intensity: 100 to 110 Number of pulses: 2,000	Treatment days: 25 (5 sessions per week for 5 weeks) Treatment sessions total: 25	Medication per treatment as usual Psychotherapy per treatment as usual	Personalized provocation designed by clinician
Harika-Germanea et al. (2019)[28]	Sham cTBS (16) Sham type: Sham coil, not specified	cTBS (14) Target location: Pre-SMA Localization technique: Image -guided Frequency: 50 Hz Intensity: 70 Number of pulses: 600	Treatment days: 30 (1 session daily for 5 days per week for 6 weeks) Treatment sessions total: 30	Medication per treatment as usual	None
Pelissolo et al. (2016)[29]	Sham rTMS (19) Sham type: Wand casing that blocks magnetic field	rTMS (20) Target location: Pre-SMA Localization technique: Image -guided Frequency: 1 Hz Intensity: 100 Number of pulses: 1,500	Treatment days: 20 (5 days per week for 4 weeks) Treatment sessions total: 20	Medication per treatment as usual	None

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
Hawken et al. (2016)[30]	Sham rTMS (12) Sham type: Angle wand away from scalp	rTMS (10) Target location: SMA) Localization technique: EEG-guided Frequency: 1 Intensity: 110 Number of pulses: 1,200	Treatment days: 25 (5 sessions per week for 4 weeks, 3 sessions in 5th week, 2 sessions in 6th week) Treatment sessions total: 25	Medication per treatment as usual	None
Kang et al. (2009)[31]	Sham (10) Sham type: Angle wand away from scalp	rTMS (11) Target location: Right DLPFC and the SMA Localization technique: Manual measurement Frequency: 1 Intensity: 110% right DLPFC and 100% SMA Number of pulses: 2,400	Treatment days: 10 (5 sessions per week for 2 weeks) Treatment sessions total: 10	Medication per treatment as usual	None
Meek et al. (2021)[32]	Sham (11) Sham type: Sham and active coil within the same device	rTMS (12) Target location: dACC Localization technique: Image-guided Frequency: 1 Intensity: 120% Number of pulses: 1,200	Treatment days: 10 (5 sessions per week for 2 weeks) Treatment sessions total: 20 (2 sessions per day)	Maximum of 1 SSRI maintained at a stable regimen throughout treatment or SNRI; no CBT	None
Prasko et al. (2006)[33]	Sham (12) Sham type: Angle wand away from scalp	rTMS (18) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 1 Intensity: 110 Number of pulses: 1,800	Treatment days: 10 (5 sessions per week for 2 weeks) Treatment sessions total: 10	Medication per treatment as usual	None
Seo et al. (2016)[34]	Sham rTMS (13) Sham type: Separate sham coil	rTMS (14) Target location: Right DLPFC Localization technique: Manual measurement Frequency: 1 Intensity: 100% Number of pulses: 1,200	Treatment days: 15 (5 days per week for 3 weeks) Treatment sessions total: 15	Medication per treatment as usual	None

Abbreviations: ACC = anterior cingulate cortices; cTBS = controlled theta-burst stimulation; CBT = cognitive behavioral therapy; dACC = dorsal anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; dTMS = deep transcranial magnetic stimulation; Hz = electromagnetic wavelength frequency; mPFC= medial prefrontal cortex; OCD = obsessive compulsive disorder; pre-SMA = presupplementary motor area; rTMS = repetitive transcranial magnetic stimulation; SMA = supplementary motor area; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TMS = transcranial magnetic stimulation.

Table C-8. Population Characteristics for Included Repetitive TMS Interventions for OCD

Author (Year)	Sample Size (Total)	Treatment History	Mean Age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
Carmi et al. (2019)[26]	100	Treatment resistant (defined liberally as any prior treatment to TMS)	38.8 (11.85)	39 (42)	White: 78 (83) Hispanic or Latino: 4 (4) Black or African American: 2 (2) Asian: 4 (4) Black or Afro-American and White: 2 (2) Hispanic or Latino and White: 1 (1) Hispanic or Latino and Indian or Alaska Native: 1 (1) Indian or Alaska Native: 2 (2)	NR
Carmi et al. (2018)[27]	41	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 36 (2.1) CG: 35 (3.5)	IG1: 7 (44) CG: 7 (50)	NR	NR
Harika-Germaneau et al. (2019)[28]	30	Treatment resistant (defined liberally as any prior treatment to TMS)	IG: 46.3 (10.1) CG: 48.2 (12.9)	IG: 9 (64) CG: 6 (43)	NR	History of MDD IG: 14.3% CG: 12.5%
Pelissolo et al. (2016)[29]	39	Treatment resistant (defined liberally as any prior treatment to TMS)	41.5 (10.7)	23 (58)	NR	MDD: 75%
Hawken et al. (2016)[30]	22	Treatment resistant (defined liberally as any prior treatment to TMS)	IG: 33 .0 (10.0) CG: 34.0 (14.0)	11 (50)	NR	NR
Kang et al. (2009)[31]	21	Treatment resistant (defined liberally as any prior treatment to TMS)	IG: 28.6 (12.7) CG: 26.2 (10.5)	IG: 2 (20) CG: 1 (10)	NR	MDD: 33%
Meek et al. (2021)[32]	23	Unspecified treatment naive or resistance	IG: 45.0 (16.7) CG: 38.3 (11.5)	IG: 6 (60) CG: 4 (40)	NR	NR

Author (Year)	Sample Size (Total)	Treatment History	Mean Age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
Prasko et al. (2006)[33]	33	Treatment resistant (defined liberally as any prior treatment to TMS)	Completers (IG=18; CG=12) IG: 28.9 (7.7) CG: 33.4 (8.7)	Completers (IG=18; CG=12) 12 (40)	NR	NR
Seo et al. (2016)[34]	28	Treatment resistant (defined liberally as any prior treatment to TMS)	IG: 34.6 (9.8) CG: 36.3 (12.5)	13 (48)	NR	MDD: 81%

Abbreviations: CG = control group; IG = intervention group; MDD = major depressive disorder; NR = not reported; TMS = transcranial magnetic stimulation.

Table C-9. Efficacy Outcomes for Included Repetitive TMS Interventions for OCD

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Carmi et al. (2019)[26] dTMS (47) Sham treatment (47)	**Remission**: NR	NR
	Response: Full response: reduction of 30% or greater in Y-BOCS score from baseline to posttreatment Partial response: reduction of 20% or greater in Y-BOCS score from baseline to posttreatment	Full response; posttreatment (6 weeks); ITT (IG plus CG=99); N (%) IG: NR (37.0) CG: NR (18.0) NNT: 5.3 *P*=0.04 Full response, 4 weeks posttreatment (10 weeks); ITT (IG plus CG=99); N (%) IG: NR (44.0) CG: NR (22.0) *P*=0.02 Full response, posttreatment (6 weeks), completers (IG=42; CG=45), N (%) IG: 16 (38.1) CG: 5 (11.1) *P*=0.003 Full response, 4 weeks posttreatment (10 weeks); completers (IG=42; CG=45); N (%) IG: 19 (45.2) CG: 8 (17.8) *P*=0.006 Partial response, posttreatment (6 weeks); completers (IG=42; CG=45) NR in text; reported in figure 3; *P*<0.01 Partial response; 4 weeks posttreatment (10 weeks); completers (IG=42; CG=45); N (%) IG: 25 (59.5) CG: 19 (42.2) *P*=0.106

Author (Year) Interventions (N Randomized)	Name of Measure	Results
	Continuous outcomes • Y-BOCS • CGI-S • CGI-I	Y-BOCS change in score from baseline to posttreatment (6 weeks); ITT (IG plus CG=99); mean (95%CI) IG: −6.0 (−3.8 to −8.2) CG: −4.1 (−1.9 to −6.2) ES: 0.48 *P*=0.09 Y-BOCS change in score from baseline to posttreatment (6 weeks); mITT (IG=47; CG=47); mean (95% CI) IG: −6.0 (−4.0 to −8.1) CG: −3.3 (−1.2 to −5.3) ES: 0.69 *P*=0.01 Y-BOCS change in score from baseline to 4 weeks posttreatment (10 weeks); mITT (IG=47; CG=47), mean (95% CI) IG: −6.5 (−4.3 to −8.7) CG: −4.1 (−1.9- to −6.2) ES: 0.62 *P*=0.03 CGI (unspecified as to I or S) change in score improved by 1 or 2 points; baseline to posttreatment (6 weeks); ITT (IG plus CG=99), N (%) IG: NR (48.0) CG: NR (25.0) *P*=0.045 CGI-I moderately or very much improved from baseline to posttreatment (6 weeks); completers (IG=41; CG=43), N (%) IG: 20 (49.0) CG: 9 (21.0) *P*=0.011 CGI-I moderately or very much improved from baseline to 4 weeks posttreatment (10 weeks); completers (IG=39; CG=40, N (%)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		IG: 19 (49.0) CG: 11 (27.5) *P*=NS CGI-S improved, baseline to posttreatment(6 weeks); completers (IG=41; CG=43); N (%) IG: 25 (61.0) CG: 14 (32.6) *P*=0.022 CGI-S improved, baseline to 4 weeks posttreatment (10 weeks); IG=39; CG=40; N (%) IG: 25 (64.0) CG: 18 (45.0) *P*=NS
	Subgroup analyses: No subgroups of interest reported	NR
Carmi et al. (2018)[27] High frequency dTMS (18) Sham (15)	**Remission**: NR	NR
	Response: Reduction in Y-BOCS score by 30% (or alternatively 35%)	Reduction in Y-BOCS by 30%, end of treatment (5 weeks); completers (IG1=16; CG=14); N (%) IG1: 7 (43.8) CG: 1 (7.1) *P*<0.05 Reduction in Y-BOCS by 35%, end of treatment (5 weeks); completers (IG1=16; CG=14); N (%) IG1: 5 (29.4) CG: 1 (7.1) *P*<0.10 Reduction in Y-BOCS by 30%, 1 week posttreatment (6 weeks); completers (IG1=11; CG=13); N (%) IG1: 5 (45.5) CG: 1 (7.7) *P*<0.05

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		Reduction in Y-BOCS by 30%, 1 month posttreatment (9 weeks); completers(IG1=9; CG=9); N (%) IG1: 4 (44.4) CG: 0 (0) *P*<0.05
	Continuous outcomes • Y-BOCS • CGI-I	Y-BOCS change in score, across all time points; completers (IG1=16; CG=14); NR IG1: NR (NR) CG: NR (NR) Group × Time effect *P*<0.001 favoring TMS Y-BOCS change in score, end of treatment (5 weeks); completers (IG1=16; CG=14); NR IG1: NR (NR) CG: NR (NR) Group effect *P*<0.01 favoring TMS Y-BOCS change in score, 1 week posttreatment (6 weeks); completers (IG1=11; CG=13); NR IG1: NR (NR) CG: NR (NR) *P*<0.05 favoring TMS Y-BOCS change in score, 1 month posttreatment (9 weeks); completers(IG1=9; CG=9); NR IG1: NR (NR) CG: NR (NR) *P*=NS CGI-I ≤ 2, baseline to end of treatment (5 weeks); completers (IG1=16; CG=14); NR Group effect *P*<0.01 favoring TMS CGI-I ≤ 2, end of treatment (5 weeks); completers (IG1=16; CG=14); N (%) IG1: 11 (68.7) CG: 1 (7.1) *P*<0.001 CGI-I ≤ 2, 1 week posttreatment (6 weeks); completers (IG1=11; CG=13); N (%)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		IG1: 7 (63.6) CG: 1 (7.7) *P*<0.01 CGI-I change in score, 1 week posttreatment (6 weeks); completers (IG1=11; CG=13); NR IG1: NR (NR) CG: NR (NR) *P*<0.05 CGI-I ≤2, 1 month posttreatment (9 weeks); completers (IG1=9; CG=9); N (%) IG1: 5 (55.6) CG: 3 (33.3) *P*=0.35 CGI-I change in score, 1 month posttreatment (9 weeks); completers (IG1=9; CG=9); NR IG1: NR (NR) CG: NR (NR) *P*=0.23
	Subgroup analyses: Sex	Male participants were significantly more likely to be responders than female participants (*P*<0.05)
Harika-Germaneau et al. (2019)[28] cTBS (14) Sham cTBS (16)	**Remission**: NR	NR
	Response: 25% decrease in Y-BOCS score	Response, posttreatment (6 weeks); mITT (IG=14; CG=14); N (%) IG: 3 (21.4) CG: 5 (35.7) *P*=0.403 Response, 6 weeks posttreatment (12 weeks); mITT (IG=14; CG=14); N (%) IG: 4 (28.4) CG: 5 (35.7) *P*=0.686 Response, 12 weeks posttreatment (18 weeks); mITT (IG=14; CG=14); N (%) IG: 4 (28.4) CG: 5 (35.7)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		P=0.686
	Continuous outcomes • Y-BOCS • CGI-S	Y-BOCS change, 6 weeks posttreatment (12 weeks); mITT (IG=14; CG=14); mean (SD) IG: NR CG: NR *P*=0.584 for group × visit interaction in repeated measures 2-way ANOVA Additional analyses using repeated Bayesian ANOVA showed similar findings of no effect CGI-S change, 6 weeks posttreatment (12 weeks); mITT (IG=14; CG=14); mean (SD) IG: NR CG: NR *P*=0.264 for group × visit interaction
	Subgroup analyses: No subgroups of interest reported	NR
Hawken et al. (2016)[30] rTMS (10) Sham rTMS (12)	**Remission**: NR	NR
	Response: Y-BOCS reduction of at least 25%	Response, posttreatment (6 weeks); ITT (IG=10; CG=12); N (%) IG: 8 (80.0) CG: 1 (8.0) P NR
	Continuous outcomes • Y-BOCS CGI (not specified)	Y-BOCS change, repeated measures (baseline to 6 weeks); ITT (IG= 10; CG= 12), NR IG: NR CG: NR *P*=0.023, favor TMS Y-BOCS score, posttreatment (6 weeks); ITT (IG=10; CG= 12) Hedge's g: 1.001 *P*<0.05, favor TMS Y-BOCS change, 2 weeks posttreatment (8 weeks); ITT (IG=10; CG=12) Between group main effect of treatment, *P*=0.044 Y-BOCS change, 4 weeks posttreatment (10 weeks); mITT (IG=8; CG=7) Between group main effect of treatment, *P*<0.001 CGI unspecified, repeated measures baseline to posttreatment (6 weeks); ITT (IG= 10; CG= 12) *P*=0.053, direction favors TMS

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		CGI unspecified, posttreatment (6 weeks); ITT (IG=10; CG=12); mean (SD) IG: 4 (2) CG: 5 (2) *P*=0.084 CGI unspecified, 2 weeks posttreatment (8 weeks); ITT (IG=10, CG=12); mean (SD) IG: 4 (2) CG: 5 (2) *P*=0.084
	Subgroup analyses: No subgroups of interest reported	NR
Kang et al. (2009)[31] rTMS (11) Sham (10)	**Remission**: NR	NR
	Response: Y-BOCS decrease of 25% or more from baseline to 2 weeks posttreatment	Response, 2 weeks posttreatment (4 weeks); completers (IG=10; CG=10); N (%) IG: 2 (20) CG: 2 (20) *P*=1.0
	Continuous outcomes: Y-BOCS	Y-BOCS change, baseline to 2 weeks posttreatment (4 weeks); completers (IG=10; CG=10) Group × time interaction; *P*=0.94
	Subgroup analyses: No subgroups of interest reported	NR
Meek et al. (2021)[32] rTMS (12) Sham (11)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes: Y-BOCS	Y-BOCS change, repeated measures baseline to 3 months posttreatment (14 weeks), completers (IG=10; CG=10); graphic depiction IG within group change *P*<0.001 CG within group change *P*=0.200 Between group change NR but 95% error bar appeared to overlap at all time points Y-BOCS change, posttreatment (2 weeks); completers (IG=10; CG=10); mean % IG: −20.1 CG: −8.0 P NR Y-BOCS change, 1 month posttreatment (6 weeks); completers (IG=10; CG=10); mean %

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		IG: −28.0 CG: −11.7 P NR Y-BOCS change, 3 months posttreatment (14 weeks); completers (IG=10; CG=10); mean % IG: −17.8 CG: −10.0 P NR Authors reported that they conducted an ITT analysis incorporating symptom assessments from the 3 noncompleters using methods to account for missing data points and produced similar results though data was not shown
	Subgroup analyses: No subgroups of interest reported	NR
Pelissolo et al. (2016)[29] rTMS (20) Sham rTMS (19)	**Remission**: NR	NR
	Response: Y-BOCS score reduction of ≥25% at posttreatment (week 4)	Response, posttreatment (week 4); mITT (IG=20; CG=16); N (%) IG: NR (10.5) CG: NR (20.0) *P*=0.63 Response, posttreatment (4 weeks); completer (IG=19; CG=15); N (%) IG: NR (NR) CG: NR (NR) *P*=0.47
	Continuous outcomes • Y-BOCS • CGI-S • CGI-I • GAF	Y-BOCS change, posttreatment (4 weeks); mITT (IG=20; CG=16); mean (SD) IG: −2.3 (5.0) CG: −3.5 (4.9) *P*=0.38 CGI-S change, posttreatment (4 weeks); mITT (IG=20; CG=16); mean (SD) IG: −0.3 (0.6) CG: −0.3 (0.6) *P*=0.72 CGI-I change, posttreatment (4 weels); mITT (IG=20; CG=16); mean (SD)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		IG: 3.6 (0.9) CG: 3.5 (1.1) *P*=0.54 GAF change, posttreatment (4 weeks); mITT (IG=20; CG=16); mean (SD) IG: 1.6 (4.4) CG: 1.9 (6.9) *P*=0.81
	Subgroup analyses: Age	No significant interaction between age and treatment effect
Prasko et al. (2006)[33] rTMS (18) Sham (12)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes • Y-BOCS • CGI-S	Y-BOCS change, posttreatment (2 weeks); completers (IG=18; CG=12); ANCOVA with baseline score as covariate IG: NR CG: NR *P*=NS Y-BOCS change, 2 weeks posttreatment (4 weeks); completers (IG=18; CG=12); ANCOVA with baseline score as covariate IG: NR CG: NR *P*=NS CGI-S, posttreatment (2 weeks); completers (IG=18; CG=12); mean (SD) IG: 4.8 (1.4) CG: 4.5 (0.9) *P*=NS CGI-S, 2 weeks posttreatment (4 weeks); completers (IG=18; CG=12); mean (SD) IG: 4.6 (1.7) CG: 3.8 (1.2) *P*=NS
	Subgroup Analyses: No subgroups of interest reported	NR
Seo et al. (2016)[34]	**Remission**: NR	NR
	Response: Y-BOCS score reduction of 25% or more	Response, posttreatment (3 weeks); mITT (IG: 14; CG: 13); N (%)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
rTMS (14) Sham rTMS (13)		IG: 7 (50.0) CG: 3 (23.1) *P*=0.148
	Continuous outcomes • Y-BOCS • CGI-S	Y-BOCS change, posttreatment (3 weeks); mITT (IG: 14; CG: 13); mean (SD) IG: −10.7 (8.2) CG: −3.7 (3.7) *P*=0.005 group × time interaction in repeated measures analysis Y-BOCS change, posttreatment (3 weeks); mITT (IG: 14; CG: 13); NR *P*=0.008 group × time interaction at single time point in post hoc analysis CGI-S change, repeated measures baseline to posttreatment (3 weeks); mITT (IG: 14; CG: 13) *P*=0.03 group × time interaction in repeated measures analysis
	Subgroup analyses: No subgroups of interest reported	NR

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; dTMS = deep transcranial magnetic stimulation; CG = control group; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; cTBS = continuous theta-burst stimulation; dTMS = deep transcranial magnetic stimulation; GAF = Global Assessment of Functioning; IG = intervention group; ITT = intention to treat; mITT = modified intention to treat; NR = not reported; NNT = number needed to treat; NS = not significant; TMS = transcranial magnetic stimulation; Y-BOCS = Yale–Brown Obsessive Compulsive Scale.

Table C-10. Safety Outcomes for Included Repetitive TMS Interventions for OCD

First Author (Year) Interventions (N Randomized)	Safety outcome	Results
Carmi et al. (2019)[26] dTMS (47) Sham treatment (47)	**Any Adverse Event**	Individuals reporting an AE, ITT (IG=49; CG=50); N (%) IG: 35 (73) CG: 35 (69) *P*=0.639
	Serious Adverse Event	Individuals reporting an SAE, ITT (IG=49; CG=50); N (%) IG: 1 (2) (significant suicidal thoughts requiring hospitalization that preceded the start of treatment) CG: 0 (0)
	Other Harms	NR
Carmi et al. (2018)[27] High frequency dTMS (18) Sham (15)	**Any Adverse Event**	NR
	Serious Adverse Event	SAE, 1 month posttreatment (9 weeks); completers (IG1=16; CG=14); N (%) IG: 0 (0) CG: 0 (0)
	Other Harms	Headache and fatigue IG1: 4 (NR) CG: 1 (NR)
Harika-Germaneau et al. (2019)[28] cTBS (14) Sham cTBS (16)	**Any Adverse Event**	AE, 6 weeks posttreatment (12 weeks); mITT(IG=14; CG=14), N (%) IG: 1 (7) CG: 2 (14) All AEs were mild headache.
	Serious Adverse Event	SAE, 6 weeks post-treatment (12 weeks); mITT (IG=14; CG=14); N (%) IG: 0 (0) CG: 0 (0)
	Other Harms	NR
Hawken et al. (2016)[30] rTMS (10) Sham rTMS (12)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	NR
Kang et al. (2009)[31] rTMS (11) Sham (10)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, 2 weeks posttreatment (4 weeks); completers (IG=10; CG=10) IG: 0 (0) CG: 0 (0)

First Author (Year) Interventions (N Randomized)	Safety outcome	Results
	Other Harms	Headache during session (IG=10; CG=10) IG: 1 (10) CG: 0 (0) Localized scalp pain during session (IG=10; CG=10) IG: 1 (10) CG: 0 (0)
Meek et al. (2021)[32] rTMS (12) Sham (11)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, 3 months posttreatment (14 weeks); completers (IG=10; CG=10); N (%) IG: 0 (0) CG: 0 (0)
	Other Harms	Incidence of specific AE, 3 months posttreatment (14 weeks); completers (IG=10; CG=10) IG Headache: 4 Fatigue: 3 Extreme fatigue: 2 Pain at the site of stimulation: 2 Numbing sensation at the back of the head: 1 Increased depression: 1 Transient difficulty with memory recall: 1 Transient confusion and trouble speaking: 1 Trouble sleeping: 1 Loss of productivity: 1 Nausea: 1 Unpleasant sensation of rTMS pulses: 5 CG Fatigue: 1 Increased anxiety: 1 Neck tension: 1
Pelissolo et al. (2016)[29] rTMS (20) Sham rTMS (19)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE (IG=NR; CG=NR); N IG: 0 CG: 0
	Other Harms	Headache (IG=NR; CG=NR); % IG: 50.0

First Author (Year) Interventions (N Randomized)	Safety outcome	Results
		CG: 37.5 *P*=0.5
Prasko et al. (2006)[33] rTMS (18) Sham (12)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, 2 weeks posttreatment (4 weeks); completers (IG=18; CG=12) IG: 0 (0) CG: 0 (0)
	Other Harms	Seizures, headaches, neurological, or cognitive difficulties, after rTMS; completers (IG=18; CG=12); N (%) IG: 0 (0) CG: 0 (0)
Seo et al. (2016)[34] rTMS (14) Sham rTMS (13)	**Any Adverse Event**	NR
	Serious Adverse Events	SAE, 3 weeks (IG: 14; CG: 13); N (%) IG: 0 (0) CG: 0 (0)
	Other Harms	Localized scalp pain, N IG: 3 CG: 0 Headache, N IG: 2 CG: 0

Abbreviations: AE = adverse event; CG = control group; dTMS = deep transcranial magnetic stimulation; IG = intervention group; ITT = intention to treat; mITT = modified intention to treat; NR = not reported; rTMS = repetitive transcranial magnetic stimulation; SAE = serious adverse event; TMS = transcranial magnetic stimulation.

Table C-11. Study Characteristics for Included Repetitive TMS Interventions for MDD

Author (Year) Country Registry #	Study Design Years conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
Anderson et al. (2007)[58] UK	Parallel RCT NR	Bolton, Salford and Trafford Mental Health Trust, and University of Modena, Italy	No	Outpatients age 17 years or older meeting DSM-IV criteria for major depressive episode using MINI; either poorly responsive to or not taking antidepressants	Safety considerations (e.g., suicidality, contraindications to TMS), organic brain disorder, nonaffective psychosis or current alcohol or drug misuse or dependence
Avery et al. (2006)[68] Wajdik et al. (2014)[131] U.S.	Parallel RCT 2001 to 2004	National Institute of Mental Health	No	Age 21 to 65 years meeting DSM-IV criteria for MDD; baseline HAMD17 score of at least 17 and not decreasing by more than 20% between screening and the first day of treatment; treatment resistant to at least 2 antidepressants	Previous TMS or failure of 9 or more ECT treatments; current major depressive episode longer than 5 years, bipolar disorder, antisocial or borderline personality disorder, symptoms of psychosis, other major psychiatric or medical comorbidity; history of seizure disorder, head injury with loss of consciousness, brain surgery, or substance abuse or dependence within the past 2 years.
Blumberger et al. (2012)[43] Canada NCT00305045	Parallel RCT 2006 to 2009	Ontario Mental Health Foundation (OMHF), Canadian Institutes of Health Research (CIHR) Clinician Scientist Award, CIHR Fellowship, National Health and Medical Research Council (NHMRC) Practitioner	No	Aged 18 to 85 years meeting DSM-IV criteria for MDD without psychotic features based on SCID, baseline HAMD17 score greater than 21; treatment resistant to at least 2 separate antidepressant medications; outpatients	History of substance dependence within previous 6 months or substance abuse within the previous month; borderline personality disorder or antisocial personality disorder; bipolar I, II, or NOS; significant unstable medical or neurological illness or history of seizures; suicidal; metal implants in the head; diagnosis of dementia; psychotropic medications in the previous 4 weeks; prior treatment with rTMS

Author (Year) Country Registry #	Study Design Years conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
		Fellowship, and National Alliance for Research on Schizophrenia and Depression (NARSAD) Lieber Young Investigator award			
Blumberger et al. (2016)[42] Canada	Parallel RCT 2008 to 2012	Ontario Mental Health Foundation (OMHF); first author receives equipment support from Brainsway Ltd. and Tonika/Magventure	Yes, partially	Age 18 to 85 years meeting DSM-IV criteria for MDD; experiencing a current major depressive episode with HAMD17 score of at least 20; having failed to achieve a clinical response to or did not tolerate at least 2 separate antidepressants from different classes for at least 6 weeks; receiving stable doses of psychotropic medications for at least 4 weeks before randomization	History of DSM-IV substance dependence (excluding nicotine) in the 6 months preceding the study or DSM-IV substance abuse in the month preceding the study; met DSM-IV criteria for borderline personality disorder or antisocial personality disorder; had an unstable medical or neurologic illness or a history of seizures; were acutely suicidal; were pregnant; had metal implants in the skull; had a cardiac pacemaker, an implanted defibrillator, or a medication pump; had a diagnosis of dementia or a current MMSE score <24; were taking lorazepam or equivalent medication during the 4 weeks preceding the study
Bretlau et al. (2008)[65] Denmark	Parallel RCT 2003 to 2005	Medicon Valley Academy; H Lundbeck A/S	Yes, partially	Age 18 to 75 years meeting the DSM-IV criteria for current MDD; failed at least 1 previous antidepressant treatment during the current depressive episode	Current episode of more than 24 months duration; organic brain disorder including mental retardation, schizophrenia, or other psychotic disorders; substance abuse; severe anxiety disorders; personality disorders; history of epilepsy; metal implant in the head or neck; pacemaker or other electronic implant; taking antipsychotics; major suicide ideation

Author (Year) Country Registry #	Study Design Years conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
Chou et al. (2020)[52] Taiwan NCT04364880	Parallel RCT 2012 to 2015	Ministry of Science and Technology, Taiwan; National Health Research Institutes, Taiwan; University of Macau, China; Ministry of Education, Taiwan; China Medical University, Taichung, Taiwan; China Medical University Hospital, Taichung, Taiwan	No	Age 18 to 70 years meeting DSM-IV criteria for MDD; symptom stability during a 1-week lead-in period with a HAMD21 score of at least 18 and decrease in score of less than 25% at the screening visits; failure in or marked intolerance to at least 1 antidepressant treatment or medication; free from antipsychotics, antidepressant, and anticonvulsant medications for more than 2 weeks	Diagnosis of other current Axis I disorders except nicotine dependence (e.g., psychotic disorders, bipolar disorders); failure in response to adequate trial of ECT, TMS, or VNS; pregnant; history or family history of seizure disorder; having known neurological disorders or evidence of central nervous system disease; have ferromagnetic material in the body or close to the head; have need for rapid clinical response due to conditions such as inanition, psychosis, or suicidality; have known preexisting noise-induced hearing loss, concurrent treatment with ototoxic medications, or with cochlear implants; are on medications known to lower seizure threshold
Cole et al. (2022)[51] U.S. NCT03068715	Parallel RCT 2017 to 2021	Stanford University, Brain and Behavior Research Foundation Young Investigator Award (to Dr. Williams), Charles R. Schwab, the David and Amanda Chao	Yes, partially	Age 22 to 80 years who had primary diagnosis of MDD, were currently expressing moderate to severe depressive episode (HAMD17 and MADRS scores of at least 20), and had moderate to severe levels of treatment resistance as measured by the Maudsley Staging Method	Any primary psychiatric diagnosis other than MDD; any condition that would increase the risk associated with receiving iTBS; prior exposure to rTMS; nonresponse to ECT; a history of psychosurgery for depression

Author (Year) Country Registry #	Study Design Years conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
		Fund II, the Amy Roth PhD Fund, the Neuromodulation Research Fund (funded by Medtronic), the Lehman Family, the Still Charitable Trust, the Marshall and Dee Ann Payne Fund, and the Gordie Brookstone Fund.			
Concerto et al. (2015)[67] Italy	Parallel RCT Recruitment occurred 2011 to 2013	NR	Sponsorship not reported	Age 40 to 65 years meeting DSM-IV-TR criteria for nonpsychotic MDD; drug-resistant MDD that had not responded to 3 different antidepressants from at least 2 different classes during the current episode; HAMD21 score of at least 20 or MADRS score of at least 25	Head injury or epilepsy; predisposition to seizure; implanted pacemaker; hearing loss; tinnitus; cochlear implants; metal in the brain, skull, or elsewhere in the body; medication infusion device; current psychotic features; history of any nonmood psychotic disorder; current neurological disease; pregnancy
Croarkin et al. (2021)[36] U.S. NCT02586688	Parallel RCT 2015 to 2018	Neuronetics	Yes, entirely	Age 12 to 21 years meeting DSM-5 criteria of unipolar MDD in a current major depressive episode (episode duration ≥4 weeks and ≤3 years) without psychotic features and having a HAMD24 score of at least 2 for item 1 and a total score of at least 20 at screening; intolerant of at least 4 prior medication trials	Having depression related to a medical condition, substance-induced depressive symptoms, or a seasonal depressive pattern as defined by DSM-5; history of psychotic disorder, intellectual disability, substance dependence or abuse (except nicotine and caffeine) in the past year, or neurologic disorder or seizures; diagnosis of bipolar disorder, OCD, PTSD, eating disorder, or unstable medical conditions;

Author (Year) Country Registry #	Study Design Years conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
					contraindications to TMS; previous exposure to TMS, ECT, or vagus nerve stimulation; cardiac pacemaker
Duprat et al. (2016)[56] Destmyter et al. (2016)[132] Belgium NCT01832805	Crossover RCT NR	University Ghent; University Hospital, Ghent	No	Right-handed; MDD; not on antidepressant; minimum of 1 unsuccessful treatment trial with SSRI or SNRI	Current or past history of epilepsy; neurosurgical intervention; pacemaker; metal or magnetic object in brain; had ECT; alcohol dependence; suicide attempt in prior 6 months
Fitzgerald et al. (2012)[57] Australia	Parallel RCT 2008 to 2010	National Health and Medical Research Council (NHMRC), Australia	No	rTMS naive patients meeting moderate to severe depression diagnosis based on a HAMD17 score of greater than 15; treatment resistant to at least 2 courses of antidepressant medications	Current diagnosis of bipolar disorder, schizophrenia spectrum disorders, or a significant medical or neurological illness; or contraindication to rTMS
Garcia-Toro et al. (2001)[71] Spain	Parallel RCT NR	Coordinadora de Minusvalidos from Mallorca and ARISPAM	No	Age 18 years or older and meeting DSM-IV criteria for unipolar major depression; unsuccessfully followed 2 trials of antidepressant medication for treatment of the current episode for at least 6 weeks	Previous seizures or neurosurgery; current serious or uncontrolled medical illness; pacemakers or hearing aids; pregnant women or of childbearing potential with no contraceptive method; high suicidal risk
Garcia-Toro et al. (2001)[62] U.S. and Spain	Parallel RCT NR; submitted for publication 2000	National Alliance for Research on Schizophrenia and Depression (NARSAD, the NAMI Stanley Vada Foundation, and the National Institute of Mental Health	No	Age 18 years or older meeting DSM-IV criteria for MDD	Taking sertaline for present depression episode; suicidal risk; contraindications for rTMS, including personal or family history of seizure, implanted medical devices and unstable medical conditions
Garcia-Toro et al. (2006)[69]	Parallel RCT	Fundacio La Marato de TV3Q	No	Age 18 years or older; meet DSM-IV criteria for unipolar major depression; no	Personal or family history of seizures; neurosurgical procedures; implanted

Author (Year) Country Registry #	Study Design Years conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
Spain	NR			adequate clinical response to 2 trials of antidepressant medication	pacemaker; inner ear prosthesis; medication pump; pregnancy, unstable medical condition; high risk of suicide
George et al. (2010)[39] Borckardt et al. (2013)[133] U.S. NCT00149838	Parallel RCT 2004 to 2009	National Institute of Mental Health; Neuronetics Inc (loaned devices through a competitive bid process)	No	Age 18 to 70 years meeting DSM-IV criteria for MDD, single episode or recurrent, current episode 5 years or less, baseline HAMD24 score of at least 20; antidepressant medication-free outpatients; stable during 2-week lead-in period; moderately treatment resistant, defined by antidepressant treatment history form	Diagnosis with other Axis I disorder; history of failed ECT, history of TMS or VNS; history of seizure disorder or neurologic disorder; ferromagnetic material in body or close to head; medications know to lower seizure threshold
Hausmann et al. (2004)[70] Austria	Parallel RCT NR; submitted for publication 2002	Lundbeck Austria provided equipment	Yes, partially	Medication-free inpatients meeting DSM-IV criteria for MDD, baseline HAMD21 score of at least 18	Current diagnosis with psychotic features, major medical problems, or suicidal ideation; contraindications to TMS
Herwig et al. (2003)[60] Germany	Parallel RCT NR; submitted for publication 2002	START program of the University of Ulm, Germany; Fa. Zeiss, Oberkochen, Germany	Yes, partially	Adults meeting DSM-IV and ICD-10 criteria for MDD, baseline score of at least 17 on 2 of the following scales: HAMD21, MADRS or BDI	Current neurological or other psychiatric disorders; safety criteria, including history of epileptic seizures, brain damage, or neurosurgical operation
Hoppner et al. (2003)[61] Germany	Parallel RCT NR	NR	Sponsorship not reported	Adult inpatients meeting DSM-IV criteria for MDD	Other relevant medical illnesses (not specified)

Author (Year) Country Registry #	Study Design Years conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
Januel et al. (2006)[46] France	Parallel RCT NR	NR	Sponsorship not reported	Aged 18 to 65 years meeting DSM-IV criteria for MDD; HAMD score >18; right-handed	History of brain trauma or seizure, bipolar disorder, abuse, or dependence to psychoactive substance
Kaster et al. (2018)[54] Canada NCT01860157	Parallel RCT 2013 to 2016	Canadian Institute for Health Research University, Brainsway Ltd.	Yes, partially	Aged 60 to 85 years with DSM-IV diagnosis of MDD; current major depressive episode with HAMD24 score of at least 22; lack of response to at least 1–2 inadequate antidepressant trials during the current episode; currently receiving stable dosages of medications for at least 4 weeks prior to screening	Primary diagnosis of psychotic disorder, OCD, PTSD, anxiety, or personality disorder; diagnosis of bipolar I or II disorder, dementia (MMSE score of <26), or unstable medical/neurologic illness; acute suicidality; substance dependence/abuse <3 months before study entry; previous rTMS treatment; history of seizures or intracranial implant; failed ECT trial during current episode; receiving bupriopion >300 mg/day, lorazepam >2 mg/day, or any anticonvulsant; significant laboratory abnormalities
Kim et al. (2019)[40] U.S. NCT01492309	Parallel RCT 2011 to 2017	NIMH; Neuronetics provided the TMS device	Yes, partially	Age 18 to 39 years old; 14 to 34 weeks gestational age by last menstrual period and first trimester ultrasound; DSM-IV primary diagnosis of MDD; HAMD17 score of ≥18; and CGI-S ≥3	History of preterm birth, psychiatric disorder other than MDD or an anxiety disorder, drug or alcohol abuse within the previous 6 months, or failure to respond to ECT; seizure disorder in self or first degree relative, any metallic object implanted in the skull, significant cardiac disease, a known abnormality in the fetus, known obstetrical complications, or active suicidal ideation
Koerselman et al. (2004)[66] The Netherlands	Parallel RCT 1997 to 2001	NR	Sponsorship not reported	Inpatients and outpatients older than 16 years meeting DSM-IV criteria for major depressive episode; score of at least 20 on HAMD17	History of epilepsy and any other medical disorder that precluded the administration of rTMS; taking psychotropic medication where dosage of antidepressive medication was changed within 6 weeks or dosage of benzodiazepine (hypnotics and anxiolytics) was changed within 2 weeks prior to study inclusion

Author (Year) Country Registry #	Study Design Years conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
Lee et al. (2018)[63] Republic of Korea	Parallel RCT 2015 to 2016	Ministry of Health & Welfare, Republic of Korea; REMED (Daejeon, Korea) provided partial funding	Yes, partially	Age 18 to 65 years of age; meeting DSM-IV criteria for unipolar MDD; no active medical conditions	Other current or history of Axis I psychiatric disorder; history of epilepsy, spontaneous seizures, or brain surgery; substance use disorder; pregnancy; contraindication for magnetic stimulation (e.g., cardiac pacemaker, implanted medication pump, or hearing aid with metal)
Levkovitz et al. (2015)[53] U.S., Israel, Germany, Canada NCT00927173	Parallel RCT 2009 to 2012	Brainsway	Yes, entirely	Age 22 to 68 years meeting DSM-IV criteria for MDD; current episode duration between 1 month and 7 years; baseline CGI-S score of at least 4 and HAMD21 score of at least 20, antidepressant medication free outpatients with symptom stability during washout period; treatment resistant to between 1 and 4 antidepressant treatments	History of psychosis, bipolar disorder, OCD, PTSD, or eating disorders; significant neurological disorder, increased risk of seizure, suicidal risk; lack of response to ECT or prior treatment with rTMS, dTMS, or VNS; presence of metal object in or near the head
Li et al. (2014)[55] Taiwan	Parallel RCT NR	Taipei Veterans General Hospital; Yen Tjing Ling Medical Foundation	No	Aged 21 to 70 years meeting DSM-IV criteria for recurrent MDD; treatment resistant; having failed at least 2 antidepressant treatments; baseline CGI score of at least 4 and HAMD17 score of at least 18	History of psychotic disorders; bipolar I or II disorders; substance abuse or dependence; personality disorders; history of major systemic illness or neurological disorder; brain implants or pacemaker
Li et al. (2020)[50] Li et al. (2021)[134] Taiwan UMIN000020892	Parallel RCT 2016 to 2018	Taipei Veterans General Hospital, Ministry of Science and Technology	No	Aged 21 to 70 years meeting DSM-IV criteria for MDD; baseline CGI-S score of at least 4 and HAMD17 score of at least 18; treatment resistant to at least 1 antidepressant treatment for current episode; antidepressant free for at least 1 week prior to present trial	Diagnosis of psychotic disorders, bipolar disorders, organic mental disorders, or strong suicidal risk
O'Reardon et al. (2007)[37] Janicak et al. (2008)[135]	Parallel RCT 2004 to 2005	Neuronetics	Yes, entirely	Age 18 to 70 years; DMS-IV diagnosis of MDD, baseline CGI-S score of at least 4 and HAMD17 sore of at least 18; required to have failed at least 1 but no more than 4 adequate antidepressant treatments	History of psychosis, bipolar disorder, OCD, PTSD, or eating disorders; lack of response to an adequate trial of ECT; presence of ferromagnetic material in or in close

Author (Year) Country Registry #	Study Design Years conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
U.S., Australia, Canada NCT00104611					proximity to the head; personal or family history of seizure or risk of seizure
Padberg et al. (2002)[48] Germany	Parallel RCT NR	German Federal Research Ministry	No	Suffering from a moderate to severe major depressive episode based on a clinical interview following DSM-IV criteria	Patients with organic brain disorders, unstable medical conditions, pacemakers, mobile metal implants, or implanted medication pumps
Pallanti et al. (2010)[44] Italy NCT00806143	Parallel RCT 2008 to 2009	Italian Department of Health; Institute of Neuroscience (Florence, Italy)	No	Adults age 18 years or older diagnosed with nonpsychotic major depression according to DSM-IV criteria, right-handed, HAMD score of at least 18, at least 2 previous failed antidepressant trials each lasting at least 6 weeks, duration of at least 4 months for current depressive episode, illness duration of at least 4 years	Any additional psychiatric comorbidity as assessed by the SCID, rTMS contraindications (e.g., metallic implants, foreign bodies, history of seizures); substance abuse in the previous 6 months; any major medical disease
Rossini et al. (2005)[45] Italy	Parallel RCT 2004 to 2005	NR	Sponsorship not reported	Aged 18 to 75 meeting DSM-IV criteria for MDD, baseline HAMD score of at least 21, right-handed	Presence of any concomitant Axis I diagnosis, manic or hypomanic episodes, or psychotic features; somatic or neurologic illnesses impairing psychiatric evaluation; history of seizures or pacemakers, metal implants, implanted medical pumps, or metal clips in the skull
Schutter et al. (2009)[59] Netherlands	Parallel RCT 2004 to 2007	NR	Sponsorship not reported	Primary diagnosis of depressive disorder (DSM-IV criteria) and a score of 15 or greater on the HAMD	History of seizures, neurological conditions, metal objects in or around the body that cannot be removed, heart disease, pregnancy, drug and alcohol abuse
Stern et al. (2007)[47] U.S.	Parallel RCT NR	The Spanish Ministerio de Educacion y Cienca (DGICYT), the Milton Fund, the	No	Outpatients age 21 to 80 years meeting DSM-IV criteria for MDD; baseline HAMD21 score of at least 20; treatment resistant having failed at least 1 course of antidepressants	History of psychosis, including schizophrenia or schizoaffective disorder, bipolar disorder, OCD, personality disorder, or substance abuse within the past year; current acute or chronic medical condition requiring psychoactive medication; history of epilepsy,

Author (Year) Country Registry #	Study Design Years conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
		Stanley Vada NAMI Foundation, the National Alliance for Research on Schizophrenia and Depression, and National Institute of Mental Health			seizures, or other neurological disorder; metal in head or implanted medical device
Taylor et al. (2018)[49] U.S. NCT01900314	Parallel RCT 2013 to 2015	National Institute of Mental Health (NIMH) Neuronetics	Yes, partially	Aged 22 to 65 years; primary diagnosis of MDD; failed at least 1 antidepressant medication trial; moderately severe depression; stable antidepressant dosage 4 weeks prior	Psychotic, bipolar, obsessive compulsive, or PTSD; current depressive episode longer than 5 years; previous ECT; contraindication to rTMS or MRI; serious suicidal ideation or behavior
Theleritis et al. (2017)[64] Greece ISRCTN71929667	Parallel RCT 2006 to 20111	First Psychiatry Department, Eginition Hospital, National and Kapodistrian University of Athens (Greece)	No	Age 18 to 59 years; meet DSM-IV-TR criteria for nonpsychotic MDD; treatment resistant (failure of at least 2 trials of 2 different antidepressants); right-handed	History of seizures, head injury with loss of consciousness, or brain surgery; dementia or other Axis I diagnosis; metal implants; substance dependence or abuse within previous 6 months; pregnancy
van Eijndhoven et al. (2020)[41] The Netherlands ISRCTN 15.535.800	Parallel RCT 2012 to 2019	NR	Sponsorship not reported	Age 18 years or older with a current depressive episode without psychotic features that lasted at least 2 years and failed to respond to at least 2 adequate trials of antidepressants and 1 adequate trial of CBT	History of substance abuse or dependence; comorbid diagnosis of bipolar or other psychotic disorders; history of traumatic brain injury; claustrophobia; metal implants; and pregnancy
Yesavage et al. (2018)[38] U.S.	Parallel RCT 2012 to 2017	VA Office of Research and Development	No	Age 18 to 80 years meeting DSM-IV criteria for MDD; HAMD score of at least 20; failing at least 2 adequate medication trials	History of or current psychosis or bipolar disease; active suicide ideation; unstable cardiac disease; risk factors for elevated seizure risk (e.g., TBI, medications, personal history, or cerebral mass); contraindication to

Author (Year) Country Registry #	Study Design Years conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
NCT01191333					MRI or magnetic therapy (implanted metal in brain, cardiac pacemaker); prior exposure to TMS

Abbreviations: CBT = cognitive behavioral therapy; CGI-S = Clinical Global Impression-Severity; DSM-IV = Diagnostic Manual of Mental Disorders, 4th edition; DSM-IV-TR = Diagnostic Manual of Mental Disorders, 4th edition (Text Revision); DSM-5 = Diagnostic Manual of Mental Disorders, 5th edition; ECT = electroconvulsive therapy; HAMD17 = Hamilton Depression Rating Scale (17 item); HAMD21 = Hamilton Depression Rating Scale (21 item); HAMD24 = Hamilton Depression Rating Scale (24 item); ICD-10 = International Classification of Disorders, 10th Edition; iTBS = intermittent theta-burst transcranial magnetic stimulation; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NOS = not otherwise specified; OCD = obsessive compulsive disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SCID = Structured Clinical Interview for DSM-5; SSNI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TBI = traumatic brain injury; TMS = transcranial magnetic stimulation; VNS = vagus nerve stimulation.

Table C-12. Intervention Characteristics for Included Repetitive TMS Interventions for MDD

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
Anderson et al. (2007)[58]	Sham rTMS (16) Sham type: Separate sham coil	rTMS (14) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 10 Hz Intensity: 110% Number of pulses: 1,000	Treatment days: 12 (with 6 more days of treatment available for partial responders) Treatment sessions total: 12 (with 6 more sessions available for partial responders)	Medication per treatment as usual	None
Avery et al. (2006)[68] Wajdik et al (2014)[131]	Sham rTMS (33) Sham type: Angle wand away from scalp	rTMS (35) Target location: Left DLPFC Localization technique: Image-guided Frequency: 10 Intensity: 110 Number of pulses: 1,600	Treatment days: 15 (all completed within a 4-week period) Treatment sessions total: 15	Psychotherapy per treatment as usual; participants were encouraged but not required to stop antidepressant medication, sedatives, and benzodiazepines at least 2 weeks prior to start of study	None
Blumberger et al. (2012)[43]	Sham rTMS (22) Sham type: Angle wand away from scalp	IG1: Bilateral rTMS (28) Target location: Bilateral DLPFC Localization technique: Manual measurement Frequency: 1 Hz right; then 10 Hz left Intensity: 100% in subjects age 60 years or younger; 120% in subjects age 60 years or older Number of pulses: 465 right; then 750 left IG2: Unilateral rTMS (24) Target location: Left DLPFC	IG1: Treatment days: 15 (with potential for 15 more for nonremitters); 5 sessions per week for 1 session per day Treatment sessions total: 15 (with potential for 15 more for nonremitters) IG2: Treatment days: 15 (with potential for 15 more for nonremitters) Treatment sessions total: 15 (with potential for 15 more for nonremitters)	IG1: Medication per treatment as usual IG2: Medication per treatment as usual	IG1: None IG2: None

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
		Localization technique: Manual measurement Frequency: 10 Hz Intensity: 100% in subjects age 60 years or younger; 120% in subjects age 60 years or younger Number of pulses: 1,450			
Blumberger et al. (2016)[42]	Sham rTMS (41) Sham type: Angle wand away from scalp	IG1: Bilateral rTMS (40) Target location: Bilateral DLPFC Localization technique: Image-guided Frequency: 1 Hz, 10 Hz Intensity: 120% Number of pulses: 600, 1,500 IG2: Unilateral rTMS (40) Target location: Left DLPFC Localization technique: Image-guided Frequency: 10 Intensity: 120% Number of pulses: 2,100	IG1: Treatment days: 15 (5 days per week for 3 weeks) for everyone 15 additional sessions for nonremitters at 3 weeks Treatment sessions total: 15 for everyone 15 additional sessions for nonremitters at 3 weeks IG2: Treatment days: 15 (5 days per week for 3 weeks) for everyone 15 additional sessions for nonremitters at 3 weeks Treatment sessions total: 15 for everyone 15 additional sessions for nonremitters at 3 weeks	IG1: Medication per treatment as usual IG2: Medication per treatment as usual	IG1: None IG2: None
Bretlau et al. (2008)[65]	Sham rTMS (24) Sham type: Separate sham coil	rTMS (25) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 8 Intensity: 90 Number of pulses: 1,289	Treatment days: 15 (5 days per week for 3 weeks) Treatment sessions total: 15	Medication per study protocol: Participants switched at baseline to open treatment with escitalopram at a dose of 10 mg daily in the first week and thereafter in a fixed dose of 20 mg daily throughout the planned acute treatment phase of 12 weeks in total; during the first 3 weeks, escitalopram was	None

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
				administered in combination with rTMS / sham TMS; the patients then continued with 20 mg escitalopram daily; as concomitant treatment for sleep problems, only oxazepam at a dose of 15 to 30 mg daily when needed was accepted; medications were discontinued prior to TMS	
Chou et al. (2020)[52]	Sham TBS (30) Sham type: Sham coil, not specified	TBS (30) Target location: Bilateral DLPFC Localization technique: Manual measurement Frequency: 50 Hz Intensity: 80% Number of pulses: 1,200 (600 continuous to the right; 600 intermittent to the left)	Treatment days: 10 (3 sessions per week for 3.2 weeks) Treatment sessions total: 10 (3 sessions per week for 3.2 weeks)	Medication per study protocol: Stopped antidepressant, antipsychotic, and anticonvulsant medications for 1 week before baseline assessments; patients were allowed limited use of either sedatives and hypnotics or anxiolytics during the lead-in or 24-week study periods	None
Cole et al. (2022)[51]	Sham iTBS (15) Sham type: Sham and active coil within the same device	iTBS (14) Target location: Left DLPFC Localization technique: Image-guided Frequency: NR Intensity: 90% RMT Number of pulses: 1,800	Treatment days: 5 (10 sessions per day) Treatment sessions total: 50	Mediction per treatment as usual	None
Concerto et al. (2015)[67]	Sham TMS (15) Sham type: Angle wand away from scalp	rTMS (15) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 10 Intensity: 120 Number of pulses: 3,000	Treatment days: 20 (5 days per week for 4 weeks) Treatment sessions total: 20	Medication per treatment as usual	None

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
Croarkin et al. (2021)[36]	Sham TMS (58) Sham type: Separate sham coil	rTMS (54) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 10 Hz Intensity: 120% (decreased to 110% during the first week if needed for tolerability) Number of pulses: 3,000	Treatment days: 30 (30 sessions over 6 weeks) Treatment sessions total: 30	Medications discontinued prior to TMS Psychotherapy per treatment as usual	None
Duprat et al. (2016)[56] Desmyter et al. (2016)[132]	Sham iTBS (47) Sham type: Separate sham coil	iTBS (47) Target location: Left DLPFC Localization technique: Image-guided Frequency: 50 Intensity: 110 Number of pulses: 1,620	Treatment days: 4 days (5 sessions per day) Treatment sessions total: 20	Medications discontinued prior to TMS with the exception of benzodiazepine	None
Fitzgerald et al. (2012)[57]	Sham rTMS (20) Sham type: Angle wand away from scalp	IG1: Bilateral rTMS (22) Target location: Bilateral DLPFC Localization technique: Image-guided Frequency: 1 Hz right side; 10 Hz left side Intensity: 120% Number of pulses: 900 right side; 1,500 left side IG2: Unilateral rTMS (24) Target location: Left DLPFC Localization technique: Image-guided	IG1: Treatment days: 15 (5 sessions per week for 3 weeks) Treatment sessions total: 15 IG2: Treatment days: 15 (5 sessions per week for 3 weeks) Treatment sessions total: 15	IG1: Medication per treatment as usual IG2: Medication per treatment as usual	IG1: None IG2: None

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
		Frequency: 10 Hz Intensity: 120% Number of pulses: 1,500			
Garcia-Toro et al. (2001)[71]	Sham (20) Sham type: Angle wand away from scalp	rTMS (20) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 20 Intensity: 90 Number of pulses: NR	Treatment days: 10 Treatment sessions total: 10	Medication per treatment as usual	None
Garcia-Toro et al. (2001)[62]	Sham rTMS (14) Sham type: Angle wand away from scalp	High frequency rTMS (14) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 20 Intensity: 90 Number of pulses: 1,200	Treatment days: 10 (5 sessions per week for 2 weeks) Treatment sessions total: 10	Medication per study protocol: all participants started on sertaline and continued through treatment; participants taking benzodiazepines remained on medication prior to study entry and continued taking them Medication per treatment as usual	None
Garcia-Toro et al. (2006)[69]	Sham rTMS (10) Sham type: Angle wand away from scalp	IG1: 20 + 1-Hz rTMS (10) Target location: Left prefrontal cortex (high frequency); right prefrontal cortex (low frequency) Localization technique: Manual measurement Frequency: 1 and 20 Intensity: 110 Number of pulses: 3,000 IG2: 20 + 1-Hz rTMS + sPECT targeting (10) Target location: Right prefrontal cortex, left prefrontal cortex, left	IG1: Treatment days: 10 (5 days per week for 2 weeks) Treatment sessions total: 10 IG2: Treatment days: 10 Treatment sessions total: 10	IG1: Medication per treatment as usual Psychotherapy per treatment as usual IG2: Medication per treatment as usual Psychotherapy per treatment as usual	IG1: None IG2: None

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
		temporoparietal , right temporoparietal Localization technique: Manual measurement Frequency: 1 and 20 Intensity: 110 Number of pulses: 3,000			
George et al. (2010)[39] Borckardt et al. (2013)[133]	Sham rTMS (Unclear (98 analyzed)) Sham type: Sham coil, not specified	rTMS (Unclear [92 analyzed]) Target location: Left DLPFC Localization technique: Image-guided Frequency: 10 Intensity: 120% Number of pulses: 3,000	Treatment days: 15 (5 sessions per week for 3 weeks) Treatment sessions total: 15	Medications discontinued prior to TMS	None
Hausmann et al. (2004)[70]	Bilateral sham rTMS (14) Sham type: Separate sham coil	IG1: Unilateral high frequency rTMS (13) Target location: Left DLPFC Localization technique: Image-guided Frequency: 20 Hz Intensity: 100 Number of pulses: 2,000 IG2: Bilateral rTMS (14) Target location: Bilateral DLPFC Localization technique: Image-guided Frequency: LDLPC: 20 Hz RDLPC: 1 Hz Intensity: LDLPC: 100 RDLPC: 120 Number of pulses: 2,600	IG1: Treatment days: 10 Treatment sessions total: 10 IG2: Treatment days: 10 Treatment sessions total: 10	IG1: Medication per study protocol: medication began on the first day of treatment through the end of treatment; choice of medication on a naturalistic basis IG2: Medication per study protocol: medication began on the first day of treatment through the end of treatment; choice of medication on a naturalistic basis	IG1: None IG2: None

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
Herwig et al. (2003)[60]	Sham rTMS (12) Sham type: Angle wand away from scalp	rTMS (13) Target location: PET-guided to find the hypometabolic DLPFC, and if no detectable hypometabolism, then alternated of the left and right DLPFC Localization technique: Image-guided Frequency: 15 Hz Intensity: 110 Number of pulses: 3,000	Treatment days: 10 (5 session per week for 2 weeks) Treatment sessions total: 10	Medication per study protocol: either remain on stable antidepressant therapy for at least 3 weeks or begin new antidepressant therapy concurrent with stimulation	None
Hoppner et al. (2003)[61]	Sham rTMS (10) Sham type: Angle wand away from scalp	IG1: High frequency rTMS (10) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 20 Intensity: 90 Number of pulses: 800 IG2: Low frequency rTMS (10) Target location: Right DLPFC Localization technique: Manual measurement Frequency: 1 Intensity: 110 Number of pulses: 120	IG1: Treatment days: 10 (5 sessions per week for 2 weeks) Treatment sessions total: 10 IG2: Treatment days: 10 (5 sessions per week for 2 weeks) Treatment sessions total: 10	IG1: Patients received an antidepressant medication in a constant dosage 2 weeks before and during simulation, but the specific medication and dosage was not prescribed IG2: Patients received an antidepressant medication in a constant dosage 2 weeks before and during simulation, but the specific medication and dosage was not prescribed	IG1: None IG2: None
Januel et al. (2006)[46]	Sham (16) Sham type: Sham coil, not specified	rTMS (11) Target location: Right DLPFC Localization technique: Manual measurement Frequency: 1 Intensity: 90 Number of pulses: NR	Treatment days: 16 (5 treatments per week for 2 weeks, then 3 treatments per week for 2 weeks) Treatment sessions total: 16	Medications discontinued prior to TMS	None

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
Kaster et al. (2018)[54]	Sham rTMS (28) Sham type: Sham and active coil within the same device	Active deep rTMS (30) Target location: Bilateral dorsolateral and ventrolateral prefrontal cortex with greater intensity and penetration of the left hemisphere Localization technique: NR Frequency: 18 Hz Intensity: 120% Number of pulses: 6,012	Treatment days: 20 (5 days per week, for 4 weeks) Treatment sessions total: 20	Medication per treatment as usual	None
Kim et al. (2019)[40]	Sham TMS (12) Sham type: Sham and active coil within the same device	TMS (14) Target location: Right DLPFC Localization technique: Manual measurement Frequency: 1 Intensity: 100% Number of pulses: 900	Treatment days: 20 (5 days per week for 4 weeks) Treatment sessions total: 20	Medication per treatment as usual	None
Koerselman et al. (2004)[66]	Sham rTMS (26) Sham type: Angle wand away from scalp	rTMS (26) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 20 Intensity: 80% Number of pulses: 800	Treatment days: 10 (5 sessions per week for 2 weeks) Treatment sessions total: 10	Medication per treatment as usual	None
Lee et al. (2018)[63]	Sham rTMS (NR [15 analyzed]) Sham type: Sham coil, not specified	rTMS (NR [15 analyzed]) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 10 Intensity: 110% Number of pulses: 3,000	Treatment days: 15 (5 sessions per week for 3 weeks) Treatment sessions total: 15	Medication per treatment as usual	None
Levkovitz et al. (2015)[53]	Sham dTMS (122) Sham type: Sham and active coil within the same device	dTMS (111) Target location: Left DLPFC Localization technique: Manual measurement	Treatment days: Active phase: 20 (5 sessions per week for 4 weeks)	Medications discontinued prior to TMS	None

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
		Frequency: 18 Intensity: 120% Number of pulses: 1,980	Maintenance phase: 24 (2 sessions per week for 12 weeks) Treatment sessions total: Active phase: 20 Maintenance phase: 24		
Li et al. (2014)[55]	Sham TBS (15) Sham type: Angle wand away from scalp	IG1: Continuous TBS (15) Target location: Right DLPFC Localization technique: Image-guided Frequency: 50 Hz Intensity: 80 Number of pulses: 1,800 IG2: Intermittent TBS (15) Target location: Left DLPFC Localization technique: Image-guided Frequency: 50 Hz Intensity: 80 Number of pulses: 1.800 IG3: Intermittent and continuous TBS (15) Target location: Bilateral DLPFC Localization technique: Image-guided Frequency: 50 Hz Intensity: 80 Number of pulses: 3,600	IG1: Treatment days: 10 (1 treatment per day for 5 days per week for 2 weeks) Treatment sessions total: 10 IG2: Treatment days: 10 (1 treatment per day for 5 days per week for 2 weeks) Treatment sessions total: 10 IG3: Treatment days: 10 (1 treatment per day for 5 days per week for 2 weeks) Treatment sessions total: 10	IG1: Medication per treatment as usual Psychotherapy per treatment as usual IG2: Medication per treatment as usual Psychotherapy per treatment as usual IG3: Medication per treatment as usual Psychotherapy per treatment as usual	IG1: None IG2: None IG3: None

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
Li et al. (2020)[50] Li et al. (2021)[134]	Sham (piTBS or rTMS) (35) Sham type: Separate sham coil	IG1: piTBS (35) Target location: Left DLPFC Localization technique: Half MRI-guided, half manual measurement Frequency: 50 Hz Intensity: 80 Number of pulses: 1,800 IG2: rTMS (35) Target location: Left DLPFC Localization technique: Half MRI-guided, half manual measurement Frequency: 10 Hz Intensity: 100 Number of pulses: 1,600	IG1: Treatment days: 10 (5 sessions per week for 2 weeks) Treatment sessions total: 10 IG2: Treatment days: 10 (5 sessions per week for 2 weeks) Treatment sessions total: 10	IG1: Medications discontinued prior to TMS IG2: Medications discontinued prior to TMS	IG1: None IG2: None
O'Reardon et al. (2007)[37] Janicak et al. (2008)[135]	Sham (160) Sham type: Wand casing that blocks magnetic field	High frequency rTMS (165) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 10 Intensity: 120 Number of pulses: 3,000	Treatment days: 30 (5 sessions per week for 6 weeks) active treatment 6 sessions over 3 weeks blinded taper Treatment sessions total: 36	Medications discontinued prior to TMS Titration onto antidepressant monotherapy starting during taper phase; cross-over to open-label treatment allowed at 4 weeks allowed if <25% reduction in baseline HAMD17 score	None
Padberg et al. (2002)[48]	Sham (10) Sham type: Angle wand away from scalp	IG1: 100% MT rTMS (10) Target location: Left DLPFC Localization technique: Image-guided Frequency: 10 Intensity: 100 Number of pulses: 1,500	IG1: Treatment days: 10 (5 sessions per week for 2 weeks) Treatment sessions total: 10 IG2:	IG1: Medication per treatment as usual IG2: Medication per treatment as usual	IG1: No IG2: No

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
		IG2: 90% MT rTMS (10) Target location: Left DLPFC Localization technique: Image-guided Frequency: 10 Intensity: 90 Number of pulses: 1,500	Treatment days: 10 (5 sessions per week for 2 weeks) Treatment sessions total: 10		
Pallanti et al. (2010)[44]	Sham rTMS (20) Sham type: Sham coil, not specified	IG1: Bilateral rTMS (20) Target location: Bilateral DLPFC Localization technique: Manual measurement Frequency: 1 for right DLPFC, 10 for left DLPFC Intensity: 110% for right DLPFC, 100% for left DLPFC Number of pulses: 420 for right DLPFC, 1,000 for left DLPFC IG2: Unilateral rTMS` (20) Target location: Right DLPFC Localization technique: Manual measurement Frequency: 1 Intensity: 110 Number of pulses: 420	IG1: Treatment days: 15 (5 sessions per week for 3 weeks) Treatment sessions total: 15 IG2: Treatment days: 15 (5 sessions per week for 3 weeks) Treatment sessions total: 15	IG1: Medication per treatment as usual IG2: Medication per treatment as usual	IG1: No IG2: No

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
Rossini et al. (2005)[45]	Sham (49) Sham type: Angle wand away from scalp	rTMS (50) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 15 Intensity: 100 Number of pulses: 900	Treatment days: 10 (5 days per week for 2 weeks) Treatment sessions total: 10	Medication per study protocol randomly assigned to escitalopram, sertraline, or venlafaxine	None
Schutter et al. (2009)[59]	Sham (17) Sham type: Wand casing that blocks magnetic field	rTMS (17) Target location: Right parietal cortex Localization technique: EEG-guided Frequency: 2 Intensity: 90 Number of pulses: 2,400	Treatment days: 10 Treatment sessions total: 10	Medication per treatment as usual	None
Stern et al. (2007)[47]	Sham rTMS (15) Sham type: Angle wand away from scalp	IG1: High frequency left-sided rTMS (10) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 10 Intensity: 110 Number of pulses: 1,600 IG2: Low frequency left-sided rTMS (10) Target location: Left DLPFC Localization technique: Manual measurement Frequency: 1 Intensity: 110 Number of pulses: 1,600 IG3:	IG1: Treatment days: 10 Treatment sessions total: 10 IG2: Treatment days: 10 Treatment sessions total: 10 IG3: Treatment days: 10 Treatment sessions total: 10	IG1: Medications discontinued prior to TMS IG2: Medications discontinued prior to TMS IG3: Medications discontinued prior to TMS	IG1: None IG2: None IG3: None

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
		Low frequency right-sided rTMS (10) Target location: Right DLPFC Localization technique: Manual measurement Frequency: 1 Intensity: 110 Number of pulses: 1,600			
Taylor et al. (2018)[49]	Sham rTMS (20) Sham type: Separate sham coil	rTMS (20) Target location: Left DLPFC Localization technique: Other Frequency: 10 Intensity: 120 Number of pulses: 3,000	Treatment days: 20 (5 sessions per week for 4 weeks) Treatment sessions total: 20	Medication per treatment as usual	None
Theleritis et al. (2017)[64]	Sham rTMS 1 (20) Sham rTMS 2 (24) Sham type: Angle wand away from scalp	IG1: rTMS 1 (27) Target location: Left DLPFC Localization technique: Image-guided Frequency: 20 Intensity: 100 Number of pulses: 1,600 IG2: rTMS 2 (27) Target location: Otherleft prefrontal cortex Localization technique: Image-guided Frequency: 20 Intensity: 100 Number of pulses: 1,600	IG1: Treatment days: 15 (1 session per day for 3 weeks) Treatment sessions total: 15 IG2: Treatment days: 15 (2 session per day for 3 weeks) Treatment sessions total: 30	IG1: Medication per study protocol; if clinically appropriate, subjects were encouraged to discontinue medication before study entry; if this was not possible, subjects were kept on a minimum antidepressant regimen to avoid the risk of a recurrence of severe depressive symptoms venlafaxine, 75–112.5 mg/d; mirtazapine, 30–45 mg/d; and citalopram, 20–30 mg/d); if taking benzodiazepines, a dosage no greater than the equivalent of 1 mg clonazepam per day was permitted. The medication regimen was kept stable for at least 4 weeks be fore study entry and throughout the study period. Medication per treatment as usual IG2: Medication per study protocol; if clinically appropriate, subjects were encouraged to dis continue medication before study	IG1: None IG2: None

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
				entry; if this was not possible, subjects were kept on a minimum antidepressant regimen to avoid the risk a recurrence of severe depressive symptoms (venlafaxine, 75–112.5 mg/d; mirtazapine, 30–45 mg/d; and citalopram, 20–30 mg/d); if taking benzodiazepines, a dosage no greater than the equivalent of 1 mg clonazepam per day was permitted. The medication regimen was kept stable for at least 4 weeks be fore study entry and throughout the study period. Medication per treatment as usual	
van Eijndhoven et al. (2020)[41]	Sham rTMS (16) Sham type: Angle wand away from scalp	rTMS (15) Target location: Left DLPFC Localization technique: EEG-guided Frequency: 10 Intensity: 110% Number of pulses: 3,000	Treatment days: 20 days (5 days per week, for 4 weeks) Treatment sessions total: 20	Medication per treatment as usual	None
Yesavage et al. (2018)[38]	Sham (83) Sham type: Wand casing that blocks magnetic field	rTMS (81) Target location: Left DLPFC Localization technique: Other Frequency: 10 Intensity: 120 Number of pulses: 4,000	Treatment days: 20 to 30 (1 per day, over 4 to 11 weeks) Treatment sessions total: 20 to 30 (additional sessions based on response)	Medication per treatment as usual	None

Abbreviations: cTBS = controlled theta-burst stimulation; DLPFC=dorsolateral prefrontal cortex; EEG = electroencephalogram; HAMD17 = Hamilton Depression Rating Scale (17 item); Hz = electromagnetic wavelength frequency; IG = intervention group; iTBS = intermittent theta-burst transcranial magnetic stimulation; LDLPC = left dorsolateral prefrontal cortex; NR = not reported; PET = positron emission tomography; piTBS = prolonged intermittent TBS; RMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation; TMS = transcranial magnetic stimulation.

Table C-13. Population Characteristics For Included Repetitive TMS Interventions for MDD

Author (Year)	Sample Size (Total)	Treatment History	Mean age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
Anderson et al. (2007)[58]	29	Both treatment naive and treatment resistant participants eligible	Active: 48 (8) Sham: 46 (12)	Active: 7 (54) Sham: 9 (56)	NR	NR
Avery et al. (2006)[68] Wajdik et al. (2014)[131]	68	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 44.3 (10.3) CG: 44.2 (9.7)	37 (54.4)	NR	NR
Blumberger et al. (2012)[43]	74	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 58.0 (12.5) IG2: 48.9 (13.4) CG: 45.8 (13.4)	IG1: 14 (54) IG2: 12 (55) CG: 14 (70)	NR	Anxiety: 7%
Blumberger et al. (2016)[42]	121	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 46.4 (12.5) IG2: 46.5 (14.1) CG: 48.1 (12.0)	IG1: 23 (58) IG2: 30 (75) CG: 24 (59)	NR	Anxiety disorder IG1: 8% IG2: 13% CG: 15%
Bretlau et al. (2008)[65]	49	Treatment resistant (defined liberally as any prior treatment to TMS)	IG: 53.1 (10.1) CG: 57.8 (10.0)	IG: 15 (68) CG: 13 (57)	NR	NR
Chou et al. (2020)[52]	60	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 43.6 (16.6) CG: 42.3 (11.1)	IG1: 15 (56) CG: 17 (65)	NR	NR
Cole et al. (2022)[51]	32	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 49 (15) CG: 52 (16)	IG1: 5 (36) CG: 5 (33)	NR	Anxiety IG1: 21% CG: 40% ADHD IG1: 7% CG: 7% PTSD IG1: 7% CG: 7% SUD (in remission) IG1: 0% CG: 20%

Author (Year)	Sample Size (Total)	Treatment History	Mean age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
						Eating Disorder IG1: 7% CG: 0%
Concerto et al. (2015)[67]	30	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 51 (6.5) CG: 53 (6.7)	IG1: 6 (40) CG: 7 (47)	NR	NR
Croarkin et al. (2021)[36]	112	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 17.6 (2.3) CG: 17.1 (2.2)	IG1: 30 (63) CG: 37 (67)	IG1: White: 43 (90) Black or African American: 1 (2) Asian: 3 (6) Other: 1 (2) Hispanic or Latino: 1 (2) Not Hispanic or Latino: 47 (98) CG: White: 47 (86) Black or African American: 5 (9) Asian: 1 (2) Other: 2 (4) Hispanic or Latino: 3 (5.5) Not Hispanic or Latino: 52 (94.5)	Secondary psychiatric diagnosis IG1: 54% CG: 66%
Duprat et al. (2016)[56] Desmyter et al. (2016)[132]	50	Treatment resistant (defined liberally as any prior treatment to TMS)	41.8 (11.8)	33 (70)	NR	NR
Fitzgerald et al. (2012)[57]	67	Treatment resistant (defined liberally as any prior treatment to TMS)	42.9 (14.4)	31 (46)	NR	Panic disorder: 27% Social phobia: 23% GAD: 30% OCD: 11% PTSD: 11%
Garcia-Toro et al. (2001)[71]	40	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 51.5 (15.9) CG: 50 (11)	IG1: 7 (41) CG: 8 (44)	NR	NR

Author (Year)	Sample Size (Total)	Treatment History	Mean age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
Garcia-Toro et al. (2001)[62]	28	Both treatment naive and treatment resistant participants eligible	IG1: 43.2 (13.1) CG: 45.0 (18.3)	12 (54.5)	NR	NR
Garcia-Toro et al. (2006)[69]	30	Treatment resistant (defined liberally as any prior treatment to TMS)	CG: 47.2 (11.8) IG1: 48.5 (13.3) IG2: 51.1 (13.8)	CG: 7 (70) IG1: 4 (40) IG2: 4 (40)	NR	NR
George et al. (2010)[39] Borckardt et al. (2013)[133]	199 (190 included in ITT set)	Treatment resistant (defined liberally as any prior treatment to TMS)	47.1 (11.5)	108 (57)	NR	NR
Hausmann et al. (2004)[70]	41	Unspecified treatment naive or resistance	46.5 (11.9)	23 (60.5)	NR	NR
Herwig et al. (2003)[60]	25	Both treatment naive and treatment resistant participants eligible	Range (all): 22 to 60 Mean IG1: 41.6 CG: 47.8	15 (60)	NR	NR
Hoppner et al. (2003)[61]	30	Unspecified treatment naive or resistance	56.4 (11.1)	22 (73)	NR	NR
Januel et al. (2006)[46]	27	Treatment naive (no prior treatment, including meds, TMS, ECT, psychotherapy)	37.78 (11.27)	21 (78)	NR	
Kaster et al. (2018)[54]	58	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 65 (5.5) CG: 65.4 (5.5)	IG1: 8 (32) CG: 12 (44)	NR	Comorbid psychiatric disorder IG1: 17% CG: 30% Comorbid personality disorder IG1: 0% CG: 4%
Kim et al. (2019)[40]	26	Unspecified treatment naive or resistance	28.3 (5.7)	22 (100)	Race Caucasian: 7 (32) African American/Black: 11 (50) Asian: 3 (14) Other: 1 (5)	Comorbid anxiety allowed if primary diagnosis was MDD IG1: 0% CG: 33%

Author (Year)	Sample Size (Total)	Treatment History	Mean age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
					Ethnicity (N=18) Non-Hispanic: 17 (95), Hispanic: 1 (6)	
Koerselman et al. (2004)[66]	55	Unspecified treatment naive or resistance	IG1: 51 (15.4) CG: 52 (13.2)	IG1: 12 (46) CG: 17 (65)	NR	Personality disorder IG1: 58% CG: 50%
Lee et al. (2018)[63]	41	Unspecified treatment naive or resistance	35.9 (12.3)	28 (76)	NR	NR
Levkovitz et al. (2015)[53]	233	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 45.1 (11.7) CG: 47.6 (11.6)	101 (47.6)	Caucasian: 192 (90.6)	NR
Li et al. (2014)[55]	60	Treatment resistant (defined liberally as any prior treatment to TMS)	Mean (range) IG1: 49.2 (27-64) IG2: 42.4 (25-61) IG3: 42.5 (23-60) CG: 46.9 (25-58)	IG1: 10 (67) IG2: 8 (53) IG3: 11 (73) CG: 11 (73)	NR	Panic disorder: 12% Social phobia: 2% GAD: 35%
Li et al. (2020)[50] Li et al. (2021)[134]	105	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 47.1 (14.2) IG2: 47.1 (13.8) CG: 47.1 (12.4)	71 (67.6)	NR	Dysthymia: 22% Panic disorder: 12% Agoraphobia: 17% Social phobia: 5% GAD: 74%
O'Reardon et al. (2007)[37] Janicak et al. (2008)[135]	325	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 47.9 (11) CG: 48.7 (10.6)	IG1: 86 (55.5) CG: 74 (50.7)	IG1 White: 146 (94.2) Other: 9 (5.8) CG White: 131 (89.7) Other: 15 (10.3)	NR
Padberg et al. (2002)[48]	31	Treatment resistant (defined liberally as any prior treatment to TMS)	Mean (SEM) IG1: 62.1 (4.6) IG2: 60.3 (4.1) CG: 52.7 (5.7)	IG1: 6 (60) IG2: 7 (70) CG: 8 (80)	NR	NR
Pallanti et al. (2010)[44]	60	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 47.6 (12. 3) IG2: 51.2 (12.5) CG: 47.9 (9.1)	IG1: 11 (55) IG2: 12 (60) CG: 12 (60)	NR	NR

Author (Year)	Sample Size (Total)	Treatment History	Mean age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
Rossini et al. (2005)[45]	99	Unspecified treatment naive or resistance	47.4 (12.9)	79 (80)	NR	NR
Schutter et al. (2009)[59]	34	Unspecified treatment naive or resistance	IG1: 44.4 (11.8) CG: 43.8 (12.5)	IG1: 10 (59) CG: 7 (41)	NR	NR
Stern et al. (2007)[47]	45	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 53.2 (12) IG2: 52.3 (9.4) IG3: 52.8 (9.5) CG: 53.3 (9.0)	28 (62.2)	NR	NR
Taylor et al. (2018)[49]	40	Treatment resistant (defined liberally as any prior treatment to TMS)	IG: 46.9 (10.7) CG: 44.1 (11.1)	IG: 11 (69) CG: 10 (63)	NR	NR
Theleritis et al. (2017)[64]	96	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 39.1 (10.1) IG2: 38.9 (13.9) CG1: 38.0 (9.9) CG2: 39.4 (8.9)	IG1: 15 (58) IG2: 11 (42) CG1: 10 (50) CG2: 7 (42)	NR	NR
van Eijndhoven et al. (2020)[41]	31	Treatment resistant (defined liberally as any prior treatment to TMS)	48.6 (11.1)	22 (71)	NR	NR
Yesavage et al. (2018)[38]	164	Treatment resistant (defined liberally as any prior treatment to TMS)	55.2 (12.4)	32 (19.5)	White: 126 (77.3)	PTSD: 49.4% Substance use: 53.7% TBI: 6.1%

Abbreviations: CG = control group; ECT = electroconvulsive therapy; GAD = generalized anxiety disorder; IG = intervention group; ITT = intention to treat; MDD = major depressive disorder; NR = not reported; OCD = obsessive compulsive disorder; PTSD = posttraumatic stress disorder; TMS = transcranial magnetic stimulation.

Table C-14. Efficacy Outcomes for Included Repetitive TMS Interventions for MDD

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Anderson et al. (2007)[58] rTMS (14) Sham rTMS (16)	**Remission**: NR	NR
	Response: At least a 50% decrease in MADRS score plus a CGI-I rating of much or very much improved	MADRS ≥50% decrease plus CGI-I much or very much improved, end of treatment (4 to 6 weeks); mITT (IG1=11; CG=14); N (%) IG1: 6 (55) CG: 1 (7) *P*<0.05 MADRS ≥50% decrease plus CGI-I much or very much improved, 6 to 8 weeks posttreatment (12 weeks); mITT (IG1=11; CG=14); N (%) IG1: 5 (45) CG: 1 (7) *P*>0.05
	Continuous outcomes • MADRS • CGI-S • GAF	MADRS, end of treatment (4 to 6 weeks); mITT (IG1=11; CG=14); mean (SD) IG1: 15 (9.7) CG: 23.4 (9.8) *P*<0.05 MADRS, 6 to 8 weeks posttreatment (12 weeks); mITT (IG1=11; CG=14); mean (SD) IG1: 14.0 (11.5) CG: 21.9 (9.7) CGI-S, end of treatment (4 to 6 weeks); mITT (IG1=11; CG=14); mean (SD) IG1: 3.0 (1.0) CG: 4.0 (0.8) *P*>0.05 CGI-S, 6 to 8 weeks posttreatment (12 weeks); mITT (IG1=11; CG=14); mean (SD) IG1: 3.0 (1.3) CG: 3.7 (1.2) *P*>0.05 GAF, end of treatment (4 to 6 weeks); mITT (IG1=11; CG=14); mean (SD) IG1: 67.2 (11.2) CG: 55.8 (8.0)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		P<0.01 GAF, 6 to 8 weeks posttreatment (12 weeks); mITT (IG1=11; CG=14); mean (SD) IG1: 65.6 (13.8) CG: 58.1 (13.0) *P*>0.05
	Subgroup analyses: No subgroups of interest reported	NR
Avery et al. (2006)[68] Wajdik et al. (2014)[131] rTMS (35) Sham rTMS (33)	**Remission**: HAMD17 score <8 at 1 and 2 weeks posttreatment	Remission, 1 and 2 weeks posttreatment (5 to 6 weeks); ITT (IG1=35; CG=33); N (%) IG1: 7 (20) CG: 1 (3) Effect size 0.58; *P*=0.033 Adjusted OR 25.5 (95% CI, 1.1 to 595.8)
	Response: At least 50% decrease in HAMD17 score at 1 and 2 weeks posttreatment	Response, 1 and 2 weeks posttreatment (5 to 6 weeks); ITT (IG1=35; CG=33); N (%) IG1: 11 (30.6) CG: 2 (33) Effect size 0.69; *P*=0.008 Adjusted OR 21.1 (95% CI, 2.1 to 214.2)
	Continuous outcomes • HAMD17 • BDI	HAMD17; 1 week posttreatment (5 weeks); ITT (IG1=35; CG=33); mean (SD) change from baseline IG1: 7.8 (7.8) CG: 3.7 (6.3) Time × treatment interaction effect size 0.64; *P*=0.002 BDI: 1 week posttreatment (5 weeks); ITT (IG1=35; CG=33); mean (SD) change from baseline IG1: 11.3 (12.8) CG: 4.8 (8.5) Time × treatment interaction effect size 0.67; *P*=0.003
	Subgroup analyses: No subgroups of interest reported	NR
Blumberger et al. (2012)[43] Bilateral rTMS (28) Unilateral rTMS (24)	**Remission**: Final HAMD17 score of 10 or less at end of treatment (either 3 or 6 weeks)	HAMD17 score of 10 or less at end of treatment (either 3 or 6 weeks); mITT (IG1=26; IG2= 22; CG=20); N (%) IG1: 9 (35) IG2: 1 (5) CG: 1 (5) *P*=0.005 IG1 vs. CG: *P*=0.028

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Sham rTMS (22)		IG2 vs. CG: *P*=0.48 Statistical significance remained after adjustment for baseline differences in age and stimulation intensity
	Response: at least a 50% decrease in HAMD17 score	Participants with at least 50% decrease in HAMD17, at end of treatment (either 3 or 6 weeks); mITT (IG1=26; IG2= 22; CG=20); N (%) IG1: 10 (39) IG2: 1 (5) CG: 2 (10) *P*=0.006 IG1 vs. CG: P=0.022 IG2 vs. CG: *P*=1.00
	Continuous outcomes: HAMD17	HAMD17, end of phase 1 (3 weeks); Completer (IG1=26; IG2= 22; CG=20); mean (SD) IG1: 15.3 (6.7) IG2: 19.6 (5.6) CG: 17.8 (4.5) Percent decrease in HAMD17 score, from baseline to end of treatment (either 3 or 6 weeks); completers (IG1=24; IG2= 19; CG=18); mean (SD) IG1: 44.0% (30.5) IG2: 23.0% (13.2) CG: 24.9% (24.5) *P*=0.008 IG1 vs. CG: *P*=0.015 IG2 vs. CG: *P*=0.97 Statistical significance remained after adjustment for baseline differences in age and stimulation intensity
	Subgroup analyses: No subgroups of interest reported	NR
Blumberger et al. (2016)[42] Bilateral rTMS (40) Unilateral rTMS (40)	**Remission**: • HAMD17 score of ≤7 • BDI-II remission definition NR	Remission HAMD17, posttreatment (3 or 6 weeks); ITT (IG1=40; IG2=40; CG=41); N (%) IG1: 8 (20) IG2: 3 (7.5) CG: 1 (2.4) *P*=0.027 Post hoc IG1 vs. CG; *P*=0.014 Post hoc IG2 vs. CG; *P*=0.27

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Sham rTMS (41)		Remission BDI-II, posttreatment (3 or 6 weeks); ITT (IG1=40; IG2=40; CG=41); N (%) IG1: 7 (17.5) IG2: 1 (2.5) CG: 1 (2.4) *P*=0.016 Post hoc IG1 vs. CG; *P*=0.029 Post hoc IG2 vs. CG; *P*>0.99
	Response: • >50% reduction in HAMD17 score • BDI-II response definition NR	Response HAMD17, posttreatment (3 or 6 weeks); ITT (IG1=40; IG2=40; CG=41); N (%) IG1: 9 (22.5) IG2: 6 (15) CG: 2 (4.9) *P*=0.07 Post hoc IG1 vs. CG; *P*=0.026 Post hoc IG2 vs. CG; *P*=0.16 Response BDI-II, posttreatment (3 or 6 weeks); ITT (IG1=40; IG2=40; CG=41); N (%) IG1: 11 (27.5) IG2: 6 (15) CG: 5 (12.2) *P*=0.17
	Continuous outcomes: HAMD17	Change in HAMD17, posttreatment or 3 weeks posttreatment (6 weeks); ITT (IG1=40; IG2=40; CG=41); mean (SD) IG1: −6.8 (7.2) IG2: −6.4 (7.0) CG: −5.0 (4.8) *P*=0.40 Additional models testing for group × time interactions were not significant.
	Subgroup analyses: No subgroups of interest reported	NR
Bretlau et al. (2008)[65] rTMS (25) Sham rTMS (24)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes • HAMD17 • HAMD-6 (6 item subscale of HAMD)	HAMD17 score, posttreatment (3 weeks); per protocol (IG: 22; CG: 23); change from baseline ES (95% CI) IG vs. CG: 0.78 (0.18 to 1.39); favors IG *P*=0.01

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		HAMD17 score, 9 weeks after end of treatment (12 weeks); per protocol (IG: 22; CG: 23); change from baseline ES (95% CI) IG vs. CG: 0.47 (−0.11 to 1.07); favors IG *P*=0.22 HAMD-6 score, posttreatment (3 weeks); per protocol (IG: 22; CG: 23); change from baseline ES (95% CI) IG vs. CG: 0.80 (0.20 to 1.42); favors IG *P*=0.01 HAMD-6 score, 9 weeks after end of treatment (12 weeks); per protocol (IG: 22; CG: 23); change from baseline ES (95% CI) IG vs. CG: 0.50 (−0.10 to 1.09); favors IG *P*=0.09
	Subgroup analyses: No subgroups of interest reported	NR
Chou et al. (2020)[52] TBS (30) Sham TBS (30)	**Remission**: HAMD21 score of <8	Remission, posttreatment (4 weeks); completers (IG1=27; CG=26); N (%) IG1: 9 (33.3) CG: 3 (11.5) *P*=0.057 Remission, 8 weeks after end of treatment (12 weeks); completers (IG1=27; CG=26); N (%) IG1: 12 (44.4) CG: 2 (7.7) *P*=0.002 Remission, 20 weeks after end of treatment (24 weeks); completers (IG1=27; CG=26); N (%) IG1: 8 (29.6) CG: 3 (11.5) *P*=0.104
	Response: 50% decrease in HAMD21	Response, posttreatment (4 weeks); completers (IG1=27; CG=26); N (%) IG1: 19 (70.3) CG: 6 (23.1) *P*=0.001

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		Response, 8 weeks after end of treatment (12 weeks); completers (IG1=27; CG=26); N (%) IG1: 21 (77.8) CG: 6 (23.1) *P*<0.001 Response, 20 weeks after end of treatment (24 weeks); completers (IG1=27; CG=26); N (%) IG1: 22 (81.5) CG: 7 (26.9) *P*<0.001
	Continuous outcomes: HAMD21	% HAMD21 change, posttreatment (4 weeks); completers (IG1=27; CG=26); mean change (SD) IG1: −56.5 (−22.6) CG: −33.1 (24.1) Cohen's d= 1.00; *P*<0.001 % HAMD21 change, 8 weeks after end of treatment (12 weeks); completers (IG1=27; CG=26); mean change (SD) IG1: −65.3 (−17.3) CG: −35.2 (−21.0) *P*<0.001 % HAMD21 change, 20 weeks after end of treatment (24 weeks); completers (IG1=27; CG=26); mean change (SD) IG1: −62.7 (−18.1) CG: −36.6 (−21.2) *P*<0.001
	Subgroup analyses: No subgroups of interest reported	NR
Cole et al. (2022)[51] iTBS (14)	**Remission**: MADRS score of ≤10	Remission based on MADRS, end of treatment (1 weeks); ITT (IG1=14; CG=15); N (%) IG1: 8 (57.1) CG: 0 (0)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Sham iTBS (15)		Remission based on MADRS, 4 weeks posttreatment (5 weeks); mITT (IG1=14; CG=15); N (%) IG1: 9 (64.3) CG: 1 (6.7) Remission based on MADRS, any week of followup (1 to 5 weeks); mITT (IG1=14; CG=15); N (%) IG1: 11 (78.6) CG: 2 (13.3)
	Response: at least 50% reduction in MADRS score	Response based on MADRS, end of treatment (1 weeks); ITT (IG1=14; CG=15); N (%) IG1: 10 (71.4) CG: 2 (13.3) Response based on MADRS, 4 weeks after end of treatment (5 weeks); mITT (IG1=14; CG=15); N (%) IG1: 9 (64.3) CG: 1 (6.7) Response based on MADRS, any week of followup (1 to 5 weeks); mITT (IG1=14; CG=15); N (%) IG1: 12 (85.7) CG: 4 (26.7)
	Continuous outcomes • HAMD17 • MADRS	Percent reduction in MADRS score, 4 weeks after end of treatment (5 weeks); mITT (IG1=14; CG=15); mean (SE) IG1: 52.5 (NR) CG: 11.1 (NR) Cohen's d=1.4 Effect of treatment group: *P*<0.005 Time × Treatment interaction: *P*=0.001 HAMD17 score, 4 weeks after end of treatment (5 weeks); mITT (IG1=14; CG=15); mean (SE) Reported on figure only, actual values NR IG1: NR (NR) CG: NR (NR)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		Effect of treatment group: *P*=0.001 Group × Time interaction: *P*<0.001
	Subgroup analyses: No subgroups of interest reported	NR
Concerto et al. (2015)[67] rTMS (15) Sham TMS (15)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes • MADRS • HAMD21	HAMD21, posttreatment (4 weeks); ITT (IG1=15; CG=15); median IG1: 9.0 CG: 20.0 *P*=0.000007 HAMD21, 12 weeks after end of treatment (16 weeks); ITT (IG1=15; CG=15); median IG1: 10.0 CG: 21.0 *P*=0.000003 HAMD21, 24 weeks after end of treatment (28 weeks); ITT (IG1=15; CG=15); median IG1: 12.0 CG: NR *P*=NR MADRS, posttreatment (4 weeks); ITT (IG1=15; CG=15); median IG1: 11.0 CG: 22.0 *P*=0.000053 MADRS, 12 weeks after end of treatment (16 weeks); ITT (IG1=15; CG=15); median IG1: 14.0 CG: 25.0 *P*=0.000003 MADRS, 24 weeks after end of treatment (28 weeks); ITT (IG1=15; CG=15); median IG1: 15.0 CG: NR *P*=NR
	Subgroup analyses: No subgroups of interest reported	NR
Croarkin et al. (2021)[36] rTMS (54)	**Remission**: NR	Remission, posttreatment (6 weeks); mITT (IG1=48; CG=55); N (%) IG1: 14 (29.2) CG: 16 (29) *P*=0.95

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Sham TMS (58)	**Response**: ≥50% reduction in total HAMD24 score compared to baseline score	Response, posttreatment (6 weeks); mITT (IG1=48; CG=55); N (%) IG1: 20 (41.7) CG: 20 (36.4) *P*=0.55
	Continuous outcomes • HAMD24 • MADRS • CGI-S • CSSRS	HAMD24 score, posttreatment (6 weeks); mITT (IG1=48; CG=55); mean (SE) IG1: 18.1 (10.91) CG: 19.2 (11.03) *P*=0.80 Difference (95% CI): −0.5 (−4.2 to 3.3) MADRS outcomes, posttreatment (6 weeks); mITT (IG1=48; CG=55); mean (SE) IG1: NR (NR) CG: NR (NR) *P*=NS CGI-S, posttreatment (6 weeks); mITT (IG1=48; CG=55); mean (SE) IG1: NR (NR) CG: NR (NR) *P*=NS CSSR-S, posttreatment (6 weeks); mITT (IG1=48; CG=55); mean (SE) IG1: NR (NR) CG: NR (NR) *P*=NS
	Subgroup analyses: No subgroups of interest reported	NR
Duprat et al. (2016)[56] Desmyter et al. (2016)[132] iTBS (47) Sham iTBS (47)	**Remission**: HAMD17 score <=7	Remission, after 1 week of treatment prior to crossover (1 week); IG1=22; IG2=25; N (%) IG1: NR CG: NR Remission, 1 week after crossover (2 weeks), N=47); N (%) 7 (15) Remission, 3 weeks after crossover (4 weeks), N=47); N (%) 14 (30)
	Response: HAMD17 score decrease >=50%	Response, after 1 week of treatment prior to crossover (1 week); IG1=22; CG=25; N (%)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		IG1: 4 (18) CG: 1 (4) Response, 1 week after crossover (2 weeks); N=46; N (%) 13 (28) Response, 3 weeks after crossover (4 weeks); N=46; N (%) 18 (38)
	Continuous outcomes • HAMD17 • BDI	HAMD17 score, after 1 week of treatment prior to crossover (1 week); (IG1=22; CG=25), change from baseline T1 to T2: *P*<0.01 IG1 vs. CG: *P*=0.31 Time × treatment interaction: *P*=0.19 HAMD17 score, 3 weeks after crossover (4 weeks); IG1=22; CG=25, change from baseline T1 to T4: *P*<0.01 IG1 vs. CG: *P*=0.47 Time × treatment interaction: *P*=0.27 BDI-I score, after 1 week of treatment prior to crossover (1 week); (IG1=22; CG=25), change from baseline T1 to T2: NR IG1 vs. CG: NR BDI -I score, 3 weeks after crossover (4 weeks); IG1=22; CG=25, change from baseline T1 to T4: *P*<0.01 IG1 vs. CG: *P*=0.93 Time × treatment interaction: *P*=0.46
	Subgroup analyses: Suicidal ideation at baseline	Subgroup reported in Desmyter, 2016[132] Focused on the 32 participants who reported suicidal ideation at baseline After 1 week of treatment prior to crossover, there was a significant decrease in BSI scores for all participants (*P*<0.01); no sign
	Remission: NR	NR

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Fitzgerald et al. (2012)[57] Bilateral rTMS (22) Unilateral rTMS (24) Sham rTMS (20)	**Response**: At least a 50% decrease in HAMD17 score	At least 50% decrease in HAMD17, end of blinded treatment phase (3 weeks); varies by group (IG1=22; IG2=24; CG=17); N (%) IG1: 1 (5) IG2: 0 (0) CG: 1 (5)
	Continuous outcomes • HAMD17 • MADRS • BDI	HAMD17, posttreatment (3 weeks); completers (IG1=19; IG2=24; CG=17); mean (SD) IG1: 22.2 (6.0) IG2: 19.6 (4.2) CG: 22.6 (5.0) Between group difference: *P*=0.05 Post hoc IG2 vs. CG, *P*=0.02 IG1 vs. CG, *P*=NS IG1 vs. IG2, *P*=0.09 MADRS, posttreatment (3 weeks); completers (IG1=19; IG2=24; CG=17); mean (SD) IG1: 31.1 (9.8) IG2: 27.5 (6.0) CG: 30.0 (6.2) Between group difference: *P*=0.29 BDI, posttreatment (3 weeks); completers (IG1=19; IG2=24; CG=17); mean (SD) IG1: 29.8 (12.6) IG2: 23.2 (10.8) CG: 26.9 (11.2) Between group difference: *P*=0.36
	Subgroup analyses: No subgroups of interest reported	NR
Garcia-Toro et al. (2001)[71] rTMS (20) Sham (20)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes • BDI • HAMD21 • CGI	HAMD21 change in score from baseline to week 1 of treatment; completers (IG1=17; CG=18); mean (SD) IG1: −4.52 (4.66) CG: −2.87 (4.27) *P*=0.297

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		HAMD21 change in score from baseline to week 2 of treatment; completers (IG1=17; CG=18); mean (SD) IG1: −7.05 (5.66) CG: −1.77 (3.78) *P*=0.003 HAMD21 change in score from baseline to week 4 (2 weeks posttreatment); completers (IG1=17; CG=18); mean (SD) IG1: −8.17 (7.69) CG: −2.05 (6.07) *P*=0.013 BDI change in score from baseline to week 1 of treatment; completers (IG1=17; CG=18); mean (SD) IG1: −1.35 (4.44) CG: −2.75 (4.28) *P*=0.365 BDI change in score from baseline to week 2 of treatment; completers (IG1=17; CG=18); mean (SD) IG1: −4.70 (6.70) CG: −2.55 (5.29) *P*=0.299 BDI change in score from baseline to week 4 (2 weeks posttreatment); completers (IG1=17; CG=18); mean (SD) IG1: −4.05 (6.72) CG: −1.66 (6.89) *P*=0.307 CGI change in score from baseline to week 1 of treatment; completers (IG1=17; CG=18); mean (SD) IG1: −0.41 (0.71) CG: −0.31 (0.60) *P*=0.729

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		CGI change in score from baseline to week 2 of treatment; completers (IG1=17; CG=18); mean (SD) IG1: −0.82 (0.80) CG: −0.27 (0.66) *P*=0.040 CGI change in score from baseline to week 4 (2 weeks posttreatment); completers (IG1=17; CG=18); mean (SD) IG1: −1.00 (1.17) CG: 0.27 (0.95) *P*=0.037
	Subgroup analyses: No subgroups of interest reported	NR
Garcia-Toro et al. (2001)[62] High frequency rTMS (14) Sham rTMS (14)	**Remission**: NR	NR
	Response: greater than 50% decrease in HAMD21	Decrease of >50% in HAMD21 from baseline to posttreatment (2 weeks); completers (IG1=11; CG=11); N (%) IG1: 4 (36.4) CG: 3 (27.3)
	Continuous outcomes • BDI • HAMD21	Decrease of >25% in HAMD21 from baseline to posttreatment (2 weeks); completers (IG1=11; CG=11); N (%) IG1: 4 (36.4) CG: 5 (45.5) HAMD21 posttreatment (2 weeks); completers (IG1=11; CG=11); mean (SD) (percent change from baseline) IG1: 16.1 (7.7) (−38.2%) CG: 17.9 (8.7) (−34.3%) HAMD21 at latest followup (4 weeks); completers (IG1=11; CG=11); mean (SD) (percent change from baseline) IG1: 14.3 (7.1) (−45.2%) CG: 14.5 (10.9) (−45.2%) BDI posttreatment (2 weeks); completers (IG1=11; CG=11); mean (SD) (percent change from baseline)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		IG1: 19.4 (6.7) (−28.1%) CG: 21.2 (7.9) (−8.2%) BDI at latest followup (4 weeks); completers (IG1=11; CG=11); mean (SD) (percent change from baseline) IG1: 19.5 (6.7) (−27.7%) CG: 21.2 (7.9) (−8.2%)
	Subgroup analyses: No subgroups of interest reported	NR
Garcia-Toro et al. (2006)[69] 20 + 1-Hz rTMS (10) 20 + 1-Hz rTMS + sPECT targeting (10) Sham rTMS (10)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes • HAMD21 CGI (I or S not specified)	HAMD21 change in score from baseline to posttreatment (2 weeks); treatment groups combined (CG=10; IG1 + IG2=20); mean (SD) IG1 + IG2: −7.05 (7.3) CG: −1.5 (5.9) *P*=0.048 HAMD21 change in score from baseline to 2 weeks posttreatment (4 weeks); treatment groups combined (CG=10; IG1 + IG2=20); mean (SD) IG1 + IG2: −7.3 (8.3) CG: −2.2 (6.5) *P*=0.121 HAMD21 score from baseline to posttreatment (2 weeks); treatment groups not combined (CG=10; IG1=10; IG2=10); mean (SD); % decrement from baseline IG1: 20.10 (8.18), −26.4% IG2: 18.10 (6.15), −27.6% CG: 23.60 (7.79), −5.9% HAMD21 score from baseline to 2 weeks posttreatment (4 weeks); treatment groups not combined (CG=10; IG1=10; IG2=10); mean (SD); % decrement IG1: 20.88 (7.26), −23.5% IG2: 16.90 (7.26), −32.4% CG: 23.67 (5.55), −5.6%

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		CGI score change from baseline to 1 week; treatment groups combined (CG=10; IG1 + IG2=20); mean (SD) IG1 + IG2: −0.7 (0.8) CG: −0.1 (0.3) *P*=0.032 CGI score from baseline to posttreatment (2 weeks); treatment groups not combined (CG=10; IG1=10; IG2=10); mean (SD) IG1: 3.80 (1.48) IG2: 3.90 (0.99) CG: 4.60 (0.97) CGI score from baseline to 2 weeks posttreatment (4 weeks); treatment groups not combined (CG=10; IG1=10; IG2=10); mean (SD), IG1: 4.00 (1.15) IG2: 3.7 (1.57) CG: 4.75 (1.16)
	Subgroup analyses: No subgroups of interest reported	NR
George et al. (2010)[39] Borckardt et al. (2013)[133] rTMS (92) Sham rTMS (98)	**Remission**: HAMD24 score of 3 or less, or 2 consecutive HAMD24 scores less than 10	Remission, posttreatment (3 weeks); mITT (IG1=92; CG=98); N (%), N (%) IG1: 13 (14) CG: 5 (5) OR: 4.2 (1.3 to 13.2)
	Response: At least a 50% decrease in HAMD24	Response, posttreatment (3 weeks); mITT (IG1=92; CG=98), N (%); OR (95% CI) IG1: 14 (15) CG: 5 (5) OR: 4.6 (1.5 to 14.4)
	Continuous outcomes • HAMD24 • MADRS • CGI-S	HAMD, posttreatment (3 weeks); completers (IG1=83; CG=91); mean (SD) IG1: 21.6 (9.7) CG: 23.4 (7.4) Between group difference 95% CI, −4.23 to 0.10; Cohen's d -0.42; *P*=0.06) MADRS, posttreatment (3 weeks); completers (IG1=83; CG=91); mean (SD) IG1: 24.6 (11.4) CG: 27.8 (9.1) Between group difference NR (95% CI, −6.1 to −0.8); Cohen's d; −0.51; *P*=0.01)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		CGI-S, posttreatment (3 weeks); completers (IG1=82; CG=90); mean (SD) IG1: 4.0 (1.1) CG: 4.3 (0.9) Between group difference NR (95% CI; −0.7 to −0.09); Cohen's d −0.55; *P*=0.01)
	Subgroup analyses: No subgroups of interest reported	NR
Hausmann et al. (2004)[70] Unilateral high frequency rTMS (13) Bilateral rTMS (14) Bilateral sham rTMS (14)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes • BDI • HAMD21	HAMD21, posttreatment (2 weeks); completers (IG1 + IG2=25; CG=13); mean (SD) IG1 + IG2: 17.6 (9.0) CG: 21.8 (8.2) Group × time interaction term: 2.8 (95% CI, −2.8 to 8.5) HAMD21, 2 weeks posttreatment (4 weeks); completers (IG1 + IG2=25; CG=13); mean (SD) IG1 + IG2: 15.8 (9.5) CG: 20.2 (10.9) Group × time interaction term: 3.0 (95% CI, −3.8 to 9.8) BDI, posttreatment (2 weeks); completers (IG1 + IG2=25; CG=13); mean (SD) IG1 + IG2: 16.9 (11.6) CG: 21.2 (14.3) Group × time interaction term: 5.0 (95% CI, −3.2 to 13.2) BDI, 2 weeks posttreatment (4 weeks); completers (IG1 + IG2=25; CG=13); mean (SD) IG1 + IG2: 14.8 (12.5) CG: 19.6 (15.8) Group × time interaction term: 5.7 (95% CI, −3.8 to 15.0)
	Subgroup analyses: No subgroups of interest reported	NR
Herwig et al. (2003)[60] rTMS (13) Sham rTMS (12)	**Remission**: NR	NR
	Response: At least a 50% decrease in the mean of the mean HAMD21 score plus the mean MADRS score	Clinical response, end of treatment (2 weeks); ITT (IG=13; CG=12); N (%) IG1: 4 (30.8) CG: 0 (0)
	Continuous outcomes • MADRS	Change in HAMD21 from baseline to end of treatment (2 weeks); ITT (IG=13; CG=12); mean (end rating percentage of initial score)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
	• BDI • HAMD21	IG: −6.9 (68.7%) CG: −0.9 (97.8%) *P*=0.002 Change in MADRS from baseline to end of treatment (2 weeks); ITT (IG=13; CG=12); mean (end rating percentage of initial score) IG: −9.5 (66.4%) CG: 0.3 (103.1%) *P*<0.001 Change in BDI from baseline to end of treatment (2 weeks); ITT (IG=13; CG=12); mean (end rating percentage of initial score) IG: −8.8 (73.4%) CG: −2.3 (90.7%) *P*=0.1
	Subgroup analyses • PET-guided stimulation vs. non-PET-guided stimulation Timing of medication start	This PET-guided stimulation showed no difference in antidepressant efficacy compared to the non-PET-guided stimulation No difference in participants stable on medication vs. started on a new medication at the initiation of TMS therapy
Hoppner et al. (2003)[61] High frequency rTMS (10) Low frequency rTMS (10) Sham rTMS (10)	**Remission**: NR	NR
	Response: At least a 50% decrease of HAMD21 or BDI	Response HAMD21, end of treatment (2 weeks); completers (IG1=9; IG2=10; CG=10); N (%) IG1: 5 (55.6) IG2: 3 (30) CG: 5 (50) Response BDI, end of treatment (2 weeks); completers (IG1=9; IG2=10; CG=10); N (%) IG1: 2 (22.2) IG2: 1 (10) CG: 2 (20)
	Continuous outcomes • BDI • HAMD21	HAMD21, end of treatment (2 weeks); completers (IG1=9; IG2=10; CG=10); mean (SD) change from baseline, within-group differences IG1: NR; *P*=0.015 IG2: NR; *P*=0.18 CG: NR; *P*≤0.001

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		Between group differences, NR BDI, end of treatment (2 weeks); completers (IG1=9; IG2=10; CG=10); mean (SD) change from baseline, within-group differences IG1: NR; *P*=0.011 IG2: NR; *P*=0.029 CG: NR; *P*=0.005 Between group differences, NR
	Subgroup analyses: No subgroups of interest reported	NR
Januel et al. (2006)[46] rTMS (11) Sham (16)	**Remission**: HAMD17 <9	Remission, posttreatment (4 weeks); ITT (IG1=11; CG=16); N(%) IG1: 7 (63.6) CG: 1 (6.3) *P*=0.002 for between group difference
	Response: HAMD17 score reduction of >50% compared to baseline score	Response, posttreatment (4 weeks); ITT (IG1=11; CG=16); N(%) IG1: 7 (63.6) CG: 1 (6.3) *P*=0.025 for between group difference
	Continuous outcomes: HAMD17	HAMD17, posttreatment (4 weeks); ITT (IG1=11; CG=16); mean (SD) IG1: 9.91 (5.95) CG: 16.69 (4.61) *P*<0.05 for ANOVA for between group difference
	Subgroup analyses: No subgroups of interest reported	NR
Kaster et al. (2018)[54] Active deep rTMS (30) Sham rTMS (28)	**Remission**: HAMD24 ≤10 and ≥60% reduction from baseline on 2 consecutive weeks	Remission, posttreatment (4 weeks); mITT (IG1=25; CG=27); N (%) IG1: 10 (40) CG: 4 (14.8) *P*<0.05
	Response: >50% reduction in HAMD24 relative to baseline on 2 consecutive weeks	Response, posttreatment (4 weeks); mITT (IG1=25; CG=27); N (%) IG1: 11 (44.0) CG: 5 (18.5) *P*<0.05
	Continuous outcomes • HAMD24 • SSI	HAMD24 change, posttreatment (4 weeks); mITT (IG1=25; CG=27); mean (SE) Actual values NR Treatment effect: *P*=0.08 Time × Treatment interaction; *P*=0.438

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		SSI change in score from baseline to 4 weeks; ITT (IG1=25; CG=27); mean (SE) IG1: 0.5 (0.9) CG: 2.3 (0.8) Change baseline week 4 active vs. sham (95% CI): 0.4 (−2.2 to 2.9)
	Subgroup analyses: No subgroups of interest reported	NR
Kim et al. (2019)[40] TMS (14) Sham TMS (12)	**Remission**: HAMD17 score <8 and a CGI-S score ≤1	Remission, posttreatment (4 weeks); mITT (IG1=11; CG=11); N (%) IG1: 3 (27.3) CG: 2 (18.2) *P*=0.613
	Response: At least a 50% decrease from baseline HAMD17 score	Response, posttreatment (4 weeks); mITT (IG1=11; CG=11); N (%) IG1: 9 (81.8) CG: 5 (45.5) *P*=0.088
	Continuous outcomes • HAMD17 • BDI • EPDS • CGI-S	HAMD17, during treatment (2 weeks); mITT (IG1=11; CG=11); mean (SD) IG1: 17 (4.45) CG: 14.09 (7.57) HAMD17, posttreatment (4 weeks); mITT (IG1=11; CG=11); mean (SD) IG1: 9.3 (6.1) CG: 13.3 (8.0) Time × treatment interaction; *P*=0.003 (this is only comparing scores 2 weeks into treatment to scores at the end of treatment adjusting for baseline score differences; this is not comparing score change from baseline) BDI, during treatment (2 weeks); mITT (IG1=11; CG=11); mean (SD) IG1: 17.8 (10.0) CG: 17.9 (11.6) BDI, posttreatment (4 weeks); mITT (IG1=11; CG=11); mean (SD) IG1: 2.1 (7.2) CG: 16.1 (10.5) Time × treatment interaction *P*=0.156 (only compares change in scores between 2 weeks and 4 weeks for active vs. sham adjusting for baseline differences)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		EPDS, during treatment (2 weeks); mITT (IG1=11; CG=11); mean (SD) IG1: 14.0 (5.5) CG: 13.1 (6.2) EPDS, posttreatment (4 weeks); mITT (IG1=11; CG=11); mean (SD) IG1: 9.55 (5.05) CG: 13 (6.59) Time × treatment interaction *P*=0.008 (only compares change in scores between 2 weeks and 4 weeks for active vs. sham, adjusting for baseline differences) EPDS, followup (6 weeks); completers with followup data (IG1=6; CG=7) values NR *P*=0.801 CGI-S, during treatment (2 weeks); mITT (IG1=11; CG=11); mean (SD) IG1: 3.8 (1.1) CG: 3.7 (1.2) CGI-S, posttreatment (4 weeks); mITT (IG1=11; CG=11); mean (SD) IG1: 2.4 (1.1) CG: 3.2 (1.3) Time × treatment interaction *P*=0.035 (only compares change in scores between 2 weeks and 4 weeks adjusted for baseline differences)
	Subgroup analyses: No subgroups of interest reported	NR
Koerselman et al. (2004)[66] rTMS (26) Sham rTMS (26)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes: HAMD17	HAMD17, posttreatment (2 weeks); mITT (IG=26; CG=26); mean (SD) IG1: 21.1 (7.47) CG: 21.9 (7.08) *P*=0.71 HAMD17, 12 weeks after treatment (14 weeks); unclear (IG=12; CG=15); mean (SD) IG1: 14.7 (7.96) CG: 18.7 (8.21) *P*=0.21

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		HAMD17 change, week 0 to 1; mITT (IG=26; CG=26); difference from sham: −0.562; *P*=0.33 HAMD17 change, week 1 to 2; mITT (IG=26; CG=26), difference from sham: 0.562; *P*=0.33 HAMD17 change, week 4 to 14; mITT (IG=26; CG=26), difference from sham: −4.4; *P*=0.05
	Subgroup analyses: No subgroups of interest reported	NR
Lee et al. (2018)[63] rTMS (15) Sham rTMS (15)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes • HAMD17 BDI	HAMD17 change, posttreatment (3 weeks); completers (IG=15; CG=15); mean (SD) IG: −7.2 (4.5) CG: −3.7 (4.2) Repeated measures time × group interaction *P*=0.04 BDI change, posttreatment (3 weeks); completers (IG=15; CG=15) IG: NR CG: NR *P*=NS
	Subgroup analyses: No subgroups of interest reported	NR
Levkovitz et al. (2015)[53] dTMS (111) Sham dTMS (122)	**Remission**: HAMD21 score <10	Remission, 1 week into maintenance treatment (5 weeks); mITT (IG1=101; CG=111); N (%) IG1: 31 (30.4) CG: 18 (15.8) *P*=0.0158 Remission, 1 week into maintenance treatment (5 weeks); PP (IG1=89; CG=92); N (%) IG1: NR (32.6) CG: NR (14.6) *P*=0.0051
	Response: At least a 50% decrease in HAMD21 from baseline	Response, 1 week into maintenance treatment (5 weeks); mITT (IG1=101; CG=111); N (%) IG1: 37 (37.0)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		CG: 31 (27.8) *P*=0.031 Response, 1 week into maintenance treatment (5 weeks); PP (IG1=89; CG=92); N (%) IG1: NR (38.4) CG: NR (21.4) *P*=0.0138
	Continuous outcomes: HAMD21	Change in HAMD21 from baseline to 1 week into maintenance treatment (5 weeks); mITT (IG=101; CG=111); slope of change (95% CI) IG1: −6.17 (−7.78 to −4.55) CG: −3.94 (−5.58 to −2.29) Between group difference: −2.23 (95% CI, −4.54 to 0.07); ES=0.58; *P*=0.0578 Change in HAMD21 from baseline to 1 week into maintenance treatment (5 weeks); PP (IG1=89; CG=92); slope of change (95% CI) Between group difference: −3.11 (95% CI, −5.40 to −0.83); ES=0.76; P=0.008
	Subgroup analyses: No subgroups of interest reported	NR
Li et al. (2014)[55] Continuous TBS (15) Intermittent TBS (15) Intermittent and continuous TBS (15) Sham TBS (15)	**Remission**: NR	NR
	Response: at least 50% decrease in HAMD17 score	Participants with at least 50% decrease in HAMD17 score at end of treatment (2 weeks); ITT (IG1=15; IG2=15; IG3=15; CG=15); N (%) IG1: 3 (25) IG2: 6 (40) IG3: 10 (67) CG: 2 (13) *P*=0.01
	Continuous outcomes: HAMD17	Percent change HAMD17 from baseline to end of treatment (2 weeks); ITT (IG1=15; IG2=15; IG3=15; CG=15); mean (range) IG1: −22.5 (13.3 to −70.0) IG2: −42.3 (4.3 to -88.9) IG3: −52.5 (-15.0 to −92.3) CG: −17.4 (30.0 to −84.6) *P*<0.01
	Subgroup analyses: Treatment refractoriness	Patients with moderate and high refractoriness (based on Maudsley refractoriness scores): intermittent TBS and a combination of intermittent and continuous TBS were more effective than continuous TBS or sham. (*p*<0.05)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Li et al. (2020)[50] Li et al. (2021)[134] Prolonged intermittent TBS (piTBS) (35) rTMS (35) Sham (piTBS or rTMS) (35)	**Remission**: HAMD17 score of 7 or below	HAMD17 ≤7, posttreatment (2 weeks); ITT (IG1=35; IG2=35; CG=35); N (%) IG1: 9 (25.7) IG2: 5 (14.3) CG: 1 (2.9) *P*=0.026 HAMD17 ≤7, 12 weeks posttreatment (14 weeks); ITT (IG1=35; IG2=35; CG=35); N (%) IG1: 7 (20) IG2: 2 (6) CG: 0 (0) *P*=NR
	Response: at least a 50% decrease in HAMD17	Decrease in HAMD17 ≥50% from baseline, posttreatment (2 weeks); ITT (IG1=35; IG2=35; CG=35); N (%) IG1: 16 (45.7) IG2: 14 (40.0) CG: 1 (2.9) *P*<0.001 Decrease in HAMD17 ≥50% from baseline, at latest followup (14 weeks); ITT (IG1=35; IG2=35; CG=35); N (%) IG1: 12 (34.3) IG2: 7 (20.0) CG: 0 (0)
	Continuous outcomes: HAMD17	LS mean change from sham in HAMD17, posttreatment (2 weeks); ITT (IG1=35; IG2=35; CG=35); LS % change (SE) IG1: −9.8 (4.6); *P*=0.037 IG2: −10.2 (4.6); *P*=0.030 HAMD17, posttreatment (2 weeks); ITT (IG1=35; IG2=35; CG=35); mean difference from sham (SE), *P* value IG1: 26.2% (5.9); *P*<0.001 IG2: 20.2 % (5.9); P=0.003 HAMD17, at latest followup (14 weeks); ITT (IG1=35; IG2=35; CG=35); mean (SD) IG1: 13.5 (6.6)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		IG2: 15.6 (7.2) CG: 20.1 (5.8) *P*<0.001
	Subgroup analyses: Measurement vs. MRI-guided	MRI navigation did not yield better results than manual measurement
O'Reardon et al. (2007)[37] Janicak et al. (2008)[135] High frequency rTMS (165) Sham (160)	**Remission**: • MADRS <10 • HAMD17 <8 • HAMD24 <11	MADRS <10, after 4 weeks of active treatment prior to allowing crossover (4 weeks); mITT (IG=155; CG=146) IG1: 11 (7.1) CG: 9 (6.2) *P*>0.10 Results also reported at 6 weeks (final 2 weeks of treatment after crossovers allowed) Between group difference, *P*<0.01 HAMD17 <8, after 4 weeks of active treatment prior to allowing crossover (4 weeks); mITT (IG=155; CG=146) IG1: 11 (7.1) CG: 9 (6.2) *P*>0.10 Results also reported at 6 weeks (final 2 weeks of treatment after crossovers allowed) Between group difference, *P*<0.05 HAMD24 <11, After 4 weeks of active treatment prior to allowing crossover (4 weeks); mITT (IG=155; CG=146) IG1: 14 (9.0) CG: 12 (8.2) *P*>0.10 Results also reported at 6 weeks (final 2 weeks of treatment after crossovers allowed) Between group difference, *P*<0.05
	Response: • MADRS, 50% improvement from baseline • HAMD17, 50% improvement from baseline • HAMD24, 50% improvement from baseline	MADRS, after 4 weeks of active treatment prior to allowing crossover (4 weeks); mITT (IG=155; CG=146) IG1: 28 (18.1) CG1: 16 (11.0) *P*<0.05 Results also reported at 6 weeks (final 2 weeks of treatment after crossovers allowed) Between group difference, *P*<0.05

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		HAMD17, after 4 weeks of active treatment prior to allowing crossover (4 weeks); mITT (IG=155; CG=146) IG1: 32 (20.6) CG1: 17 (11.6) *P*<0.05 Results also reported at 6 weeks (final 2 weeks of treatment after crossovers allowed) Between group difference, *P*=NS HAMD24, after 4 weeks of active treatment prior to allowing crossover (4 weeks); mITT (IG=155; CG=146) IG1: 30 (19.4) CG1: 17 (11.6) *P*<0.05 Results also reported at 6 weeks (final 2 weeks of treatment after crossovers allowed) Between group difference, *P*<0.05
	Continuous outcomes • HAMD24 • HAMD17 • MADRS • CGI-S	MADRS, after 4 weeks of active treatment prior to allowing crossover (4 weeks); mITT (IG=155; CG= 146); mean (SD) IG1: 27 (11.1) CG: 29.8 (10.1) *P*=0.057 Results excluded the participants with mild depression at baseline (imbalance between groups); *P*=0.038 Results also reported at 6 weeks (final 2 weeks of treatment after crossovers allowed) Between group difference, *P*=0.057 HAMD17, after 4 weeks of active treatment prior to allowing crossover (4 weeks); mITT (IG=155; CG= 146); mean (SD) IG1: 17.4 (6.5) CG: 19.4 (6.5) *P*=0.006 Results also reported at 6 weeks (final 2 weeks of treatment after crossovers allowed) Between group difference, *P*=0.005 HAMD24, after 4 weeks of active treatment prior to allowing crossover (4 weeks); mITT (IG=155; CG= 146); mean (SD)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		IG1: 23.4 (8.9) CG: 25.9 (8.8) *P*=0.012 Results also reported at 6 weeks (final 2 weeks of treatment after crossovers allowed) Between group difference, *P*=0.015 CGI-S change in score, after 4 weeks of active treatment prior to allowing crossover (4 weeks); mITT (IG1=155; CG=146); mean (SD) IG1: NR (NR) CG: NR (NR) *P*=0.009 Results also reported at 6 weeks (final 2 weeks of treatment after crossovers allowed) Between group difference, *P*=0.012
	Subgroup analyses: No subgroups of interest reported	NR
Padberg et al. (2002)[48] 100% MT rTMS (10) 90% MT rTMS (10) Sham (10)	**Remission**: HAMD21 score <9	Remission, posttreatment (2 weeks); completers (IG1=10; IG2=10; CG=10); N (%) IG1=2 (20) IG2=1 (10) CG=0 (0)
	Response: • Response: HAMD21 reduction of 50% or greater Partial response: HAMD21 reduction of 25% or greater	Response, posttreatment (2 weeks); completers (IG1=10; IG2=10; CG=10); N (%) IG1=3 (30) IG2=2 (20) CG=0 (0) Partial response, posttreatment (2 weeks); completers (IG1=10; IG2=10; CG=10); N (%) IG1=2 (20) IG2=1 (10) CG=2 (20)
	Continuous outcomes • MADRS • HAMD21 • CGI-S	Percent reduction in MADRS, posttreatment (2 weeks); completers (IG1=10; IG2=10; CG=10); mean (SEM) IG1=33.2 (8.9) IG2= 15.1 (6.6) CG=4.1 (5.2)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		Mean MADRS score, mid-treatment (1 week) and posttreatment (2 weeks); completers (IG1=10; IG2=10; CG=10) Reported in figure only, actual values NR Linear effect F=2.9; *P*<0.05 Percent reduction in HAMD21, posttreatment (2 weeks); completers (IG1=10; IG2=10; CG=10); mean (SEM) IG1= 29.6 (8.7) IG2=14.9 (8.9) CG=7.1 (5.8) Mean HAMD21 score, mid-treatment (1 week) and posttreatment (2 weeks); completers (IG1=10; IG2=10; CG=10) Reported in figure only, actual values NR Linear effect F=1.4; *P*=NS CGI-S, mid-treatment (1 week) and posttreatment (2 weeks); completers (IG1=10; IG2=10; CG=10), time × treatment interaction Values NR F=3.8 *P*<0.05
	Subgroup analyses: No subgroups of interest reported	NR
Pallanti et al. (2010)[44] Bilateral rTMS (20) Unilateral rTMS` (20) Sham rTMS (20)	**Remission**: HAMD-28 score ≤8	Remission, posttreatment (3 weeks); ITT (IG1=20; IG2=20; CG=20); N (%) IG1: 2 (10) IG2: 6 (30) CG: 1 (5) *P*=0.064
	Response: At least 50% reduction in baseline HAMD-28 score	Response, posttreatment (3 weeks); ITT (IG1=20; IG2=20; CG=20); N (%) IG1: 4 (20) IG2: 7 (35) CG: 2 (10) *P*=0.04
	Continuous outcomes: HAMD-28	HAMD-28, posttreatment (3 weeks); ITT (IG1=20; IG2=20; CG=20) Reported on figure only; actual values NR *P*<0.001 (unadjusted)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		P=0.021 (adjusted for age, duration of illness, duration of current episode, number of previous failed drug trials) Post hoc comparison IG1 vs. CG: *P*=NS IG2 vs. CG: *P*<0.05
	Subgroup analyses: No subgroups of interest reported	NR
Rossini et al. (2005)[45] rTMS (50) Sham (49)	**Remission**: HAMD21 score ≤ 8	Remission, end of TMS treatment (2 weeks); completers (IG1=49; CG=47); N (%) IG1: 18 (36.7) CG: 5 (10.6) *P*=0.003 No difference among the 3 groups randomized to the 3 different pharmacologic agents *P*=0.837 for active treatment; *P*=0.501 for sham treatment Remission, 5 weeks (3 weeks post-TMS treatment); completers (IG1=45; CG=44); N (%) IG1: 33 (73.3) CG: 24 (54.5) *P*=0.064 No difference among the 3 groups randomized to the 3 different pharmacologic agents *P*=0.764 for active treatment; *P*=0.780 for sham treatment
	Response: ≥ 50% decrease in the HAMD21 total score from baseline	Response, end of TMS treatment (2 weeks); completers (IG1=49; CG=47); N (%) IG1: 25 (51) CG: 10 (21.3) *P*=0.002 No difference among the 3 groups randomized to the 3 different pharmacologic agents *P*=0.764 for active treatment; *P*=0.901 for sham treatment Response, 5 weeks (3 weeks post-TMS treatment); completers (IG1=45; CG=44); N (%) IG1: 36 (80.0) CG: 32 (72.7) *P*=0.419 No difference among the 3 groups randomized to the 3 different pharmacologic agents *P*=0.278 for active treatment; *P*=0.708 for sham treatment
	Continuous outcomes • HAMD21 • CGI-S	HAMD 21, end of treatment (2 weeks); completers (IG1=49; CG=47); mean (SE) change from baseline IG1: −12.9 (1.03)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		CG: −8.3 (1.06) Between group difference (95% CI): −4.6 (−7.6 to −1.7) *P*=0.002 HAMD 21, 2 weeks posttreatment (4 weeks); completers (IG1=46; CG=47); mean (SE) change from baseline IG1: −17.9 (1.02) CG: −14.0 (1.01) Between group difference (95% CI): −3.9 (-6.8 to −1.1) *P*=0.007 HAMD 21, 3 weeks post-TMS treatment (5 weeks); completers (IG1=45; CG=44); mean (SE) change from baseline IG1: −19.1 (1.12) CG: −16.2 (1.14) Between group difference (95% CI): −2.9 (−6.1 to 0.2) *P*=0.068 Repeated measures ANOVA baseline to 5 weeks: Time × treatment interaction: ITT population, *P*=0.0029; completers population, *P*=0.0015 CGI-S, baseline to 5 weeks, repeated measures ANOVA Time × treatment interaction ITT population: *P*=0.002 Completers population: *P*=0.002
	Subgroup analyses: No subgroups of interest reported	NR
Schutter et al. (2009)[59] rTMS (17) Sham (17)	**Remission**: NR	NR
	Response: ≥50% reduction in HAMD17 score (clinical responders) ≥30% reduction in HAMD17 score (partial clinical responders)	Response, posttreatment (2 weeks); mITT (IG1=16; CG=16); N (%) IG1: 3 (18.8) CG: 1 (6.3) *P*=0.60 Partial response, posttreatment (2 weeks); mITT (IG1=16; CG=16); N (%) IG1: 7 (43.8) CG: 1 (6.3) *P*=0.04

Author (Year) Interventions (N Randomized)	Name of Measure	Results
	• **Continuous outcomes:** HAMD17	Percentage change from baseline in HAMD17, posttreatment (2 weeks); mITT (IG1=16; CG=16); mean (SD) IG1: −19.9 (32.8) CG: −5.6 (28.4) F=1.75 *P*=0.20
	Subgroup analyses • Age • Sex	Partial clinical responders did not significantly differ from nonresponders on baseline HAMA scores, age, and MT (all *p* values >0.43); Fisher's exact probability tests did not demonstrate significant medication or sex differences between partial clinica
Stern et al. (2007)[47] High frequency left-sided rTMS (10) Low frequency left-sided rTMS (10) Low frequency right-sided rTMS (10) Sham rTMS (15)	**Remission:** HAMD21 score ≤10	Remission, end of treatment (2 weeks); ITT (IG1=10; IG2=10; IG3=10; CG=15); N (%) IG1: 3 (33.3) IG2: 0 (0) IG3: 1 (10) CG: 0 (0) *P*=NR Remission, at latest followup (4 weeks); ITT (IG1=10; IG2=10; IG3=10; CG=15); N (%) IG1: 4 (40) IG2: 0 (0) IG3: 3 (33.3) CG: Unclear whether this was reported for this group (text and table in manuscript are in conflict) *P*=NR
	Response: At least a 50% decrease in HAMD21 score from baseline	Response, end of treatment (2 weeks); ITT (IG1=10; IG2=10; IG3=10; CG=15); N (%) IG1: 5 (50) IG2: 0 (0) IG3: 5 (50) CG: 0 (0) *P*=NR Response, at last followup (4 weeks); ITT (IG1=10; IG2=10; IG3=10; CG=15); N (%) IG1: 4 (40) IG2: 0 (0) IG3: 6 (60)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		CG: Unclear whether this was reported for this group (text and table in manuscript are in conflict)
	• **Continuous outcomes:** HAMD21	HAMD21, posttreatment (2 weeks); completers (IG 1=10; IG2=8; IG3= 10; CG=14); mean (SD) IG1: 15.1 (6) IG2: 27.6 (5.9) IG3: 15.8 (4.8) CG: 26.7 (3.6) Between group comparison of % change in HAMD score: *P*=0.0001 Post hoc pairwise comparison IG1>CG, *P*<0.0005 IG3>CG, *P*<00005 No significant differences between IG2 and CG HAMD21, at latest followup (4 weeks); completers (IG 1=10; IG2=5; IG3= 10; CG=11); mean (SD) IG1: 13.4 (5.6) IG2: 26.6 (3.0) IG3: 14.9 (5.9) CG: 26.8 (2.3) Between group comparison of % change in HAMD score: *P*=0.0001 IG1>CG, *P*<0.0005 IG3>CG, *P*<00005 No significant differences between IG2 and CG
	Subgroup analyses • Age • Sex	No correlation between gender or age and improvement
Taylor et al. (2018)[49] rTMS (20) Sham rTMS (20)	**Remission**: MADRS score less than 10	Remission at posttreatment (4 weeks); completers (IG=16; CG=16); N (%) IG: 4 (25) CG: 5 (31) *P*=0.69
	Response: 50% change from baseline MADRS	Response at posttreatment (4 weeks); completers (IG=16; CG=16); N (%) IG: 7 (44) CG: 5 (31)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		P=0.46
	Continuous outcomes • HAMD17 • MADRS • QIDS-SR • GAF	MADRS score posttreatment (4 weeks); completers (IG=16; CG=16); mean (SE) IG1: 15.6 (8.3) CG: 15.6 (8.3) Time × treatment interaction, beta (SE): −0.64 (0.49); favors IG *P*=0.19 HAMD17 score posttreatment (4 weeks); completers (IG=16; CG=16); mean (SE) IG1: 9.1 (4.8) CG: 10.1 (5.3) Time X treatment interaction; beta (SE): −0.42 (0.33); favors IG *P*=0.21 QIDS-SR score posttreatment (4 weeks); completers (IG=16; CG=16); mean (SE) IG1: 11.4 (6.7) CG: 10.9 (5.5) Time × treatment interaction, beta (SE): −0.34 (0.39); favors IG *P*=0.38 GAF score change from baseline to posttreatment (4 weeks); completers (IG=16; CG=16); mean (SE) IG1: 64.6 (9.9) CG: 64.5 (11.7) Time × treatment interaction; beta (SE): −0.27 (1.09); favors IG *P*=0.80
	Subgroup analyses: No subgroups of interest reported	NR
Theleritis et al. (2017)[64] rTMS 1 (27) rTMS 2 (27) Sham rTMS 1 (20) Sham rTMS 2 (24)	**Remission**: • HAMD score of 8 or less • CGI-S endpoint rating of 2 or 1	HAMD score of 8 or less at 2 weeks posttreatment (5 weeks); completed followup (IG1: 25; IG2: 25; CG1: 18; CG2: 21); N (%): IG1 + IG2: 12 (24.5) CG1: 0 (0) CG2: 0 (0) *P*=0.001 CGI-S endpoint rating of 2 or 1 at 2 weeks posttreatment (5 weeks); completed followup (IG1: 25; IG2: 25; CG1: 18; CG2: 21); N (%):

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		IG1 + IG2: NR (51) CG1 + CG2: NR (2.5) *P*=0.001 CGI-S endpoint rating of 2 or 1, likelihood, OR IG1 vs. IG2: 1.5 (favors IG2) *P*=0.018
	Response: • HAMD score decrease of 50% or more from baseline • CGI-S endpoint rating of 3 or less	HAMD score decrease of 50% or more at 2 weeks posttreatment (5 weeks); (IG1 + IG2=49; CG1 + CG2=40) IG1 + IG2: 29 (59.2) CG1 + CG2: 1 (2.5) *P*<0.001 CGI-S endpoint rating of 3 or less at 2 weeks posttreatment (5 weeks); (IG1 + IG2=49; CG1 + CG2=40) IG1 + IG2: 49 (100.0) CG1 + CG2: 5 (12.5) *P*<0.001
	Continuous outcomes • HAMD17 • CGI-S	HAMD17 score; baseline (IG1=26; IG2=26; CG1= 20; CG2=24); mITT; mean (SD) IG1: 30.6 (3.2) IG2: 29.7 (4.6) CG1: 29.4 (3.2) CG2: 30.3 (3.6) HAMD17 score, posttreatment (3 weeks); (IG1=26; IG2=26; CG1= 20; CG2=24); mITT; mean (SD) IG1: 15.6 (3.7) IG2: 13.1 (4.5) CG1: 25.4 (5.3) CG2: 27.0 (4.0) *P*=NR HAMD17 score, 2 weeks posttreatment (5 weeks); (IG1=26; IG2=26; CG1= 20; CG2=24); mITT; mean (SD) IG1: 14.9 (4.1)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		IG2: 12.3 (5.1) CG1: 25.9 (5.8) CG2: 27.4 (4.1) *P*=NR CGI-S score, baseline (IG1=26; IG2=26; CG1= 20; CG1=24); mITT; mean (SD) IG1: 4.8 (0.6) IG2: 4.5 (0.6) CG1: 4.8 (0.7) CG2: 5.0 (0.7) CGI-S score, posttreatment (3 weeks); (IG1=26; IG2=26; CG1= 20; CG1=24); mITT; mean (SD) IG1: 2.6 (0.7) IG2: 2.1 (0.9) CG1: 4.2 (0.8) CG2: 4.4 (0.7) *P*=NR CGI-S score, 2 weeks posttreatment (5 weeks); (IG1=26; IG2=26; CG1= 20; CG1=24); mITT; mean (SD) IG1: 2.5 (0.7) IG2: 1.9 (0.8) CG1: 4.3 (0.9) CG2: 4.5 (0.7) *P*=NR
	Subgroup analyses: No subgroups of interest reported	NR
van Eijndhoven et al. (2020)[41] rTMS (15) Sham rTMS (16)	**Remission**: HAMD17 score ≤7	Remission, posttreatment (5 weeks); ITT (IG1=15; CG=16); N (%) IG1: 0 (0) CG: 0 (0) *P*=NR Trial stopped for futility after interim analysis.
	Response: ≥50% decrease of the baseline HAMD17 score	Response, posttreatment (5 weeks); ITT (IG1=15; CG=16); N (%) IG1: 0 (0) CG: 1 (6)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		P=0.11 Trial stopped for futility after interim analysis
	Continuous outcomes: HAMD17	HAMD17 score, posttreatment (5 weeks); ITT (IG1=15; CG=16); mean (SD) IG1: 21.0 (5.4) CG: 18.6 (4.2) *P*=0.23 Change in HAMD17, posttreatment (5 weeks); ITT (IG1=15; CG=16); mean (SE) IG1: −3.7 (4.0) CG: −4.1 (3.9) Time × treatment interaction *P*=0.50 Trial stopped for futility after interim analysis.
	Subgroup analyses: No subgroups of interest reported	NR
Yesavage et al. (2018)[38] rTMS (81) Sham (83)	**Remission**: HAMD24 score of ≤10	Remission, end of treatment (4 to 11 weeks); ITT (IG1=81; CG=83); N (%) IG1: 33 (40.7) CG1: 31 (37.4) OR 1.16 (0.59 to 2.26); *P*=0.67 Remission, 12 to 18 weeks posttreatment (24 weeks); ITT (IG1=81; CG=83); N (%) IG1: 16 (19.8) CG1: 13 (15.7) OR 1.55 (0.62 to 3.86); *P*=0.35
	Response: NR	NR
	Continuous outcomes • HAMD24 • MADRS • BDI • BSI • CSSRS	Adjusted for baseline, site, and comorbid PTSD or substance use HAMD24, posttreatment (4 to 11 weeks); mITT(IG1=73, CG=77); mean (SD) IG1: 14.8 (9.1) CG: 14.4 (8.6) Adjusted Effect Estimate (95% CI): 1.28 (−1.42 to 3.97); *P*=0.34 HAMD24, 12 to 18 weeks posttreatment (24 weeks), completers (IG=60; CG=65), mean (SD) IG1: 16.3 (0.5) CG: 17.1 (8.9) Adjusted Effect Estimate (95% CI): 0.67 (−2.59 to 3.94); *P*=0.68

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		MARDS, posttreatment (4 to 11 weeks), mITT (IG1=73; CG=77), mean (SD) IG1: 14.3 (11.1) CG: 13.1 (10.5) Adjusted Effect Estimate (95% CI): 2.26 (−0.91 to 5.44); *P*=0.16 MARDS, 12 to 18 weeks posttreatment (24 weeks), completers (IG=60; CG=65), mean (SD) IG1: 13.7 (10.2) CG: 15.0 (9.7) Adjusted Effect Estimate (95% CI): −0.03 (−3.45 to 3.39); *P*=0.99 BDI-II, posttreatment (4 to 11 weeks); mITT (IG1=73; CG=77); mean (SD) IG1: 14.2 (10.9) CG: 13.0 (9.5) Adjusted Effect Estimate (95% CI): 2.22 (−0.64 to 5.08); *P*=0.12 BDI-II, 12 to 18 weeks posttreatment (24 weeks); completers (IG=60; CG=65); mean (SD) IG1: 9.0 (8.3) CG: 12.8 (10.8) Adjusted Effect Estimate (95% CI): -1.59 (−6.08 to 2.89); *P*=0.48 Adjusted for baseline, site, and comorbid PTSD or substance use BSI, posttreatment (4 to 11 weeks); mITT (IG=73; CG=77); mean(SD) IG1: 2.0 (4.6) CG: 2.7 (4.9) Adjusted Effect Estimate (95% CI): 0.08 (−1.46 to 1.62); *P*=0.91 BSI, 12 to 18 weeks posttreatment (24 weeks); completers (IG=60; CG=65); mean(SD) IG1: 1.5 (4.2) CG: 2.5 (4.9) Adjusted Effect Estimate (95% CI): −0.54 (−2.25 to 1.17); *P*=0.53 Suicidal ideation (based on CSSRS), posttreatment (4 to 11 weeks); mITT (IG=73; CG=77); N (%)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		IG1: 18 (25.7) CG: 21 (28.8) OR (95% CI): 0.90 (0.40 to 2.00); *P*=0.79 Suicidal ideation (based on CSSRS), 12 to 18 weeks posttreatment (24 weeks); completers (IG=60; CG=65), N (%) IG1: 14 (24.6) CG: 15 (23.8) OR (95% CI): 1.02 (0.43 to 2.46); *P*=0.96
	Subgroup analyses • Sex • Comorbidity	Differences by sex: no difference in remission by sex Differences by PTSD comorbidity: rates of remission were higher for MDD (without PTSD) for active compared to sham conditions, whereas there was little difference for MDD with PTSD (*P*=0.03)

Abbreviations: ANOVA = analysis of variance; BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory II; BSI = Beck Scale for Suicide Ideation; CG = control group; CGI-S = Clinical Global Impression-Severity; CSSRS = Columbia Suicide Severity Rating Scale; EPDS = Edinburgh Postnatal Depression Scale; GAF = Global Assessment of Functioning Scale; GCI = Global Clinical Inventory; HAMA = Hamilton Anxiety Rating Scale; HAMD = Hamilton Depression Rating Scale; HAMD-6 = Hamilton Depression Rating Scale (6 item); HAMD-8 = Hamilton Depression Rating Scale (8 item); HAMD17 = Hamilton Depression Rating Scale (17 item); HAMD24 = Hamilton Depression Rating Scale (24 item); HAMD-28 = Hamilton Depression Rating Scale (28 item); IG = intervention group; LS = least square; MADRS = Montgomery Asberg Depression Rating Scale; mITT = modified intention-to-treat; NR = not reported; NS = not significant; PP = per protocol; QIDS-SR = Quick Inventory of Depressive Symptoms, Self-rated; SSI = Scale for Suicidal Ideation; TMS = transcranial magnetic stimulation.

Table C-15. Safety Outcomes for Included Repetitive TMS Interventions for MDD

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
Anderson et al. (2007)[58] rTMS (14) Sham rTMS (16)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, 6 weeks, mITT (IG1=11, CG=14), N (%) IG1: 1 (9) (1 hypomanic, the same participant had a series of epileptic seizures 4 days posttreatment, primary cause not identified) CG: 0 (0)
	Other Harms	AEs leading to withdrawal, 2 weeks, ITT (IG1=13, CG=16), N (%) IG1: 2 (15) CG: 2 (13)
Avery et al. (2006)[68] Wajdik et al. (2014)[131] rTMS (35) Sham rTMS (33)	**Any Adverse Event**	No significant differences between TMS and sham in any emerging symptoms from the Systematic Assessment for Treatment Emergent Effects (SAFTEE)
	Serious Adverse Events	NR
	Other Harms	Seizures, posttreatment (4 weeks), ITT (IG1=35, CG=33) IG1: 0 (0) CG: 0 (0) At the first session, 0/33 in the sham group experienced pain, while 14/35 (41%) in the TMS group experienced pain. At the final session, 1/30 (3%) in the sham group and 11/33 (33%) in the TMS group experienced pain.
Blumberger et al. (2012)[43] Bilateral rTMS (28) Unilateral rTMS (24) Sham rTMS (22)	**Any Adverse Event**	NR
	Serious Adverse Events	Withdrawal due to SAE, end of treatment (6 weeks), mITT (IG1=26, IG2=22, CG=20), N (%) IG1: 1 (4) (myocardial infarction, judged unrelated to treatment) IG2: 2 (9) (1 suicidality requiring hospitalization, judged unrelated to treatment; 1 insomnia, possibly related to treatment) CG: 1 (5) (1 suicidality requiring hospitalization, judged unrelated to treatment)
	Other Harms	Scalp discomfort, end of treatment (6 weeks), unclear ITT or completer (IG1=unclear, IG2= unclear, CG=unclear), N (%) IG1: 0 (0) IG2: 1 (5) CG: 0 (0) Recurrent headaches, end of treatment (6 weeks), unclear ITT or completer (IG1=unclear, IG2= unclear, CG=unclear), N (%) IG1: 0 (0) IG2: 1 (5) CG: 0 (0)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
Blumberger et al. (2016)[42] Bilateral rTMS (40) Unilateral rTMS (40) Sham rTMS (41)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 1 (2.5); hospitalization for anxiety IG2: 0 (0) CG: 0 (0)
	Other Harms	Headache, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 7 (18) IG2: 7 (18) CG: 7 (17) Pain, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 7 (18) IG2: 8 (20) CG: 2 (5) Fatigue, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 2 (5) IG2: 2 (5) CG: 1 (2) Difficulty sleeping, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 2 (5) IG2: 2 (5) CG: 1 (2) Racing thoughts, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 1 (3) IG2: 0 (0) CG: 1 (2) Worsening mood, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 1 (3) IG2: 0 (0) CG: 0 (0) Suicidal thoughts, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 0 (0) IG2: 0 (0) CG: 1 (2) Nightmares, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 1 (3)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
		IG2: 0 (0) CG: 0 (0) Anger, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 0 (0) IG2: 1 (3) CG: 0 (0) Tremor, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 0 (0) IG2: 0 (0) CG: 1 (2) Lightheadness, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 1 (3) IG2: 0 (0) CG: 0 (0) Confusion, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 0 (0) IG2: 1 (3) CG: 0 (0) Sore hip, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 0 (0) IG2: 0 (0) CG: 1 (2) Tinnitus, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 1 (3) IG2: 0 (0) CG: 0 (0) Flu, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 1 (3) IG2: 1 (3) CG: 1 (2) Scraping feeling, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 0 (0) IG2: 1 (3) CG: 1 (2) Metallic taste, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 1 (3)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
		IG2: 0 (0) CG: 0 (0) Neck stiffness, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 0 (0) IG2: 1 (2) CG: 0 (0) Lactation, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 1 (3) IG2: 0 (0) CG: 0 (0) Vomiting, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 0 (0) IG2: 1 (2) CG: 0 (0) Anxiety, 6 weeks, ITT (IG1=40, IG2=40, CG=41), N (%) IG1: 1 (3) IG2: 3 (8) CG: 0 (0)
Bretlau et al. (2008)[65] rTMS (25) Sham rTMS (24)	**Any Adverse Event**	Major side effects, 12 weeks, completers (IG=22, CG=23), N (%) IG: 0 (0) CG: 0 (0)
	Serious Adverse Events	NR
	Other Harms	NR
Chou et al. (2020)[52] TBS (30) Sham TBS (30)	**Any Adverse Event**	Any AE, 24 weeks, (IG1=27, CG=26), N (%) IG1: 8 (30) CG: 10 (38) *P*=0.50
	Serious Adverse Events	NR
	Other Harms	NR
Cole et al. (2022)[51] iTBS (14) Sham iTBS (15)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, 4 weeks posttreatment (5 weeks), ITT (IG1=14, CG=15) IG1: 0 (0) CG: 0 (0)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
	Other Harms	Discomfort at treatment site, time point NR, mITT (IG1=14, CG=15), N (%) IG1: 5 (36) CG: 2 (27) Neck/back discomfort, time point NR, mITT (IG1=14, CG=15), N (%) IG1: 7 (50) CG: 5 (33) Post-SNT headache, time point NR, mITT (IG1=14, CG=15), N (%) IG1: 9 (57) CG: 2 (13) *P*=NS Fatigue, time point NR, mITT (IG1=14, CG=15), N (%) IG1: 8 (57) CG: 8 (53) *P*=NS Nausea, time point NR, mITT (IG1=14, CG=15), N (%) IG1: 0 (0) CG: 0 (0) Anxiety, time point NR, mITT (IG1=14, CG=15), N (%) IG1: 4 (29) CG: 3 (20) Dental issues, time point NR, mITT (IG1=14, CG=15), N (%) IG1: 1 (7) CG: 0 (0) Jaw discomfort, time point NR, mITT (IG1=14, CG=15), N (%) IG1: 2 (14) CG: 0 (0)
Concerto et al. (2015)[67] rTMS (15) Sham TMS (15)	**Any Adverse Event**	Any AE, 24 weeks after end of treatment (28 weeks), ITT (IG1=15, CG=15), N (%) IG1: 0 (0) CG: 0 (0)
	Serious Adverse Events	Any SAE, 24 weeks after end of treatment (28 weeks), ITT (IG1=15, CG=15), N (%) IG1: 0 (0) CG: 0 (0)
	Other Harms	NR
Croarkin et al. (2021)[36]	**Any Adverse Event**	NR

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
rTMS (54) Sham TMS (58)	**Serious Adverse Events**	Any SAE, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%) Total: 5 All classified as probably not or definitely not related to the study device Suicidal ideation, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%) IG1: 2 (4) CG: 2 (4)
	Other Harms	Any AE, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%) Total: 60 (NR) Headaches, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%) IG1: 17 (32) CG: 10 (17) Eye pain, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%) IG1: 3 (6) CG: 0 (0) Nausea, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%) IG1: 6 (11) CG: 3 (5) Vomiting, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%) IG1: 3 (6) CG: 2 (3) Facial twitching, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%) IG1: 4 (7) CG: 1 (2) Pain at application site, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%) IG1: 2 (4) CG: 0 (0) Neck pain, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%) IG1: 3 (6) CG: 3 (5) Twitching of limbs, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%) IG1: 2 (4) CG: 0 (0) Insomnia, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%) IG1: 2 (4) CG: 0 (0) Panic attacks, posttreatment (6 weeks), randomized (IG1=54, CG=58), N (%)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
		IG1: 2 (4) CG: 0 (0)
Duprat et al. (2016)[56] Desmyter et al. (2016)[132] iTBS (47) Sham iTBS (47)	**Any Adverse Event**	NR
	Serious Adverse Events	Suicide attempt, after 1 week of treatment prior to crossover (1 week), N=47 IG1: 0 CG: 1 Selected SAEs (seizure, hypomanic or manic switches, other), during treatment, N=47 0 (0) Suicide up to 6 months posttreatment, N=unclear 0 (0)
	Other Harms	Authors did not report the following as harms but included in the manuscript when discussing individuals excluded from the analysis: Local discomfort at the stimulation site: unclear ("majority of participants") Headache: Unclear ("majority of participants") Dropouts due to intolerance: 0 (0)
Fitzgerald et al. (2012)[57] Bilateral rTMS (22) Unilateral rTMS (24) Sham rTMS (20)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, posttreatment (3 weeks), mITT (IG1=22; IG2=24; CG=20), N (%) IG1: 0 (0) IG2: 0 (0) CG: 0 (0)
	Other Harms	Withdrawal due to AE, posttreatment (3 weeks), mITT (IG1=22; IG2=24; CG=20), N (%) IG1: 3 (14) IG2: 0 (0) CG: 1 (5)
Garcia-Toro et al. (2001)[71] rTMS (20) Sham (20)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	The most frequent side effects were scalp discomfort and slight and transitory headaches in approximately a third of the cases, nearly all from the real stimulation group
Garcia-Toro et al. (2001)[62] High-frequency rTMS (14)	**Any Adverse Event**	Any treatment-emergent AE, posttreatment (2 weeks), completers (IG1=11, CG=11) N (%) IG1: 3 (27.3) CG: 0 (0)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
Sham rTMS (14)	**Serious Adverse Events**	NR
	Other Harms	Tension headache, posttreatment (2 weeks), completers (IG1=11, CG=11) N (%) IG1: 3 (27.3) CG: 0 (0)
Garcia-Toro et al. (2006)[69] 20 + 1-Hz rTMS (10) 20 + 1-Hz rTMS + sPECT targeting (10) Sham rTMS (10	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	Scalp discomfort during administration (IG1=10, IG2=10), N (%) IG1: 1 (10) IG2: 1 (10) Headaches during active stimulation (IG1 + IG2=20), N (%) IG1+IG2: 7 (35)
George et al. (2010)[39] Borckardt et al. (2013)[133] rTMS (92) Sham rTMS (98)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, posttreatment (3 weeks), ITT (IG1=92, CG=98), N (%) IG1: 1 (1) (1 syncope, unlikely related to the study) CG: 1 (1) (1 paranoid ideation, possibly related to the study)
	Other Harms	Procedural pain, posttreatment (3 weeks), mITT (IG1=92; CG=98), mean (SD) IG1: 46.4 (29.5) CG: 30.5 (33.3) Any AE leading to discontinuation, posttreatment (3 weeks), mITT (IG1=92; CG=98), N (%) IG1: 5 (5) CG: 0 (0) Headache, posttreatment (3 weeks), mITT (IG1=92; CG=98), N (%) IG1: 29 (32) CG: 23 (23) Discomfort at stimulation site, posttreatment (3 weeks), mITT (IG1=92; CG=98), N (%) IG1: 17 (18) CG: 10 (10) Insomnia, posttreatment (3 weeks), ITT (IG1=92; CG=98), N (%) IG1: 7 (8) CG: 10 (10) Worsening of depression or anxiety, posttreatment (3 weeks), mITT (IG1=92; CG=98), N (%) IG1: 6 (7)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
		CG: 8 (8) Gastrointestinal, posttreatment (3 weeks), mITT (IG1=92; CG=98), N (%) IG1: 6 (7) CG: 3 (3) Fatigue, posttreatment (3 weeks), m ITT (IG1=92; CG=98), N (%) IG1: 5 (5) CG: 4 (4) Muscle aches, posttreatment (3 weeks), mITT (IG1=92; CG=98), N (%) IG1: 4 (4) CG: 4 (4) Vertigo, posttreatment (3 weeks), mITT (IG1=92; CG=98), N (%) IG1: 2 (2) CG: 2 (2) Skin pain, posttreatment (3 weeks), mITT (IG1=92; CG=98), N (%) IG1: 1 (1) CG: 1 (1) Facial muscle twitching, posttreatment (3 weeks), mITT (IG1=92; CG=98), N (%) IG1: 0 (0) CG: 1 (1) Other, posttreatment (3 weeks), mITT (IG1=92; CG=98), N (%) IG1: 18 (20) CG: 15 (15)
Hausmann et al. (2004)[70] Unilateral, high-frequency rTMS (13) Bilateral rTMS (14) Bilateral sham rTMS (14)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	Seizure-like phenomena, at latest follow-up (4 weeks), completers (IG1+IG2=25, CG=13), N (%) IG1+IG2: 0 (0) CG: 0 (0)
Herwig et al. (2003)[60] rTMS (13) Sham rTMS (12)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, 2 weeks, ITT (IG1=13, IG2=12), N (%) IG1: 0 (0) CG: 0 (0)
	Other Harms	3 patients reported headache, but their group was not reported

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
Hoppner et al. (2003)[61] High-frequency rTMS (10) Low-frequency rTMS (10) Sham rTMS (10)	**Any Adverse Event**	Any AE, posttreatment (2 weeks), ITT (IG1=10, IG2=10, CG=10), N (%) IG1: 1 (10) IG2: 0 (0) CG: 0 (0)
	Serious Adverse Events	NR
	Other Harms	Withdrawal due to AE, posttreatment (2 weeks), ITT (IG1=10, IG2=10, CG=10), N (%) IG1: 1 (10) IG2: 0 (0) CG: 0 (0)
Januel et al. (2006)[46] rTMS (11) Sham (16)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	Except headache (8% principally in the first session), no serious event was noted in the patients during the study
Kaster et al. (2018)[54] Active deep rTMS (30) Sham rTMS (28)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, posttreatment (4 weeks), mITT (IG1=25, CG=27) IG1: 0 (0) CG: 0 (0)
	Other Harms	Pain at stimulation site, posttreatment (4 weeks), ITT (IG1=25, CG=27), N (%) IG1: 4 (16) CG: 0 (0) *P*<0.05 Headache after treatment, posttreatment (4 weeks), ITT (IG1=25, CG=27), N (%) IG1: 14 (56) CG: 10 (37) *P*=NS Nasopharyngitis, posttreatment (4 weeks), ITT (IG1=25, CG=27), N (%) IG1: 1 (4) CG: 0 (0) *P*=NS Aphthous ulcer, posttreatment (4 weeks), ITT (IG1=25, CG=27), N (%) IG1: 1 (4) CG: 0 (0) *P*=NS

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
		Corneal abrasion, posttreatment (4 weeks), ITT (IG1=25, CG=27), N (%) IG1: 1 (4) CG: 0 (0) *P*=NS Dermatitis, posttreatment (4 weeks), ITT (IG1=25, CG=27), N (%) IG1: 1 (4) CG: 0 (0) *P*=NS Sinusitis, posttreatment (4 weeks), ITT (IG1=25, CG=27), N (%) IG1: 1 (4) CG: 0 (0) *P*=NS Nausea, posttreatment (4 weeks), ITT (IG1=25, CG=27), N (%) IG1: 1 (4) CG: 1 (4) *P*=NS Dental pain, posttreatment (4 weeks), ITT (IG1=25, CG=27), N (%) IG1: 0 (0) CG: 1 (4) *P*=NS Increased anxiety, posttreatment (4 weeks), ITT (IG1=25, CG=27), N (%) IG1: 0 (0) CG: 1 (4) *P*=NS
Kim et al. (2019)[40] TMS (14) Sham TMS (12)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	Headache, during treatment (2 weeks), ITT (IG1=11, CG=11), N (%) IG1: 4 (36) CG: 1 (9) *P*=0.311 Headache, 1 week after finishing treatment (5 weeks), ITT (IG1=11, CG=11), N (%) IG1: 1 (9) CG: 0 (0) *P*=1.00

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
		Dizziness/nausea/site pain/supine hypotension/jaw pain/eye twitch, time point NR, ITT (IG1=11, CG=11), N (%) values NR *P*=NS No significant differences in infant outcomes among groups (APGAR scores, delivery complications, NICU admissions, normal assessment by pediatrician, gestational age at delivery, birth length, birth weight, major congenital malformations, preterm birth.
Koerselman et al. (2004)[66] rTMS (26) Sham rTMS (26)	**Any Adverse Event**	NR
	Serious Adverse Events	Suicidal ideation, posttreatment (2 weeks), total randomized (56), N (%) NR by groups Total: 1 (2) Extreme dizziness, posttreatment (2 weeks), total randomized (56), N (%) NR by groups Total: 1 (2)
	Other Harms	Dropout because of increase of symptoms, 12 weeks after treatment (14 weeks), mITT (IG=26, CG=26), N (%) IG1: 2 (8) CG: 1 (4) Dropout because of strong increase of symptoms, 12 weeks after treatment (14 weeks), mITT (IG=26, CG=26), N (%) IG1: 0 (0) CG: 1 (4)
Lee et al. (2018)[63] rTMS (15) Sham rTMS (15)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	NR
Levkovitz et al. (2015)[53] dTMS (111) Sham dTMS (122)	**Any Adverse Event**	Number of AE, 5 weeks, mITT (IG1=101, CG=111), N (%) IG1: 41 (40.6) CG: 32 (28.8) A single participant could experience more than 1 AE
	Serious Adverse Events	Any SAE, 5 weeks, mITT (IG1=101, CG=111), N (%) IG1: 2 (2.0) (3 SAE in 2 subjects: 1 elbow fracture, 1 cluster headache, 1 seizure) CG: 4 (3.6) (2 suicidal ideation, 1 nausea and vomiting, 1 nephrolithiasis) The only SAE considered to be device related was the seizure: occurred in a participant during the end of her 9th TMS session and occurred following the excessive consumption of alcohol on the night before treatment.
	Other Harms	Treatment-emergent SAE, 5 weeks, mITT (IG1=101, CG=111), N (%) IG1: 1 (1.0) (1 seizure)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
		CG: 0 (0) The only AE class with a significant difference between dTMS and sham was "application site pain." IG1: 5 (5) CG: 2 (1.8) *P*=0.02
Li et al. (2014)[55] Continuous TBS (15) Intermittent TBS (15) Intermittent and continuous TBS (15) Sham TBS (15)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	Seizure, end of treatment (2 weeks), ITT (IG1=15, IG2=15, IG3=15, CG=15), N (%) IG1: 0 (0) IG2: 0 (0) IG3: 0 (0) CG: 0 (0) Headache, end of treatment (2 weeks), ITT (IG1=15, IG2=15, IG3=15, CG=15), N (%) IG1: 1 (6.7) IG2: 3 (20.0) IG3: 1 (6.7) CG: 2 (13.3) Dizziness, end of treatment (2 weeks), ITT (IG1=15, IG2=15, IG3=15, CG=15), N (%) IG1: 1 (6.7) IG2: 2 (13.3) IG3: 5 (33.3) CG: 1 (6.7) Other adverse events (palpitation, nausea), end of treatment (2 weeks), ITT (IG1=15, IG2=15, IG3=15, CG=15), N (%) IG1: 0 (0) IG2: 2 (13.3) IG3: 1 (6.7) CG: 0 (0)
Li et al. (2020)[50] Li et al. (2021)[134] Prolonged, intermittent TBS (piTBS) (35) rTMS (35)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	Temporary headaches, at latest follow-up (14 weeks), ITT (IG1=35, IG2=35, CG=35), N (%) IG1: 5 (14.2) IG2: 6 (17.1)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
Sham (piTBS or rTMS) (35)		CG: 4 (11.4) *P*=0.793 Temporary dizziness, at latest follow-up (14 weeks), ITT (IG1=35, IG2=35, CG=35), N (%) IG1: 4 (11.4) IG2: 5 (14.3) CG: 4 (11.4) *P*=0.916 Exacerbation of tinnitus, at latest follow-up (14 weeks), ITT (IG1=35, IG2=35, CG=35), N (%) IG1: 0 (0) IG2: 1 (2.9) CG: 0 (0) Seizure or mania, at latest follow-up (14 weeks), ITT (IG1=35, IG2=35, CG=35), N (%) IG1: 0 (0) IG2: 0 (0) CG: 0 (0)
O'Reardon et al. (2007)[37] Janicak et al. (2008)[135] High-frequency rTMS (165) Sham (160)	**Any Adverse Event**	NR
	Serious Adverse Events	Time point for all reported events is posttreatment and after allowing crossover at 4 weeks (6 weeks) Total SAE, ITT (IG1=165, CG=158), N (%) IG1: 9 (5.4) CG: 7 (4.4) Worsening depression only, ITT (IG1=165, CG=158), N (%) IG: 0 (0) CG: 2 (0.01) Suicidal ideation only, ITT (IG1=165, CG=158), N (%) IG: 2 (0.01) CG: 2 (0.01) Device malfunction/first-degree burn, ITT (IG1=165, CG=158), N (%) IG: 2 (0.01) CG: 0 (0) Device malfunction/severe pain at treatment site, ITT (IG1=165, CG=158), N (%) IG: 1 (0.01) CG : 0 (0)
	Other Harms	Time point for all reported events is posttreatment and after allowing crossover at 4 weeks (6 weeks) Discontinuations due to AE, N (%) IG1: NR (4.5)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
		CG: NR (3.4) Eye pain, ITT (IG1=165, CG=158), N (%) IG1: 10 (6.1) CG: 3 (1.9) Toothache, ITT (IG1=165, CG=158), N (%) IG1: 12 (7.3) CG: 1 (0.6) Application site discomfort, ITT (IG1=165, CG=158), N (%) IG1: 18 (10.9) CG: 2 (1.3) Application site pain, ITT (IG1=165, CG=158), N (%) IG1: 59 (35.8) CG: 6 (3.8) Facial pain, ITT (IG1=165, CG=158), N (%) IG1: 11 (6.7) Cg: 5 (3.2) Muscle twitching, ITT (IG1=165, CG=158), N (%) IG1: 34 (20.6) CG: 5 (3.2) Pain of skin, ITT (IG1=165, CG=158), N (%) IG: 14 (8.5) CG: 1 (0.6)
Padberg et al. (2002)[48] 100% MT rTMS (10) 90% MT rTMS (10) Sham (10)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, 2 weeks, Completes, (IG1=10, IG2=10, CG=10), N (%) IG1: 0 (0) IG2: 0 (0) CG: 0 (0)
	Other Harms	Aversive tactile artifact, posttreatment (2 weeks), completer (IG1=10, IG2=10, CG=10), N (%) IG1: 2 (20) IG2: 3 (30) CG: 0 (0) Experienced rTMS as unpleasant, posttreatment (2 weeks), completer (IG1=10, IG2=10, CG=10), N (%) IG1: 2 (20) IG2: 3 (30) CG: 0 (0)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
		Duration of hospital stay, posttreatment, completer (IG1=10, IG2=10, CG=10), mean (SEM) IG1: 42.6 (10.2) IG2: 60.6 (12.7) CG: 135.0 (38.0) Mild headaches and numbness of the left temple reported by 2 patients (group NR) Migraine attack within 4 hours after sham rTMS
Pallanti et al. (2010)[44] Bilateral rTMS (20) Unilateral rTMS` (20) Sham rTMS (20)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	Headache, 3 weeks, ITT (IG1=20, IG2=20, CG=20), N (%) IG1: 1 (5) IG2: 1 (5) CG: 1 (5) Pain/burning in the scalp, 3 weeks, ITT (IG1=20, IG2=20, CG=20), N (%) IG1: 1 (5) IG2: 0 (0) CG: 2 (10) Cognitive complaints, 3 weeks, ITT (IG1=20, IG2=20, CG=20), N (%) IG1: 3 (15) IG2: 2 (10) CG: 6 (30) Dizziness, 3 weeks, ITT (IG1=20, IG2=20, CG=20), N (%) IG1: 0 (0) IG2: 0 (0) CG: 0 (0) Anxiety, 3 weeks, ITT (IG1=20, IG2=20, CG=20), N (%) IG1: 0 (0) IG2: 0 (0) CG: 1 (5) Seizure episode, 3 weeks, ITT (IG1=20, IG2=20, CG=20), N (%) IG1: 0 (0) IG2: 0 (0) CG: 0 (0)
Rossini et al. (2005)[45]	**Any Adverse Event**	NR

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
rTMS (50) Sham (49)	**Serious Adverse Events**	NR
	Other Harms	Dropouts during TMS treatment by day 12, N (%) (events reported) IG1: 1 (2) (headache and cervical pain) CG: 2 (4.1) (intolerable agitation, gastric symptoms) Dropouts during 3 weeks following TMS 2 patients for lack of improvement of depressive symptoms 2 patients because they went on holiday 2 patients because they did not come to the planned visit 1 patient for consent withdrawal
Schutter et al. (2009)[59] rTMS (17) Sham (17)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	No seizures occurred Most common reported side effects were headache and stimulation of the right facial muscles during the first sessions
Stern et al. (2007)[47] High-frequency, left-sided rTMS (10) Low-frequency, left-sided rTMS (10) Low-frequency right-sided, rTMS (10) Sham rTMS (15)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, end of treatment (2 weeks), completers (IG1=10, IG2=8, IG3= 10, CG=14), N (%) IG1: 0 (0) IG2: 0 (0) IG3: 0 (0) CG: 0 (0)
	Other Harms	Seizures, end of treatment (2 weeks), completers (IG 1=10, IG2=8, IG3=10, CG=14), N (%) IG1: 0 (0) IG2: 0 (0) IG3: 0 (0) CG: 0 (0) Withdrawals due to adverse events, end of treatment (2 weeks), ITT (IG 1=10, IG2=8, IG3=10, CG=14), N (%) IG1: 0 (0) IG2: 2 (20) IG3: 0 (0) CG: 1 (6.7) 9/45 participants reported headaches rated as “severe” on at least 1 of the TMS days
Taylor et al. (2018)[49]	**Any Adverse Event**	NR

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
rTMS (20) Sham rTMS (20)	**Serious Adverse Events**	Any SAE, 4 weeks, completers (IG=16, CG=16) IG: 0 (0) CG: 0 (0)
	Other Harms	NR
Theleritis et al. (2017)[64] rTMS 1 (27) rTMS 2 (27) Sham rTMS 1 (20) Sham rTMS 2 (24)	**Any Adverse Event**	Proportion of subjects with various adverse events *P*=NS
	Serious Adverse Events	Seizures, completed follow-up (IG1=25, IG2=25, CG1=18, CG2=21), N (%) IG1: 0 (0) IG2: 0 (0) CG1: 0 (0) CG2: 0 (0)
	Other Harms	Discomfort at the site of stimulation, completed follow-up (IG1=25, IG2=25, CG1=18, CG2=21), N (%) IG1: 7 (28.0) IG2: 6 (24.0) CG1: 5 (27.8) CG2: 6 (28.6) Exacerbation of preexisting headache, completed follow-up (IG1=25, IG2=25, CG1=18, CG2=21), N (%) IG1: 3 (12.0) IG2: 2 (8.0) CG1: 1 (5.6) CG2: 3 (14.3) Discontinued due to headache, completed follow-up (IG1=25, IG2=25, CG1=18, CG2=21), N (%) IG1: 1 (4.0) IG2: 0 (0) CG1: 0 (0) CG2: 1 (4.8)
van Eijndhoven et al. (2020)[41] rTMS (15) Sham rTMS (16)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, 5 weeks, ITT (IG1=15, CG=16), N (%) IG1: 0 (0) CG: 0 (0)
	Other Harms	Mild to moderate headache symptoms, 5 weeks, ITT (IG1=15, CG=16), N (%) IG1: 9 (60) CG: 10 (63) *P*=NR

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
Yesavage et al. (2018)[38] rTMS (81) Sham (83)	**Any Adverse Event**	NR
	Serious Adverse Events	Suicidal ideation, posttreatment (4-11 weeks), ITT (IG1 NR, CG NR), N (%) IG1: 3 (NR) CG1: 4 (NR) No suicides or seizures or deaths occurred during the study
	Other Harms	Specific AE, posttreatment (4–11 weeks), ITT (IG1 NR, CG NR), N (%) Nasopharyngitis IG1: 8 (NR) CG1: 8 (NR) Falls IG1: 3 (NR) CG1: 7 (NR) Headache IG1: 15 (NR) CG1: 16 (NR) Abnormal hearing IG1: 18 (NR) CG1: 18 (NR) Audiometry results believed to be an artifact of frequent, imprecise testing

Abbreviations: AE = adverse event; APGAR = Appearance, Pulse, Grimace, Activity, and Respiration; CG = control group; dTMS = deep transcranial magnetic stimulation; IG = intervention group iTBS = intermittent theta-burst stimulation; ITT = intention-to-treat; MDD = major depressive disorder; mITT = modified intention-to-treat; MT = motor threshold; N = number; NICU = neonatal intensive care unit; NR = not reported; NS = not significant; pITBS = prolonged, intermittent theta-burst stimulation; rTMS = repetitive transcranial magnetic stimulation; SAE = serious adverse event; SAFTEE = Systematic Assessment for Treatment Emergent Effects; SD = standard deviation; SEM = standard error of the mean; SNT = Stanford Neuromodulation Therapy; TBS = theta-burst stimulation; TMS = transcranial magnetic stimulation.

Table C-16. Study Characteristics for Included Repetitive TMS Interventions for PTSD

Author (Year) Country Registry Number	Study Design Years Conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
Isserles et al. (2021)[75] 11 sites in the U.S., 2 sites in Israel, 1 site in Canada, 1 in Europe NCT02479906	Parallel RCT 2016 to 2020	BrainsWay, Inc.	Yes, entirely	Aged 22 to 68 years meeting DSM-5 criteria for PTSD, baseline CAPS-5 score of at least 25 and HAMD score of 26 or less; outpatients	Other primary Axis 1 disorder or severe personality disorder, past TMS treatment, suicide risk, recent history of substance or alcohol abuse, history of head trauma with loss of consciousness longer than 5 minutes, or other significant brain disorder
Kozel et al. (2018)[76] U.S. NCT01391832	Parallel RCT 2011 to 2016	Department of Defense, Texas Health and Human Services Commission	No	Veterans aged 18 to 60 years with diagnosis of combat-related PTSD	Safety reasons (including contraindicated medication use), history of significant neurological or medical disorder (including moderate or severe TBI), history of psychiatric comorbidities, current substance dependence or abuse, presence of metal objects in close proximity to the head, pregnant or breastfeeding
Philip et al. (2019)[78] U.S. NCT02769312	Parallel RCT 2016 to 2017	U.S. Veterans Affairs	No	Aged 18 to 70 years meeting DSM-5 criteria for chronic PTSD assessed by SCID-5, trauma exposure assessed by Life Events Checklist, symptomatic despite stable treatment for at least 6 weeks prior	History of psychotic disorders, bipolar I, current moderate-to-severe substance use disorder, or active suicidality; presence of implanted devices or metal in close proximity to the head; pregnancy risk; history of traumatic brain injury or unstable medical conditions; or history of seizure, CNS tumors, stroke, or cerebral aneurysm
Watts et al. (2012)[77] U.S.	Parallel RCT NR	Hitchcock Foundation	No	Aged 20 to 70 years diagnosed with PTSD using SCID, CAPS score > 50, stable psychotropic medication and psychotherapy for 2 months before treatment	Presence of metal object or implant in or in close proximity to the head or implantable device, such as pacemaker or defibrillator; seizure in the last year; substance abuse in the last 3 months; acute medical illness or CNS disorder; treatment with medication that decreases seizure threshold

Abbreviations: CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CNS = central nervous system; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; HAMD = Hamilton Rating Scale for Depression; NR = not reported; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SCID-5 = Structured Clinical Interview for DSM-5; TBI = traumatic brain injury; TMS = transcranial magnetic stimulation; U.S. = United States.

Table C-17. Intervention Characteristics for Included Repetitive TMS Interventions for PTSD

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
Isserles et al. (2021)[75]	Sham dTMS (65) Sham type: Sham and active coil within the same device	dTMS (60) Target location: Bilateral mPFC and ACC Localization technique: Manual measurement Frequency: 18 Hz Intensity: 100 Number of pulses: 2,880	Treatment days: 14 total: 12 sessions (3 sessions/week x 4 weeks), plus a booster treatment at weeks 5 and 9 during the follow-up period Treatment sessions total: 14 total	Medication per treatment as usual Psychotherapy per treatment as usual	A prerecorded audio script of the participant's most traumatic event was played before each session, and the participants were then instructed to imagine the event for 30 seconds.
Kozel et al. (2018)[76]	sham rTMS + CPT (49) Sham type: Sham coil, not specified	rTMS + CPT (54) Target location: Right DLPFC Localization technique: EEG-guided Frequency: 1 Hz Intensity: 110% Number of pulses: 1,800	Treatment days: 12 (up to 3 additional sessions of CPT allowed) Treatment sessions total: 12 (up to 3 additional sessions of CPT allowed)	Medication per treatment as usual Psychotherapy, per study protocol	None
Philip et al. (2019)[78]	Sham iTBS (25) Sham type: Separate sham coil	iTBS (25) Target location: Right DLPFC Localization technique: Manual measurement Frequency: 50Hz Intensity: 80% Number of pulses: 1,800	Treatment days: 10 (5 sessions/week x 2 weeks) Treatment sessions total: 10	Medication per treatment as usual Psychotherapy per treatment as usual	None
Watts et al. (2012)[77]	Sham rTMS (10) Sham type: Wand casing that blocks magnetic field	rTMS (10) Target location: Right DLPFC Localization technique: Manual measurement Frequency: 1 Hz Intensity: 90% Number of pulses: 400	Treatment days: 10 (5 sessions/week x 2 weeks) Treatment sessions total: 10	Medication per treatment as usual Psychotherapy per treatment as usual	None

Abbreviations: ACC = anterior cingulate cortex; CPT = cognitive processing therapy; cTBS =controlled theta-burst stimulation, a variation of rTMS; DLPFC=dorsolateral prefrontal cortex; dTMS = deep TMS; EEG = electroencephalogram; Hz =electromagnetic wavelength frequency; iTBS = intermittent theta-burst stimulation; mPFC = medial prefrontal cortex; N = number; PTSD = posttraumatic stress disorder; rTMS = repetitive transcranial magnetic stimulation; TMS = transcranial magnetic stimulation.

Table C-18. Population Characteristics for Included Repetitive TMS Interventions for PTSD

First Author (Year)	Sample Size (Total)	Treatment History	Mean Age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
Philip et al. (2019)[78]	50	Both treatment-naive and treatment-resistant participants eligible	Active: 48 (13) Sham: 53 (12)	Active: 5 (20) Sham: 3 (12)	White: Active: 22 (88) Sham: 20 (80) African American: Active: 0 (0) Sham: 2 (8) American Indian/Alaska Native: Active: 1 (4) Sham: 0 (0) Multiracial: Active: 2 (8) Sham: 1 (4)	MDD: Active: 92% Sham: 88% Bipolar II: Active: 8% Sham: 12% SUD, mild severity: Active: 64% Sham: 44% OUD: Active: 24% Sham: 20%
Isserles et al. (2021)[75]	134	Unspecified treatment naivety or resistance	Active: 44.8 (13.2) Sham: 43.7 (12.3)	Active: 39 (65.0) Sham: 44 (67.7)	White: Active: 54 (90) Sham: 53 (81.5) African American: Active: 3 (5) Sham: 4 (6.2) Hispanic: Active: 4 (6.7) Sham: 3 (4.6) Other: Active: 1 (1.7) Sham: 5 (7.7)	NR
Kozel et al. (2018)[76]	103	Unspecified treatment naivety or resistance	Withdrew from treatment: Active: 31.2 (7.5) Sham: 31.5 (6.3) Completed treatment: Active: 34.1 (7.6) Sham: 32.9 (6.0)	NR Authors reported participants were predominantly male	White: Active: 42 (78) Sham: 42 (86) Black: Active: 7 (13) Sham: 6 (12) Other: Active: 5 (9) Sham: 1 (2)	MDD: 33% Depression NOS: 1% Dysthymic: 13% GAD: 5% OCD: 0% Bipolar: 2% Panic disorder: 1% Psychotic disorder: 0%

First Author (Year)	Sample Size (Total)	Treatment History	Mean Age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
Watts et al. (2012)[77]	20	Treatment-resistant (defined liberally as any prior treatment to TMS)	Active: 54.0 (12.3) Sham: 57.8 (11.8)	Active: 1 (10) Sham: 1 (10)	White: Active: 10 (100) Sham: 10 (100)	MDD: Active: 90% Sham: 70% Panic disorder: Active: 30% Sham: 40% OCD: Active: 30% Sham: 10% SUD: Active: 30% Sham: 0%

Abbreviations: GAD = generalized anxiety disorder; MDD = major depressive disorder; N = number; NOS = not otherwise specified; NR = not reported; OCD = obsessive compulsive disorder; OUD = opioid use disorder; PTSD = posttraumatic stress disorder; SD = standard deviation; SUD = substance use disorder; TMS = transcranial magnetic stimulation.

Table C-19. Efficacy Outcomes for Included Repetitive TMS Interventions for PTSD

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Isserles et al. (2021)[75] dTMS (60) Sham dTMS (65)	**Remission**: NR	"Remission rates were very low and did not statistically differ between groups."
	Response: At least a 50% improvement from baseline in CAPS-5 score	Response, end of treatment (5 weeks), unclear whether this is mITT or completer, N (%) IG1: NR (42.5) CG: NR (54.9) *P*>0.05 Response, 4 weeks after end of treatment (9 weeks), unclear whether this is mITT or completer, N (%) IG1: NR (53.8) CG: NR (68) *P*>0.05
	Continuous outcomes: • CAPS • MPSS	CAPS-5 change, end of treatment (5 weeks), mITT (IG1=60; CG=65), mean (95% CI) IG1: 15.5 (11.9 to 19.1) CG: 19.1 (16.0 to 22.1) P=0.059 CAPS-5 change, 4 weeks after end of treatment (9 weeks), mITT (IG1=60; CG=65), mean (95% CI) IG1: 17.0 (13.0 to 21.1) CG: 22.9 (19.4 to 26.3) *P*=0.011 MPSS change, end of treatment (5 weeks), mITT (IG1=60; CG=65), mean (95% CI) IG1: -5.9 (-8.4 to -3.3) CG: -10.5 (-12.7 to -8.2) Mean difference: 4.6 (1.7 to 7.5) *P*<0.05 MPSS change, 4 weeks after end of treatment (9 weeks), mITT (IG1=60; CG=65), mean (95% CI) IG1: -7.5 (-10.5 to -4.5) CG: -13.1 (-15.7 to -10.6) MD: 5.65 (2.1 to 9.2) *P*<0.05

Author (Year) Interventions (N Randomized)	Name of Measure	Results
	Subgroup Analyses: No subgroups of interest reported	NR
Kozel et al. (2018)[76] rTMS + CPT (54) Sham rTMS + CPT (49)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes • CAPS • PCL • M-PTSD	CAPS change in score, over all time points measures through 6 months' posttreatment, ITT (IG1=54, CG=49), group x time interaction effects Cohen's *d*=0.79; *P*=0.023, one-tailed CAPS change in score, 1 month posttreatment (number of weeks NR) , ITT (IG1=54, CG=49), SMD using Cohen's *d* = 0.61; *P*>0.05, one-tailed CAPS change in score, 3 months' posttreatment (number of weeks NR), ITT (IG1=54, CG=49), SMD using Cohen's *d* = 0.84; *P*<0.05, one-tailed CAPS change in score, 6 months' posttreatment (number of weeks NR), ITT (IG1=54, CG=49), SMD using Cohen's *d* = 0.82; *P*<0.05, one-tailed PCL change in score, 1 month posttreatment (number of weeks NR), ITT (IG1=54, CG=49), SMD using Cohen's *d* = 1.0; *P*<0.05, one-tailed PCL change in score, 3 months' posttreatment (number of weeks NR), ITT (IG1=54, CG=49), SMD using Cohen's *d* = 1.1; *P*<0.05, one-tailed PCL change in score, 6 months' posttreatment (number of weeks NR), ITT (IG1=54, CG=49), SMD using Cohen's *d* = 1.5; *P*<0.05, one-tailed M-PTSD change in score, 6 months' posttreatment (number of weeks NR), ITT (IG1=54, CG=49), group x time interaction effects Cohen's *d* = 1.12; *P*=0.004, one-tailed (Between-group differences for other time points NR)
	Subgroup Analyses: No subgroups of interest reported	NR
Philip et al. (2019)[78]	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes • CAPS	CAPS score at 2 weeks, ITT (IG1=25, CG=25), mean (SD) IG1: 38.6 (11.4)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
iTBS (25) Sham iTBS (25)	• PCL	CG: 39.4 (13.8) CAPS change in score from baseline to 2 weeks, ITT (IG1=25, CG=25), SMD using Cohen's *d* = -0.12 *P*=0.61 PCL score at 2 weeks, ITT (IG1=25; CG=25), mean (SD) IG1: 35.5 (13.9) CG: 39.4 (16.8) PCL change in score from baseline to 2 weeks, ITT (IG1=25, CG=25), SMD using Cohen's *d* = -0.34 *P*=0.31
	Subgroup Analyses: No subgroups of interest repored	NR
Watts et al. (2012)[77] rTMS (10) Sham rTMS (10)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes: NR • CAPS • PCL	CAPS score, baseline and posttreatment (2 weeks), ITT (IG1=10, CG=10), mean (SD) Baseline IG1: 81.6 (9.5) Posttreatment IG1: 53.9 (15.3) Baseline CG: 72.3 (12.2) Posttreatment CG: 61.7 (11.1) Between-group difference NR; *P*=0.009 PCL score, baseline and posttreatment (2 weeks), ITT (IG1=10, CG=10), mean (SD) Baseline IG1: 64.9 (6.5) Posttreatment IG1: 48.7 (9.9) Baseline CG: 57.3 (3.7) Posttreatment CG: 54.8 (5.0) Between-group difference NR; *P*=0.0002 Data for the 1- and 2-month follow-up time points were NR, but authors reported "erosion of clinical effect"
	Subgroup Analyses: No subgroups of interest reported	NR

Abbreviations: CAPS = Clinician Administered PTSD scale; CG = control group; IG = intervention group; iTBS = intermittent theta-burst stimulation; ITT = intention-to-treat; mITT = modified intention-to-treat; M-PTSD = Mississippi Scale for Combat Related PTSD; N = number; NR = not reported; PCL = PTSD Checklist; PTSD = posttraumatic stress disorder; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; SMD = standardized mean difference; TMS = transcranial magnetic stimulation.

Table C-20. Safety Outcomes for Included Repetitive TMS Interventions for PTSD

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
Isserles et al. (2021)[75] dTMS (60) Sham dTMS (65)	**Any Adverse Event**	Any AE, mITT (IG1=60; CG=65), N (%) IG1: 46 (76.7) CG: 41 (63.1) *P*=0.099
	Serious Adverse Events	NR
	Other Harms	Moderate or severe anxiety, mITT (IG1=60; CG=65), N (%) IG1: 3 (5) CG: 4 (6.2) Suicidal ideation, mITT (IG1=60; CG=65), N (%) IG1: 2 (3.3) (1 in context of alcohol intoxication, 1 had acute exacerbation of chronic suicidal ideation) CG: 0 (0)
Kozel et al. (2018)[76] rTMS + CPT (54) Sham rTMS + CPT (49)	**Any Adverse Event**	NR
	Serious Adverse Events	Any treatment-emergent SAE, 9 months (IG1=54, CG=49), N (%) IG1: 0 (0) CG: 0 (0)
	Other Harms	Seizures, 12 weeks (IG1=54, CG=49), N (%) IG1: 0 (0) CG: 0 (0) Headache, 12 weeks (IG1=54, CG=49), N (%) IG1: 2 (4) CG: 1 (2)
Philip et al. (2019)[78] iTBS (25) Sham iTBS (25)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, 2 weeks, (IG1=25, CG=25), N (%) IG1: 0 (0) CG: 2 (8) (1 emergent homicidal ideation, 1 hospitalization for suicidality) *P*>0.1
	Other Harms	Treatment site discomfort, 2 weeks (IG1=25; CG=25), N (%) IG1: 6 (24) CG: 0 (0) *P*>0.1

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
Watts et al. (2012)[77] rTMS (10) Sham rTMS (10)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	NR

Abbreviations: AE = adverse event; CG = control group; CPT = cognitive processing therapy; dTMS = deep transcranial magnetic stimulation; IG = intervention group; iTBS = intermittent theta-burst stimulation; mITT = modified intention-to-treat; N = number; NR = not reported; PTSD = posttraumatic stress disorder; rTMS = repetitive transcranial magnetic stimulation; SAE = serious adverse event.

Table C-21. Study Characteristics for Included Repetitive TMS Interventions for Smoking Cessation

Author (Year) Country Registry #	Study Design Years Conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
Dieler et al. (2014)[82] Germany	Parallel RCT NR	No study sponsor	No	No age indicated; FTND of at least 3, diagnosis of nicotine dependence by ICD-10 (F17.25)	History of or current neurological or mental health disorders, prior TMS experience, or contraindication to TMS
Li et al. (2020)[80] U.S. NCT02401672	Parallel RCT 2014 to 2018	NIH - National Institute on Drug Abuse; Neuronetics Inc. donated a piece of equipment but otherwise had no role in the study	Yes, partially	Aged 18 to 60 years, smoking 10 or more cigarettes per day and CO level greater than 10 ppm; motivated to quit	Psychoactive substance use, contraindications to MRI or TMS, use of nicotine replacement or electronic cigarettes, or taking smoking cessation medication
Sheffer et al. (2018)[79] U.S.	Parallel RCT 2015 to 2016	NIH - National Cancer Institute and National Institute on Drug Abuse	No	Aged 21 to 65 years, smoked 5 to 20 cigarettes daily, motivated to quit, negative urine drug screen, able to undergo MRI and passed TMS Adult Safety and Screening Questionnaire	Medications that lower seizure threshold, medications for smoking cessation, pregnancy, brain abnormalities that increase participant risk, and inability to achieve at least 24 hours of abstinence from smoking immediately prior to the first stimulation session
Trojak et al. (2015)[81] France	Parallel RCT 2011 to 2014	University Hospital of Dijon, France	No	Aged 18 to 65 years, desire to quit smoking, FTND score greater than or equal to 7, history of at least 2 unsuccessful quit attempts using any method	Smoking abstinence in the preceding 3 months; current NRT or smoking cessation aids; pregnancy or breastfeeding; current of history of neurologic, psychiatric, or cardiac diseases; current psychiatric medication use; or history of SUD in the prior year
Zangen et al. (2021)[83] US and Israel	Parallel RCT 2014 to 2019	Brainsway, Ltd.	Yes, entirely	Aged 22 to 70 years, chronic smoker (at least 10 cigarettes/day for at least 1 year) meets DSM-5 criteria for tobacco use disorder, motivated to quit, no period of	Current treatment for smoking, use of nicotine other than through cigarettes, other psychiatric diagnosis including SUD in the past 12 months, use of psychotropic medication on a regular

Author (Year) Country Registry #	Study Design Years Conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
NCT02126124				abstinence of more than 3 months in the past year.	basis, history of or increased risk of seizures, neurological disorder, history of metal in the head or metallic implant, pregnancy or lactation

Abbreviations: CO = carbon monoxide; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition; FTND = Fagerstrom Test For Nicotine Dependence; ICD-10 = 10th revision of the International Statistical Classification of Diseases and Related Health Problem; MRI = magnetic resonance imaging; NIH = National Institutes of Health; ppm = parts per million; RCT = randomized controlled trial; TMS = transcranial magnetic stimulation; U.S. = United States.

Table C-22. Intervention Characteristics for Included Repetitive TMS Interventions for Smoking Cessation

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-Interventions	Exposures During Treatment
Dieler et al. (2014)[82]	Sham (36) Sham type: Motor threshold <60% and coil tilted 45 degrees	iTBS (38) Target location: Right DLPFC Localization technique: Not reported Frequency: 50 Intensity: 80 Number of pulses: 600	Treatment days: 4 Treatment sessions total: 4	Psychotherapy, per study protocol	None
Li et al. (2020)[80]	Sham rTMS (20) Sham type: 10 Hz electrical stimulation without magnetic intervention	rTMS (22) Target location: Left DLPFC Localization technique: Image guided Frequency: 10 Hz Intensity: 100 Number of pulses: 3,000	Treatment days: 10 (1 session/day, 5 days/week x 2 weeks) Treatment sessions total: 10	None	1.5-minute interactions with real-life smoking paraphernalia (cigarettes, ashtray, lighter) immediately before each session; smoking-cued videos during TMS session
Sheffer et al. (2018)[79]	Sham (13) Sham type: Sham coils	rTMS (16) Target location: Left DLPFC Localization technique: Image guided Frequency: 20 Intensity: 110 Number of pulses: 900	Treatment days: 8 (4 days/week x 2 weeks) Treatment sessions total: 8	Medications discontinued before TMS Evidence-based self-help relapse prevention booklets	None
Trojak et al. (2015)[81]	Sham (19) Sham type: Wand casing that blocks magnetic field	rTMS (18) Target location: Right DLPFC Localization technique: Image guided Frequency: 1 Intensity: 120 Number of pulses: 360	Treatment days: 10 Treatment sessions total: 10	Medication per study protocol: nicotine replacement therapy, including transdermal patches q 24 hour, tapered over 6 weeks, and nicotine gum (2 pieces/day max)	None
Zangen et al. (2021)[83]	Sham (139) Sham type: Sham and active coil within the same device	rTMS (123) Target location: Bilateral lateral prefrontal cortex and insula Localization technique: Manual measurement	Treatment days: 18 (5 days/week x 3 weeks, then 1/week x 3 weeks) Treatment sessions total: 18	Short (~2 min) motivational talk based on the booklet "Clearing the Air," and supporting the decision to quit, was read to each participant	Included participants imagining their greatest trigger for craving, listening to an audio script with instructions to handle a cigarette and a lighter, and

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-Interventions	Exposures During Treatment
		Frequency: 10 Intensity: 120 Number of pulses: 1,800			viewing pictures of smoking

Abbreviations: DLPFC=dorsolateral prefrontal cortex; Hz = electromagnetic wavelength frequency; iTBS = intermittent theta-burst stimulation; N = number; rTMS = repetitive transcranial magnetic stimulation; TMS = transcranial magnetic stimulation.

Table C-23. Population Characteristics for Included Repetitive TMS Interventions for Smoking Cessation

Author (Year)	Sample Size (Total)	Treatment History	Mean Age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
Dieler et al. (2014)[82]	74	Unspecified treatment naivety or resistance	45.46 (10.64)	34 (46)	NR	NR
Li et al. (2020)[80]	42	Unspecified treatment naivety or resistance	IG1: 41.2 (11.8) CG: 44.1 (9.1)	IG1: 12 (57) CG: 9 (53)	NR	NR
Sheffer et al. (2018)[79]	29	Unspecified treatment naivety or resistance	49.6 (8.3)	12 (41)	White: 3 (10) Black: 21 (72) Other (Asian/Pacific Islander, American Indian/Alaska Native/Multiracial [more than 1 race/ethnicity]): 5 (17)	NR
Trojak et al. (2015)[81]	37	Treatment resistant (defined liberally as any prior treatment to TMS)	IG1: 47.6 (13.5) CG: 42.3 (12.1)	IG1: 8 (22) CG: 9 (24)	NR	NR
Zangen et al. (2021)[83]	262	Unspecified treatment naivety or resistance	IG1: 45 (13) CG: 44.8 (13.4)	IG1: 60 (49) CG: 66 (48)	NR	NR

Abbreviations: CG = control group; IG = intervention group; N = number; NR = not reported; SD = standard deviation; TMS = transcranial magnetic stimulation.

Table C-24. Efficacy Outcomes for Included Repetitive TMS Interventions for Smoking Cessation

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Dieler et al. (2014)[82] iTBS (38) Sham (36)	**Remission**: Continuous abstinence—no consumption of cigarettes since treatment	Continuous abstinence, 3 months after end of treatment, ITT (IG1=38, CG=36) IG1= 19 (50.0) CG= 10 (27.8) OR (95% CI) = 2.6 (1.15 to 5.86) *P*<0.05 Continuous abstinence, 6 months after end of treatment, ITT (IG1=38, CG=36) IG1= 12 (31.6) CG= 10 (27.8) OR (95% CI) = 1.20 (0.52 to 2.78) *P*>0.05 Continuous abstinence, 12 months after end of treatment, ITT ((IG1=38, CG=36) IG1= 10 (26.3) CG= 5 (13.9) OR (95% CI) = 2.21 (0.82 to 6.01) *P*>0.05
	Response: NR	NR
	Continuous outcomes: NR	NR
	Subgroup analyses: No subgroups of interest reported	NR
Li et al. (2020)[80] rTMS (22) Sham rTMS (20)	**Remission**: At least 2 days of abstinence after target quit date (TQD) and CO <5 ppm (TQD = within 7–10 days of starting TMS treatments)	Quit, on target quit date (7–10 days), completers (IG1=21, CG=17), N (%) IG1: 5 (23.8) CG: 0 (0) OR: 11.7 (90% CI, 0.96 to 141.32) (note: 90% CI used here) (Adjusted for years of smoking and previous quit attempts) Chi-squared: 4.66, *P*=0.031 Quit, on target quit date (7–10 days), ITT (IG1=22, CG=20), N (%) IG1: 5 (22.7) CG: 0 (0) OR: 12.89 (90% CI, 1.07 to 155.1) (note: 90% CI used here) (Adjusted for years of smoking and previous quit attempts) Chi-squared: 4.32, *P*=0.037

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		CQR (7 days' continuous abstinence), 1 month posttreatment (6 weeks), completers (IG1=unclear, CG=unclear), N (%) IG1: 4 (19) CG: 0 (0) Chi-squared: 3.62, *P*=0.057 CQR (7 days' continuous abstinence), 1 month posttreatment (6 weeks), ITT (IG1=22, CG=20), N (%) IG1: 4 (18) CG: 0 (0) Chi-squared: 3.83, *P*=0.0502 CQR, 3 months' posttreatment (14 weeks), completers (IG1=13, CG=6), N (%) IG1: 3 (23) CG: 0 (0) Chi-squared: 2.64, *P*=0.10
	Response: At least 50% reduction in cigarettes smoked	Response, posttreatment (10 days), completers (IG1=21, CG=17), N (%) IG1: 16 (76.1) CG: 6 (35.3) OR: 9.73 (1.82 to 52.01) (Adjusted for previous quit attempts and years of smoking) Chi-squared: 6.45, *P*=0.008 Response, posttreatment (10 days), ITT (IG1=22, CG=20), N (%) IG1: 16 (72.7) CG: 6 (30.0) OR: 6.2 (95% CI, 1.63 to 23.8) Adjusted OR: 10.04 (2.10 to 47.96); *P*=0.006 (Adjusted for previous quit attempts and years of smoking) Chi-squared: 7.67, *P*=0.006
	Continuous outcomes • FTND • NUI • Urine cotinine levels • CO levels	Number of cigarettes smoked, posttreatment (2 weeks), completers (IG1=21, CG=17), mean (SD) IG1: 11.6 (6.9) CG: 13.7 (9.2) F=9.43 *P*<0.005

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		Number of cigarettes smoked, 1 month posttreatment (6 weeks), completers (IG1=20; CG=15), mean (SD) IG1: 7.9 (7.2) CG: 12.8 (9.5) F=10.66 *P*<0.001 Urine cotinine, 1 month posttreatment (6 weeks), Completers (IG1=21, CG=17); mean ng/ml (SD) IG1: 1,008 (557) CG: 1,206 (631) F=5.22 *P*=0.024 CO, posttreatment (2 weeks), completers (IG1=21, CG=17); daily mean ppm (SD) IG1: 9.3 (5.2) CG: 10.8 (5.5) F=2.25 *P*=0.019 FTND, 1 month posttreatment (6 weeks), completers (IG1=21, CG=17); mean score (SD) IG1: 3.4 (2.3) CG: 4.6 (2.1) F=10.60 *P*=0.001
	Subgroup Analyses No subgroups of interest reported	NR
Sheffer et al. (2018)[79] rTMS (16) Sham (13)	**Remission**: Abstinence from smoking, exhaled carbon monoxide less than or equal to 8 ppm.	Abstinence, 10 weeks' posttreatment (12 weeks), ITT (IG1=16, CG=13), N (%) IG1: 8 (50) CG: 2 (15.4) Chi-squared=3.80 *P*=0.05
	Response: NR	NR

Author (Year) Interventions (N Randomized)	Name of Measure	Results
	Continuous outcomes: Mean latency to relapse in days	Risk of relapse, 10 weeks' posttreatment (12 weeks), unclear completers or ITT (IG=unclear, CG, unclear) RR 0.29 (95% CI 0.10 to 0.76) Chi-squared=6.40 *P*=0.01 Covariates of Cox Proportional Hazards Model not reported Mean latency to relapse, 10 weeks' posttreatment (12 weeks), ITT (IG1=16, CG=13), mean days (SD) IG1: 45.19 (9.42) CG: 20.46 (7.46) Median latency to relapse, 10 weeks' posttreatment (12 weeks), ITT (IG1=16, CG=13), median days (IQR) IG1: 33.5 (7 to 85) CG: 8.0 (2 to 37)
	Subgroup Analyses: No subgroups of interest reported	NR
Trojak et al. (2015)[81] rTMS (18) Sham (19)	**Remission**: Continuous abstinence defined by zero self-reported cigarettes since first day of quitting and CO concentration < 10 ppm	Remission, end of TMS treatment (2 weeks), completers (IG1=18, CG=18), N (%) IG1: 16 (88.8) CG: 9 (50) *P*=0.027 Remission, 4 weeks post TMS treatment (6 weeks), completers (IG1=unclear, CG=unclear), N (%) IG1: NR (44.4) CG: NR (38.8) *P*>0.05 Remission, 10 weeks' post-TMS treatment (12 weeks), completers (IG1= unclear, CG=unclear), N (%) IG1: NR (27.7) CG: NR (27.7) *P*>0.05
	Response: NR	NR

Author (Year) Interventions (N Randomized)	Name of Measure	Results
	Continuous outcomes: NR	NR
	Subgroup Analyses: No subgroups of interest reported	NR
Zangen et al. (2021)[83] rTMS (123) Sham (139)	**Remission**: Abstinence, defined as self report of no smoking confirmed by urine cotinine levels < 200 ng/mL	Abstinence, 12-week follow-up after end of treatment (18 weeks), completers analysis (IG1=75, CG=94), N (%) IG1: 12 (16) CG: 3 (3) *P*=0.003 CQR, posttreatment (6 weeks), mITT (IG1=108, CG=126), N (%) IG1: 19 (17.6) CG: 6 (4.8) *P*=0.0015 CQR, 12-week follow-up posttreatment (18 weeks), mITT (IG1=108, CG=126), N (%) IG1: 21 (19.4) CG: 11 (8.7) *P*=0.0174
	Response: NR	NR
	Continuous outcomes • FTND • NUI	Number of cigarettes smoked, posttreatment (6 weeks), mITT (IG1=108, CG=126), adjusted mean (95% CI) IG1: 31.38 (20.92 to 41.83) CG: 47.52 (38.24 to 56.80) Adjusted mean difference (active minus sham): -16.14 (-28.79 to -3.48) *P*=0.012 FTND, change in score from baseline to posttreatment (6 weeks), mITT (IG1=108, CG=126), adjusted mean (95% CI) IG1: -2.21 (0.00 to -1.49) CG: -1.65 (0.00 to -1.00) Adjusted mean difference (active minus sham): -0.55 (01.18 to 0.07) *P*=0.0815 FTND, change in score from baseline to 12-week follow-up posttreatment (18 weeks), mITT (IG1=108, CG=126), adjusted mean (95% CI) IG1: -3.32 (0.00 to -2.34)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		CG: -3.27 (0.00 to -2.18) Adjusted mean difference (active minus sham): -0.05 (-1.22 to 1.13) *P*=0.9389
	Subgroup Analyses: No subgroups of interest reported	NR

Abbreviations: CG = control group; CI = confidence interval; CO=carbon monoxide; CQR = continuous quit rate; FTND=Fagerstrom Test of Nicotine Dependence; IG = intervention group; IQR = interquartile range; iTBS = intermittent theta-burst stimulation; ITT = intention-to-treat; mITT = modified intention-to-treat; NR = not reported; NUI = Nicotine Use Inventory; OR = odds ratio; RR = relative risk; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; TMS = transcranial magnetic stimulation; TQD = target quit date.

Table C-25. Safety Outcomes for Included Repetitive TMS Interventions for Smoking Cessation

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
Dieler et al. (2014)[82] iTBS (38) Sham (36)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	NR
Li et al. (2020)[80] rTMS (22) Sham rTMS (20)	**Any Adverse Event**	Side effects reported during at least 1 visit, 14 weeks, completers (IG1=21; CG=17), N (%) IG1: NR (66) CG: NR (47) *P*=0.375 No side effects required any treatment.
	Serious Adverse Events	NR
	Other Harms	NR
Sheffer et al. (2018)[79] rTMS (16) Sham (13)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	Headache, 10 weeks' posttreatment (12 weeks), ITT (IG=16, CG=13), N (%) IG: 3 (30.8) CG: 2 (15.4)
Trojak et al. (2015)[81] rTMS (18) Sham (19)	**Any Adverse Event**	No AEs reported
	Serious Adverse Events	No SAEs reported
	Other Harms	NR
Zangen et al. (2021)[83] rTMS (123) Sham (139)	**Any Adverse Event**	Any AE, 12 weeks' follow-up (18 weeks), ITT (IG1=123, CG=139) IG1: 66 (53.7) CG: 50 (36.0) *P*=0.004
	Serious Adverse Events	Any SAE possibly related to treatment, 12 weeks' follow-up (18 weeks), ITT (IG1=123, CG=139) IG1: 1 (0.01) CG: 0 (0) Tinnitus
	Other Harms	Headache, 12 weeks' follow-up posttreatment (18 weeks), ITT (IG1=123, CG=139), N (%)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
		IG1: 30 (24) CG: 25 (18) *P*=NS No significant differences between the treatment groups for any specific adverse event, except for application site discomfort (*P*=0.0043).

Abbreviations: AE = adverse event; CG =control group; IG = intervention group; iTBS = intermittent theta-burst stimulation; ITT = intention-to-treat; NR = not reported; NS = not significant; rTMS = repetitive transcranial magnetic stimulation; SAE = serious adverse event; TMS = transcranial magnetic stimulation.

Table C-26. Study Characteristics for Included Repetitive TMS Interventions for SUD

Author (Year) Country Registry #	Study Design Years Conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
Belgers et al. (2022)[84] Netherlands NCT01973127	Parallel RCT 2015 to 2019	No external funding	No	Aged 20 to 65 years meeting DSM-5 criteria for AUD as their primary diagnosis and successful recent (<6 weeks) inpatient detoxification of alcohol	Any psychiatric condition that interfered with TAU due to severity of symptoms, rTMS contraindications (history of epilepsy, ferromagnetic implants in the head, a history of neurosurgical operations, or a pacemaker implant), use of medication known to substantially lower the threshold of epileptic seizures, intellectual disabilities or major somatic disabilities
Harel et al. (2021)[86] Israel NCT02691390	Parallel RCT 2016 to 2020	European Union's Horizon 2020 Research and Innovation Program and the Swedish Research Council	No	Aged 18 to 65 years with DSM-5 diagnosis of moderate-to-severe alcohol dependence and were treatment seeking, alcohol use in the past month but not in the 5 days before the first MRI scan or the first treatment session	Pregnant or breastfeeding; more than mild cognitive impairment (score on the Montreal Cognitive Assessment <25); DSM-5 diagnosis of schizophrenia, bipolar disorder, or other psychotic disorder; use in the past 2 weeks of medication or illicit drug with known high pro-convulsant action; presence of ferromagnetic objects in the body that are contraindicated for MRI of the head; history of seizures or clinically significant neurological disorders; clinically significant hearing impairment
Lolli et al. (2021)[88] Italy NCT03607591	Parallel RCT 2017 to 2020	Guido Mannaioni—Azienda Ospedaliera Universitaria di Careggi, Fondazione Cassa di Risparmio di Firenze	No	Aged 18 to 65 years meeting DSM-5 criteria for CUD and having a positive cocaine test in urine	Modified pharmacological treatment within 4 weeks, previous rTMS treatment, concomitant alcohol or drug use, a major psychiatric or neurological disorder, illiteracy or cognitive impairment, pregnancy or lactation

Author (Year) Country Registry #	Study Design Years Conducted	Sponsor	Industry Sponsored	Inclusion Criteria	Exclusion Criteria
Martinotti et al. (2022)[85] Italy NCT03333460)	Parallel RCT 2017 to 2019	Department of Neuroscience, Imaging and Clinical Sciences of University "G. d'Annunzio" of Chieti and Intramural Research Program of the National Institute of Drug Abuse	No	Treatment-seeking individuals with moderate to severe CUD, as identified with the Structured Clinical Interview for DSM-5	History of schizophrenia or bipolar disorder; current moderate to severe SUD on any substance except cocaine, nicotine or THC; satisfaction of withdrawal criteria regarding alcohol, sedatives, hypnotics or anxiolytic; proconvulsant drug therapy; current suicidality; and changes in prescribed psychoactive therapy in the preceding 4 weeks
Perini et al. (2020)[87] Sweden NCT02643264	Parallel RCT 2015 to 2018	Swedish Research Council and European Union's Horizon 2020 research and innovation programme	No	Aged 25 to 64 years meeting DSM-IV criteria for alcohol dependence, alcohol use during the past month, and right handedness	More than mild cognitive impairment assessed using MMSE < 24; schizophrenia, bipolar, or other psychotic disorder; any clinically significant neurological disorder or lesion; hearing impairment; pregnancy; use of illicit drugs or medications known to increase the risk for seizures
Schluter et al. (2019)[89] Netherlands Netherlands Trial Register number 5291	Parallel RCT NR	Vidi grant	No	Aged 20 to 65 years with recent DSM-IV diagnosis of alcohol dependence (i.e., less than 4 months after detoxification)	Montreal Cognitive Assessment score below 10, current DSM-IV diagnosis of depression, schizophrenia or another psychotic disorder, current recreational drug use, and HF-rTMS contraindications (e.g., history of epileptic seizures, metal implants near the head, use of the certain medications)

Abbreviations: AUD = alcohol use disorder; CUD = cocaine use disorder; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; HF = high frequency; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NCT = National

Clinical Trial; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SUD = substance use disorder; TAU = treatment as usual; THC = tetrahydrocannabinol; TMS = transcranial magnetic stimulation.

Table C-27. Intervention Characteristics for Included Repetitive TMS Interventions for SUD

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
Belgers et al. (2022)[84]	rTMS (18) Sham type: Angle wand away from scalp	rTMS (16) Target location: Right DLPFC Localization technique: EEG-guided Frequency: 10 Intensity: 110 Number of pulses: 3,000	Treatment days: 10 Treatment sessions total: 10	Medication per treatment as usual Psychotherapy per treatment as usual	None
Harel et al. (2021)[86]	Sham dTMS (24) Sham type: Sham and active coil within the same device	dTMS (27) Target location: Other midline frontocortical areas: Anterior cingulate cortex (ACC) and medial PFC (mPFC) Localization technique: Image guided Frequency: 10 Intensity: 100 Number of pulses: 3,000	Treatment days: 15 Treatment sessions total: 15	None	3 minutes of holding and smelling, but not consuming, the alcoholic beverage of choice for each participant; sham group water
Lolli et al. (2021)[88]	Sham (30) Sham type: Angle wand away from scalp	rTMS (32) Target location: LDLPFC Localization technique: Manual measurement Frequency: 15 Intensity: 100 Number of pulses: 2,400	Treatment days: 15 Treatment sessions total: 15	Medication per treatment as usual Psychotherapy per treatment as usual	None
Martinotti et al. (2022)[85]	Sham (33) Sham type: Angle wand away from scalp	rTMS (42) Target location: LDLPFC Localization technique: Other Frequency: 15 Intensity: 100 Number of pulses: 2,400	Treatment days: 34 Active phase: 2 sessions/day, 5 days/week, 2 weeks Maintenance phase: 1 session/day, 2 day/week, 12 weeks Treatment sessions total: 44	Medication per treatment as usual Psychotherapy per treatment as usual	Video containing cocaine-related images

Author (Year)	Control Group (N Randomized)	Intervention Group(s) (N Randomized)	Duration Intervention	Co-interventions	Exposures During Treatment
Perini et al. (2020)[87]	Sham rTMS (27) Sham type: Sham and active coil within the same device	Deep rTMS (29) Target location: Other insular cortex and overlaying regions Localization technique: Manual measurement Frequency: 10 Intensity: 120 Number of pulses: 1,500	Treatment days: 15 Treatment sessions total: 15	Medication per treatment as usual	Participants poured a glass of water and smelled/handled the contents of the glass for 3 minutes; process was then repeated with their preferred alcohol beverage
Schluter et al. (2019)[89]	Sham (41) Sham type: Angle wand away from scalp	HF-rTMS (41) Target location: Right DLPFC Localization technique: EEG-guided Frequency: 10 Intensity: 110 Number of pulses: 60	Treatment days: 10 Treatment sessions total: 10	Medication per treatment as usual Psychotherapy per treatment as usual	None

Abbreviations: ACC = anterior cingulate cortex; cTBS = controlled theta-burst stimulation, a variation of rTMS; DLPFC=dorsolateral prefrontal cortex; EEG = electroencephalogram; HF = high frequency; Hz = electromagnetic wavelength frequency; LDLPFC = left dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; PFC = prefrontal cortex; rTMS = repetitive transcranial magnetic stimulation; SUD = substance use disorder; TMS = transcranial magnetic stimulation.

Table C-28. Population Characteristics for Included Repetitive TMS Interventions for SUD

Author (Year)	Sample Size (Total)	Treatment History	Mean Age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
Belgers et al. (2022)[84]	34	Both treatment-naive and treatment-resistant participants eligible	47.4 (8.9)	2 (6)	NR	PTSD: 26% Depression: 15% OCD: 12% Panic disorder: 0% Tobacco use disorder: 88% Cannabis use: 3% Stimulants use: 3% Benzodiazepine use: 3%
Harel et al. (2021)[86]	51	Unspecified treatment naive or resistance	IG1: 43.7 (8.7) CG: 42.5 (9.8)	IG1: 8 (35) CG: 8 (35)	NR	NR
Lolli et al. (2021)[88]	62	Unspecified treatment naive or resistance	40.7 (9)	11 (18)	NR	NR
Martinotti et al. (2022)[85]	80	Unspecified treatment naive or resistance	37 (7.4)	9 (12)	NR	Co-occurrent substance abuse Alcohol IG1: 83% CG: 79% Cannabis IG1: 46% CG: 27% Heroin IG1: 20% CG: 3% Other drugs IG1: 17% CG: 6% Psychiatric comorbidity Mood disorders IG1: 8% CG: 12% Anxiety disorders IG1: 8% CG: 18%
Perini et al. (2020)[87]	56	Unspecified treatment naive or resistance	IG1: 50.6 (10.4) CG: 53.5 (7.5)	IG1: 4 (17) CG: 4 (18)	NR	NR

Author (Year)	Sample Size (Total)	Treatment History	Mean Age (SD)	N (% Female)	N (%) Race/Ethnicity	% Mental Health Comorbidity
Schulter et al. (2019)[89]	82	Unspecified treatment naive or resistance	IG1: 44.95 (10.03) CG: 43.75 (11.41)	IG1: 11 (28) CG: 9 (23)	NR	PTSD: IG1: 13% CG: 15% Cocaine dependence IG1: 23% CG: 13% Cannabis dependence IG1: 20% CG: 20%

Abbreviations: CG = control group; IG = intervention group; N = number; NR = not reported; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; SUD = substance use disorder; TMS = transcranial magnetic stimulation.

Table C-29. Efficacy Outcomes for Included Repetitive TMS Interventions for SUD

Author (Year) Interventions (N Randomized)	Name of Measure	Results
Belgers et al. (2022)[84] rTMS (16) rTMS (18)	**Remission**: Percentage abstinence	Remission, 1-year follow-up, mITT, (IG1=15; sham=16), mean IG1: 0.14 IG2: 0.00 F=14.27 *P*=0.126
	Response: NR	NR
	Continuous outcomes • Severity of addiction measure (generic) Total number of abstinent days	Alcohol use (total in mg), 1-year follow-up, mITT(IG1=14; CG=16), mean (SD) IG1: 3,161 (2716) CG: 5,866 (3694) F=1.349 *P*=0.032 Alcohol use (per day in mg), 1-year follow-up, mITT (IG1=14; CG=16), mean (SD) IG1: 31.27 (26.80) CG: 57.94 (36.59) F=1.42 *P*=0.03 Time to relapse, 1-year follow-up, mITT (IG1=14; CG=16), mean (SD) IG1: 256.4 (146.8) CG: 115.1 (133.2) F=0.458 *P*=0.010 Total number of HDD days, 1-year follow-up, mITT (IG1=14; CG=16), mean (SD) IG1: 25.36 (20.18) CG: 47.25 (26.41) F=1.478 *P*=0.018 Total number of abstinent days, 1-year follow-up, mITT (IG1=14; CG=16), mean (SD) IG1: 70.07 (23.44) CG: 29.63 (18.65)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		F=0.004 *P*=0.000
	Subgroup analyses: No subgroups of interest reported	NR
Harel et al. (2021)[86] dTMS (27) Sham dTMS (24)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes • UDS • Severity of addiction measure (generic) • Percentage of heavy drinking days	Reduction in the percentage of heavy drinking days, 12 weeks' follow-up after treatment phase (15 weeks), mITT (IG1=23; CG=23), mean (SEM) IG1: 2.9 (0.8) CG: 10.6 (1.9) *P*=0.037 favoring treatment Weekly alcohol consumption in grams of ethanol, 12 weeks' follow-up after treatment phase (15 weeks), mITT (IG1=23; CG=23), mean difference Mean difference (CG-IG1): 121.78 F=5.21 Cohen's *d*=0.47 *P*=0.02 favoring treatment Percentage of positive urine ethyl glucuronide samples, 12 weeks' follow-up after treatment phase (15 weeks), mITT (IG1=23; CG=23), group effect F=3.32 *P*=0.069 favoring treatment
	Subgroup analyses: No subgroups of interest reported	NR
Lolli et al. (2021)[88] rTMS (32) Sham (30)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes • UDS • Severity of addiction measure (generic) • Time to negativization	Urine negativity (two consecutive drug negative urine tests), end of follow-up 8 weeks' posttreatment (12 weeks), mITT (IG1=33; CG=27), N (%) IG1: 10 (33) CG: 4 (14) OR: 2.88 (0.9 to 10) *P*=0.18 Self-reported days of cocaine use, end of follow-up 8 weeks' posttreatment (12 weeks), mITT (IG1=unclear; CG=unclear), N (%) IG1: NR (35)

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		CG: NR (52) OR: 3.4 (1.1 to 10) *P*<0.03 Average time to negativization of urine drug screen, end of follow-up 8 weeks' posttreatment (12 weeks), mITT (IG1=30, CG=27) IG1: 61 days (95% CI 40 to 83) CG: 90 days (95% CI 69 to 112) Mantel-cox log-rank test X^2=1.57 *P*=0.20
	Subgroup Analyses: No subgroups of interest reported	NR
Martinotti et al. (2022)[85] rTMS (42) Sham (33)	**Remission**: Longest period of cocaine abstinence (in days)	Remission, end of TMS treatment (14 weeks), completers (IG1=32; CG=27), mean (SD) IG1: 60.1 (30.6) CG: 52.9 (31.8) *P*=NS Remission, follow-up (3 months after end of treatment), completers (IG1=14; CG=17), mean (SD) IG1: 73.3 (52.2) CG: 55.2 (42.08) *P*=NS Test for trend favored active group *P*=0.09
	Response: NR	NR
	Continuous outcomes • UDS • Cocaine use (days per week)	Proportion of positive urine testing, end of intensive treatment (10 days), completers (IG1=36; CG=33), N (%) IG1: 10 (27.8) CG: 8 (24.2) AOR: 1.64 (0.43 to 6.21) *P*=0.7 Proportion of positive urine testing, difference between baseline and end of intensive treatment (10 days), completers (IG1=36; CG=33), % IG1: 19.3 CG: 24.3

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		P=0.6 Proportion of positive urine testing, end of TMS treatment (14 weeks), completers (IG1=35; CG=32), N (%) IG1: 12 (34.3) CG: 8 (25.0) AOR: 1.56 (0.43 to 5.66) *P*=0.4 Proportion of positive urine testing, difference between baseline and end of TMS treatment (14 weeks), completers (IG1=35; CG=32), % IG1: 12.8 CG: 23.5 *P*=0.25 Cocaine use (days per week), end of intensive treatment (10 days), completers (IG1=36; CG=33), mean (SD) IG1: 0.3 (0.6) CG: 0.3 (0.5) Coefficient: -0.07 (-0.37 to 0.23) *P*=0.8 Cocaine use (days per week), difference between baseline and end of intensive treatment (10 days), completers (IG1=36; CG=33), mean (SD) IG1: -3.5 (2.3) CG: -3.3 (2.1) *P*=0.6 Cocaine use (days per week), end of TMS treatment (13 weeks), completers (IG1=35; CG=30), mean (SD) IG1: 0.1 (0.3) CG: 0.1 (0.3) Coefficient: -0.09 (-0.26 to 0.08) *P*=0.9

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		Cocaine use (days per week), difference between baseline and end of TMS treatment (13 weeks), completers (IG1=35; CG=30), mean (SD) IG1: -3.8 (2.3) CG: -3.3 (2.0) *P*=0.4 Cocaine use (days per week), follow-up (3 months after end of treatment), completers (IG1=30; CG=23), mean (SD) IG1: 0.3 (1.3) CG: 0.1 (0.6) Coefficient: -0.34 (-1.05 to 0.36) *P*=0.6 Cocaine use (days per week), difference between baseline and follow-up (3 months after end of treatment), completers (IG1=30; CG=23), mean (SD) IG1: 3.6 (2.3) CG: 3.4 (2.1) *P*=0.8
	Subgroup Analyses: Comorbidity	rTMS was found to have a significant effect on cocaine craving and days of consumption in a subsample of subjects with baseline MADRS scores greater than 20 (values NR, *P*<0.05)
Perini et al. (2020)[87] Deep rTMS (29) Sham rTMS (27)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes • PEth • TLFB	PEth, during treatment (treatment weeks 1, 2, and 3), completers (IG1=unclear; CG=unclear), time x group interaction Reported on figure only, actual values NR *P*=0.6 PEth, posttreatment (2-, 4-, 8-, and 12-week follow-up), completers (IG1=14; CG=14), time x group interaction Reported on figure only, actual values NR *P*=0.8 TLFB, during treatment (treatment weeks 1, 2, and 3), completers (IG1=unclear; CG=unclear), time x group interaction Reported on figure only, actual values NR

Author (Year) Interventions (N Randomized)	Name of Measure	Results
		P>0.4 TLFB, posttreatment (-2, 4-, 8-, and 12-week follow-up), completers (IG1=unclear; CG=unclear), time x group interaction Reported on figure only, actual values NR *P*>0.4
	Subgroup analyses: No subgroups of interest reported	NR
Schluter et al. (2019)[89] HF-rTMS (41) Sham (41)	**Remission**: NR	NR
	Response: NR	NR
	Continuous outcomes: NR	NR
	Subgroup Analyses: No subgroups of interest reported	NR

Abbreviations: AOR = adjusted odds ratio; CG = control group; CI = confidence interval; dTMS = deep transcranial magnetic stimulation; HDD = heavy drinking days; HF = high frequency; IG=intervention group; mITT = modified intention-to-treat; NR = not reported; NS = not significant; OR = odds ratio; PEth = phosphatidylethanol; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; SEM = standard error of the mean; SUD = substance use disorder; TLFB = timeline followback; TMS = transcranial magnetic stimulation; UDS = urine drug test.

Table C-30. Safety Outcomes for Included Repetitive TMS Interventions for SUD

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
Belgers et al. (2022)[84] rTMS (16) rTMS (18)	**Any Adverse Event**	NR
	Serious Adverse Events	No serious side effects reported or observed
	Other Harms	Some participants experienced the treatment as uncomfortable due to muscle twitches around the eye
Harel et al. (2021)[86] dTMS (27) Sham dTMS (24)	**Any Adverse Event**	NR
	Serious Adverse Events	Any SAE, 12 weeks' follow-up after treatment phase (15 weeks), mITT (IG1=23; CG=23), N (%) IG1: 0 (0) Sham: 0 (0)
	Other Harms	Moderate to severe headache, 12 weeks' follow-up after treatment phase (15 weeks), mITT (IG1=23; CG=23), N (%) IG1: 4 (17) Sham: 3 (13) *P*=0.68
Lolli et al. (2021)[88] rTMS (32) Sham (30)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	A minor treatment-related adverse event was observed in a single patient undergoing 1 sham treatment session and experienced mild and transient paraesthesia
Martinotti et al. (2022)[85] rTMS (42) Sham (33)	**Any Adverse Event**	NR
	Serious Adverse Events	No serious adverse events reported
	Other Harms	N participants reporting adverse events during study period Site discomfort IG1: 2 CG: 0 Headaches IG1: 7 CG: 6 Auditory alterations IG1: 1 CG: 2

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
		Mood alterations: IG1: 4 CG: 3 Difficulties in attentive tasks after treatment IG1: 0 CG: 3 Drowsiness IG1: 0 CG: 2 Confusion IG1: 3 CG: 3
Perini et al. (2020)[87] Deep rTMS (29) Sham rTMS (27)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	23 of the participants (equally distributed across sham and rTMS sessions) reported feeling moderate to strong headaches after the session
Schluter et al. (2019)[89] HF-rTMS (41) Sham (41)	**Any Adverse Event**	NR
	Serious Adverse Events	NR
	Other Harms	Headache after stimulation, total number of AEs per group (IG1=372 stimulation sessions; CG=366 stimulation sessions), N events (%) IG1: 7 (1.9) CG: 17 (4.6) Chi squared=4.477 *P*=0.034 Pain or beep in ear, total number of AEs per group (IG1=372 stimulation sessions; CG=366 stimulation sessions), N events (%) IG1: 3 (0.8) CG: 0 (0) *P*=0.249 Tiredness after stimulation, total number of AEs per group (IG1=372 stimulation sessions; CG=366 stimulation sessions), N events (%) IG1: 2 (0.54)

Author (Year) Interventions (N Randomized)	Safety Outcome	Results
		CG: 2 (0.55) *P*=1.000 Unpleasant sensation at stimulation site after stimulation, total number of AEs per group (IG1=372 stimulation sessions; CG=366 stimulation sessions), N events (%) IG1: 9 (2.4) CG: 2 (0.55) Chi squared=4.407 *P*=0.036

Abbreviations: AE = adverse event; CG = control group; dTMS = deep transcranial magnetic stimulation; HF = high frequency; IG = intervention group; mITT = modified intention-to-treat; NR = not reported; rTMS = repetitive transcranial magnetic stimulation; SAE = serious adverse event; TMS = transcranial magnetic stimulation.

Table C-31. Study Characteristics and Findings Related to Cost Outcomes

Author (Year) Country; Sponsor; Condition	Intervention; Comparator	Study Methods	Results
Gregory et al. (2022)[35] U.S.; BrainsWay OCD	dTMS; ADM ADM+AP ADM+CBT effectiveness ADM+CBT trials IOP PHP PHP to IOP stepdown	Study design: Decision analysis Study population: Hypothetical cohort of 100,000 adults aged 18 to 64 years with treatment refractory OCD Year/unit of currency reported: 2012–2015/U.S. Dollar Discount rate: NR Perspective: Payer Time horizon: 1 year Costs included: Total direct or reimbursement costs inclusive of the intervention; including continuance of pharmacology, medication management, behavioral therapy. Costs equivalent to those reimbursed by payers in the U.S. (i.e. government, commercial, private pay); costs were dervied from actual costs from encounters in the Truven Marketscan database. Sensitivity analysis: Monte Carlo simulation Key assumptions: Mean (SD) age: 30.5 (12.3) % Female: 51 Mean (SD) Y-BOCS at baseline: 29.2 (7.8) Mean (SD) change in Y-BOCS with treatment (effectiveness) ADM: 2.6 (1.5) ADM+AP: 3.5 (1.7) ADM+CBT trials: 11.2 (1.1) ADM+CBT effectiveness: 5.3 (0.66) IOP: 8.7 (6.9) PHP: 9.6 (6.7) PHP to IOP: 10.9 (6.5) dTMS: 6.5 (0.73) Mean (SD) costs ADM (annual): $1,576 ($1,174) ADM+AP: $5,000 (NR) ADM+CBT effectiveness: $9,540 ($4,388) ADM+CBT trial: $11,609 ($150) IOP: $11,744 ($9,276) PHP: $14,562 ($11,039)	Incremental cost, incremental effectiveness, incremental cost-effectiveness ratio (ICER, cost/unit change in Y-BOCS) compared to ADM monotherapy ADM+CBT trials: $10,035; 8.6; $1,167 dTMS: $6,425; 3.9; $1,647 ADM+AP: $3,420; 1.1; $3,110 PHP to IOP: $27,769; 8.3; $3,346 Incremental cost, incremental effectiveness, ICER (cost/unit change in Y-BOCS) compared to other comparators dTMS: $3,006; 3.0; $1,002 (compared to ADM+AP) ADM+CBT trials: $3,610; 4.7; $768 (compared to dTMS) PHP to IOP: $17,734; 1.3; $13,641 (compared to ADM+CBT trials) The following strategies were dominated (cost more and were less effective so do not represent a rationale next choice for treatment) ADM+CBT effectiveness; IOP; PHP

Author (Year) Country; Sponsor; Condition	Intervention; Comparator	Study Methods	Results
		PHP to IOP: $29,386 ($16,638)	
Simpson et al. (2009)[73] U.S.; Neuronetics, Inc. Depression	rTMS with the following parameters (120% RMT, 3,000 pulses per session) for 6 weeks followed by 3 week taper phase in which participants were transitioned off TMS and onto a stable regimen of single-drug antidepressant therapy. Sham control or open label	Study design: Decision analysis Study population: Markov model based on data from participants in sham-controlled trial or in the follow-on open-label extension trials; 1 extension trial enrolled those without sufficient response and 1 extension trial enrolled persons who participated in either the main trial or the extension trial who met criteria for remission. Participants had unipolar MDD with moderate-to-severe symptoms and moderate to severe resistance to pharmaceutical treatment, as measured by the Antidepressant Treatment History Form. Participants had to have failed to receive clinical benefit from at least 1 but no more than 4 agents in their current depressive episode. Study population was about 1/2 female with mean age of 48 years and a mean duration of current episode of 13 months. Year/unit of currency reported: 2006/U.S. dollar Discount rate: NR Perspective: Payor and societal Time horizon: 1 year Costs included: Estimates based on clinical studies TMS treatment Lost productivity Lost wages per treatment Estimates based on Medicaid billing data (2004, inflated to 2006 costs using medical consumer price index) Hospital cost/day ER cost/day MD office visit Marginal cost of hospital care for suicide Red Book 2006 Antidepressant maintenance drug cost/day Follow-up drug cost to treat failure/day Re-treatment cost for patients in severe health state Sensitivity analysis: Varied treatment failure rates, costs per treatment session, and cost of suicide	Acute treatment, sham-controlled (estimates were robust in sensitivity analyses) ICER with productivity costs included: $3,544/QALY ICER without productivity costs: $36,551/QALY Acute treatment, open-label vs. pharmacotherapy treatment as usual ICER with productivity costs included: -$7,243/QALY (cost savings) ICER without productivity costs included -$746/QALY (cost savings)

Author (Year) Country; Sponsor; Condition	Intervention; Comparator	Study Methods	Results
		Key assumptions: Treatment failure based on starting MADRS scores: 23% to 33% Treatment failure for severe patients: 14% Utility associated with various depression scores: 0.30 to 0.83 Utility associated with in-hospital failure: 0.09	
Voigt et al. (2017)[74] U.S.; Magstim Depression	rTMS (not further described); Anti-depressant medication therapy	Study design: Cost-effectiveness analysis Study population: Hypothetical cohort of adults with new diagnosis of MDD in 20s, 30s, 40s, and 50s and a single failed medication trial. Year/unit of currency reported: 2016/U.S. dollar Discount rate: 3% Perspective: Payor Time horizon: Lifetime Costs included: Based on 2016 national average Medicare reimbursement rates for: rTMS procedures Psychotherapy Medications ECT Periodic physician evaluation/management Additional direct medical costs (inpatient, outpatient, ED care) Sensitivity analysis: Monte Carlo simulation and one-way sensitivity analyses of the variables that affected the model most (number of rTMS session/year, monthly cost of antidepressant medication, and cost of repeat rTMS sessions) Key assumptions: Model assumed up to 4 attempts to achieve remission; ECT employed after fourth nonresponse to either rTMS of antidepressant medication Treatment effectiveness based on published literature Number of treatment sessions, duration of treatment derived from literature and existing health payor policies -Euro-QOL VAS utilities derived from the literature for each health state	Base case: rTMS was the dominant strategy regardless of age (more effective, cost less) Lifetime costs/lifetime QALYs Mid20s rTMS: $278,103/15.22 Pharmacotherapy: $289,243/14.79 Mid-30s rTMS: $257,686/14.06 Pharmacotherapy: $266,665/13.62 Mid-40s rTMS: $226,126/12.26 Pharmacotherapy: $232,518/11.83 Mid-50s rTMS: $164,769/8.77 Pharmacotherapy: $167,721/8.45 ICERs Assuming the upper end of rTMS treatments per month needed in order to have a response (n=43 sessions) Mid-20s: $29,895 Mid-30s: $31,505 Mid-40s: $34,107 Mid 50s: $45,747 Assuming the cost of pharmacotherapy ~$100/month (was $372.50 in the base case) Mid-20s: $47,193

Author (Year) Country; Sponsor; Condition	Intervention; Comparator	Study Methods	Results
			Mid-30s: $46,427 Mid-40s: $46,691 Mid 50s: $56,875

Abbreviations: ADM = antidepressant medication; AP = antipsychotic; CBT = cognitive behavioral therapy; dTMS = deep transcranial magnetic stimulation; ECT = electroconvulsive therapy; ED =emergency department ; ICER = incremental cost-effectiveness ratio; IOP= intensive outpatient program; MADRS = Montgomery–Åsberg Depression Rating Scale; NR = not reported; OCD = obsessive-compulsive disorder; PHP=Partial Hospitalization Program = QALY = quality-adjusted life-year; QOL = quality of life; RMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviations; TMS = transcranial magnetic stimulation; Y-BOCS = Yale–Brown Obsessive-Compulsive Scale.

Table C-32. Other Mental Health and Quality of Life Outcomes Not Abstracted

Author (Year)	Condition	Outcome(s)
Diefenbach et al. (2016)[25]	GAD	HRSD: Depression Anxiety Stress Scales-Depression Subscale Penn State Worry Questionnaire
Carmi et al. (2019)[26]	OCD	HAMD Sheehan Disability Scale
Harika-Germaneau et al. (2019)[28]	OCD	MADRS Brown Assessment of Belief Scale (BABS) Brief Anxiety Scale (BAS) Hospital Anxiety and Depression Scale (HAD)
Hawken et al. (2016)[30]	OCD	HAMD21
Kang et al. (2009)[31]	OCD	MADRS HAMA BDI STAI-S
Meek et al. (2021)[32]	OCD	Beck Depression Inventory (BDI) Beck Anxiety Inventory (BAI)
Pelissolo et al. (2016)[29]	OCD	MADRS Beck Anxiety Scale (BAS) Obsessive Thoughts List Maudsley Obsessive Compulsive Inventory
Prasko et al. (2006)[33]	OCD	Hamilton Rating Scale for Anxiety (HAMA) Beck Anxiety Inventory (BAI)
Seo et al. (2016)[34]	OCD	HAMD HAMA BDI
Anderson et al. (2007)[58]	MDD	HAD Anxiety HAD Depression
Cole et al. (2022)[51]	MDD	QUIDS Scale for suicide ideation YMRS
Croarkin et al. (2021)[36]	MDD	Children's Depression Rating Scale Revised QIDS-Adolescent
Duprat et al. (2016)[56]	MDD	VAS for mood rating for fatigue, power, anger, cheerfulness, tension, depression, and happiness
Garcia-Toro et al. (2001)[71]	MDD	HAMA
Garcia-Toro et al. (2001)[62]	MDD	Global clinical inventory

Author (Year)	Condition	Outcome(s)
George et al. (2010)[39]	MDD	Inventory of Depressive Symptoms—Self Report
Kaster et al. (2018)[54]	MDD	Brief Symptom Inventory anxiety subscale (BSI) SF-36
Lee et al. (2018)[63]	MDD	HAMA-14
O'Reardon et al. (2007)[37]	MDD	Inventory of Depressive Symptoms—Self Report Patient Global Impressions Improvement Scale
Taylor et al. (2018)[49]	MDD	Generalized Anxiety Disorder Assessment (GAD7) Work and Social Adjustment Scale
Yesavage et al. (2018)[38]	MDD	CAPS PCL-M SF-36
Isserles et al. (2021)[75]	PTSD	HAMD21
Kozel et al. (2018)[76]	PTSD	QIDS Inventory of Psychosocial Functioning
Philip et al. (2019)[78]	PTSD	QLESQ IDSSR Social and Occupational Function Scale
Watts et al. (2012)[77]	PTSD	BDI STAI BNCE
Sheffer et al. (2018)[79]	Smoking cessation	CES-D STAI BIS
Harel et al. (2021)[86]	SUD	BDI Comprehensive Psychopathological Rating Scale (CPRS) for depression and anxiety
Lolli et al. (2021)[88]	SUD	Symptoms of Depression Questionnaire (SDQ) UPPS-P Impulsive Behavior Scale
Martinotti et al. (2022)[85]	SUD	MADRS
Perini et al. (2020)[87]	SUD	CPRS-SA, nicotine consumption
Schluter et al. (2019)[89]	SUD	Impulsivity

Abbreviations: BABS = Brown Assessment of Belief Scale; BAI = Beck Anxiety Inventory; BAS = Brief Anxiety Scale; BDI = Beck Depression Inventory; BIS = Brief Symptom Inventory anxiety subscale; BNCE = Brief Neurobehavioral Cognitive Examination; BSI = Brief Symptom Inventory anxiety subscale; CAPS = Clinician-Administered PTSD Scale for DSM-IV; CES-D = Center for Epidemiologic Studies Depression Scale; CPRS = Comprehensive Psychopathological Rating Scale; CPRS-SA = Comprehensive Psychopathological Rating Scale, Self Rate; GAD = generalized anxiety disorder; GAD7 = Generalized Anxiety Disorder Assessment; HAD = Hospital Anxiety and Depression Scale; HAMA = Hamilton Rating Scale for Anxiety; HAMA = Hamilton Rating Scale for Anxiety; HAMA-14 = Hamilton Rating Scale for Anxiety (14 item); HAMD = Hamilton depression score; HAMD21 = Hamilton Depression Rating Scale (21 item); HRSD = Hamilton Rating Scale for Depression; IDSSR = Inventory of Depressive Symptomatology Self-Report; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PCL-M = PTSD Checklist for DSM-5; PTSD = posttraumatic stress disorder; QIDS = Quick Inventory of Depressive Symptomatology; QLESQ = Quality of Life Enjoyment and Satisfaction Questionnaire;

SDQ = Symptoms of Depression Questionnaire; SF-36 = 36-item Short Form Survey; STAI = State-Trait Anxiety Inventory; STAI-S = State-Trait Anxiety Inventory; SUD = substance use disorder; VAS = visual analogue scale; YMRS = Young Mania Rating Scale.

Table C-33. Neurocognitive Outcomes Not Abstracted

Author (Year)	Condition	Neurocognitive Outcome(s)
Kang et al. (2009)[31]	OCD	Cognitive function (Stroop Task)
Meet et al. (2021)[32]	OCD	Erikson Flanker tasks
Avery et al (2006)[68]	MDD	Rey Auditory Verbal Learning Test (RAVLT), Digit Symbol Test and Digit Span (from the Wechsler Adult Intelligence Scale-Revised [WAIS-R]), TMT Parts A and B, Mini-Mental State Examination (MMSE), the Controlled Word Association Test (COWAT)
Blumberger et al. (2012)[43]	MDD	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Hopkins Verbal Learning Test revised (HVLT-R), Brief Visual Memory Test–Revised (BVMT-R), and the Grooved Peg Board test
Cole at al. (2022)[51]	MDD	Hopkins Verbal Learning Test–Revised, Delis-Kaplan Executive Function, Trail Making Test, Color-Word Interference Test
Concerto et al. (2015)[67]	MDD	Frontal Assessment Battery (FAB), Stroop Color-Word Test Interference (Stroop T)
Croarkin et al. (2021)[36]	MDD	NIHTB-CB
Fitzgerald et al. (2012)[57]	MDD	Wechsler Test of Adult Reading (WTAR), Rey Auditory Verbal Learning Test (Word List), Brief Visual Spatial Memory Test (BVMT), Digit Span (WAIS-III), TMT A & B, Stroop, and COWAT phonemic fluency
Hoppner et al. (2003)[61]	MDD	Motor Agitation and Retardation Scale (MARS)
Januel et al. (2006)[46]	MDD	Grober and Buschke's Test (verbal memory) Stroop test (response suppression) TMT (time visuomotor sequencing) Auditory and visual attention span Cardebat's Fluency Visuospatial reasoning
Kaster et al. (2018)[54]	MDD	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Delis–Kaplan Executive Function System (DKEFS), Color Word Interference (CWI), Trail Making Test (TMT)
Kim et al. (2019)[40]	MDD	Letter number sequencing (LNS) working memory tasks
Vanneste et al. (2012)[37]	MDD	Global cognitive function Short-term and delayed recall Retrieval of long-term autobiographical memory.
Watts et al. (2012)[77]	PTSD	BNCE
[83]	Smoking cessation	MMSE Buschke Selective Reminding Test (BSRT)
Perini et al. (2020)[87]	SUD	Monetary incentive delay task, negative-affect picture processing
Harel et al. (2021)[86]	SUD	Functional connectivity of brain areas implicated in the pathophysiology of alcohol addiction

Abbreviations: BNCE = Brief Neurobehavioral Cognitive Examination; BSRT = Buschke Selective Reminding Test; BVMT = Brief Visual Spatial Memory Test; BVMT-R = Brief Visual Memory Test–Revised; COWAT = Controlled Word Association Test; CWI = Color Word Interference; DKEFS = Delis–Kaplan Executive Function System; FAB = Frontal Assessment Battery; HVLT-R = Hopkins Verbal Learning Test revised; LNS = Letter number sequencing; MARS = Motor Agitation and Retardation Scale; MDD = major depressive disorder; MMSE = Mini-Mental State Examination; NIHTB-CB = National Institutes of Health Toolbox Cognition Battery; OCD = obsessive-compulsive disorder;

PTSD = posttraumatic stress disorder; RAVLT = Rey Auditory Verbal Learning Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SUD = substance use disorder; TMT = Trail Making Test; WAIS-III = Wechsler Adult Intelligence Scale, Third Edition; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WTAR = Wechsler Test of Adult Reading.

Appendix D. Excluded Articles

List of Exclusion Codes

X1: Ineligible population/indication

X2: Ineligible intervention

X3: Ineligible or no comparator

X4: Ineligible outcomes

X5: Ineligible study design

X6: Ineligible setting

X7: Abstract only

X8: Duplicate or superseded

X9: Study protocol or in progress

X10: Cost with ECT comparator

X11: Primary outcome not clinical

X12: Neurocognitive outcomes

X13: Harms observational study

X14: Intervention single session

X15: Non-eligible primary mental health diagnosis and comorbid eligible diagnosis

X16: Sample size <10/study arm

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3. Addolorato G, Antonelli M, Cocciolillo F, et al. Deep transcranial magnetic stimulation of the dorsolateral prefrontal cortex in alcohol use disorder patients: effects on dopamine transporter availability and alcohol intake. *Eur Neuropsychopharmacol*. 2017 May;27(5):450-61. doi: 10.1016/j.euroneuro.2017.03.008. PMID: 28390775. Exclusion Code: X16.
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Appendix E. Individual Study Risk-of-Bias Assessments

Table E-1. Risk-of-Bias Ratings for Randomized Controlled Trials for GAD—Randomization Process

Author (Year)	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Did baseline differences between intervention groups suggest a problem with the randomization process?	Risk of bias arising from the randomization process
Diefenbach et al. (2016)[25]	Y	PY	PY	Some concerns
Dilkov et al. (2017)[24]	Y	PY	PN	Low

Abbreviations: GAD = generalized anxiety disorder; PN = probably no; PY = probably yes; Y = yes.

Table E-2. Risk of Bias for Randomized Controlled Trials for GAD—Deviations From Intended Interventions

Author (Year)	Were the participants aware of their assigned intervention during the trial?	Were carers and people delivering the interventions aware of participants' assigned intervention during the trials?	Were there deviations from the intended intervention that arose because of the experimental process?	Were these deviations from intended intervention balanced between groups?	Were these deviations likely to have affected the outcome?	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Was there potential for a substantial impact of the failure to analyze participants in the group to which they were randomized?	Risk of bias arising from deviations from intended interventions
Diefenbach et al. (2016)[25]	N	N	NA	NA	NA	N	PN	Some concerns
Dilkov et al. (2017)[24]	N	NI	Y	N	NI	PY	NA	Some concerns

Abbreviations: GAD = generalized anxiety disorder; N = no; NA = not applicable; NI = no information; PN = probably no; PY = probably yes; Y = yes.

Table E-3. Risk of Bias for Randomized Controlled Trials for GAD—Missing Outcome Data

Author (Year)	Were outcome data available for all, or nearly all, participants randomized?	Is there evidence that result was not biased by missing outcome data?	Could missingness in the outcome depend on its true value?	Is it likely that missingness in the outcome depended on its true value?	Risk of bias arising from missing outcome data
Diefenbach et al. (2016)[25]	Y	NA	NA	NA	Low
Dilkov et al. (2017)[24]	PN	NI	Y	NI	High

Abbreviations: mITT = modified intention-to-treat; GAD = generalized anxiety disorder; NA = not applicable; NI = no information; PN = probably no; Y = yes.

Table E-4. Risk of Bias for Randomized Controlled Trials for GAD—Measurement of the Outcome

Author (Year)	Was the method of measuring the outcome inappropriate?	Could measurement or ascertainment of the outcome have differed between intervention groups?	Were outcome assessors aware of the intervention received by study participants?	Could assessment of the outcome have been influenced by knowledge of intervention received?	Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Risk of bias arising from measurement of the outcome
Diefenbach et al. (2016)[25]	N	PN	N	NA	NA	Low
Dilkov et al. (2017)[24]	N	N	N	NA	NA	Low

Abbreviations: GAD = generalized anxiety disorder; N = no; NA = not applicable; PN = probably no; PY = probably yes; Y = yes.

Table E-5. Risk of Bias for Randomized Controlled Trials for GAD—Selection of the Reported Result and Overall Risk of Bias Rating

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Comments	Overall rating	Rationale/comments
Diefenbach et al. (2016)[25]	PY	PN	PN	Low	None	Some concerns	Some concerns for bias because of differences in baseline anxiety severity between groups; it does not appear that these differences were adjusted for in the analysis, but these differences would likely bias the results to the null effect, suggesting the findings are conservative with respect to showing efficacy for TMS.
Dilkov et al. (2017)[24]	Y	PN	N	Low	None	High	High overall attrition and differential attrition; reporting of patient flow through study opaque.

Abbreviations: GAD = generalized anxiety disorder; N = no; PN = probably no; PY = probably yes; TMS = transcranial magnetic stimulation; Y = yes.

Table E-6. Risk-of-Bias Ratings for Randomized Controlled Trials for OCD—Randomization Process

Author (Year)	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Did baseline differences between intervention groups suggest a problem with the randomization process?	Risk of bias arising from the randomization process
Carmi et al. (2018)[27]	Y	Y	PN	Low
Carmi et al. (2019)[26]	Y	Y	N	Low
Harika-Germaneau et al. (2019)[28]	Y	Y	N	Low
Hawken et al. (2016)[30]	NI	NI	NI	Some concerns
Kang et al. (2009)[31]	Y	PY	N	Low
Meek et al. (2021)[32]	Y	NI	N	Some concerns
Pelissolo et al. (2016)[29]	Y	Y	N	Low
Prasko et al. (2006)[33]	PY	NI	Y	High
Seo et al. (2016)[34]	Y	NI	N	Some concerns

Abbreviations: N = no; NA = not applicable; NI = no information; OCD = obsessive-compulsive disorder; PN = probably no; PY = probably yes; Y = yes.

Table E-7. Risk of Bias for Randomized Controlled Trials for OCD—Deviations From Intended Interventions

Author (Year)	Were the participants aware of their assigned intervention during the trial?	Were carers and people delivering the interventions aware of participants' assigned intervention during the trials?	Were there deviations from the intended intervention that arose because of the experimental process?	Were these deviations from intended intervention balanced between groups?	Were these deviations likely to have affected the outcome?	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Was there potential for a substantial impact of the failure to analyze participants in the group to which they were randomized?	Risk of bias arising from deviations from intended interventions
Carmi et al. (2018)[27]	N	N	NA	NA	NA	PN	PY	High
Carmi et al. (2019)[26]	N	N	NA	NA	NA	Y	NA	Some concerns
Harika-Germaneau et al. (2019)[28]	N	N	NA	NA	NA	Y	NA	Low
Hawken et al. (2016)[30]	PN	PY	PN	NA	NA	Y	NA	Low
Kang et al. (2009)[31]	PN	Y	N	NA	NA	PN	PN	Some concerns
Meek et al. (2021)[32]	N	NI	N	NA	NA	Y	NA	Low
Pelissolo et al. (2016)[29]	N	Y	PN	NA	NA	Y	NA	Some concerns
Prasko et al. (2006)[33]	PN	Y	PN	NA	NA	PN	PN	High
Seo et al. (2016)[34]	N	Y	PN	NA	NA	PY	NA	Low

Abbreviations: N = no; NA = not applicable; NI = no information; OCD = obsessive-compulsive disorder; PN = probably no; PY = probably yes; Y = yes.

Table E-8. Risk of Bias for Randomized Controlled Trials for OCD—Missing Outcome Data

Author (Year)	Were outcome data available for all, or nearly all, participants randomized?	Is there evidence that result was not biased by missing outcome data?	Could missingness in the outcome depend on its true value?	Is it likely that missingness in the outcome depended on its true value?	Risk of bias arising from missing outcome data
Carmi et al. (2018)[27]	N	NI	Y	NI	High
Carmi et al. (2019)[26]	Y	NA	NA	NA	Low
Harika-Germaneau et al. (2019)[28]	Y	NA	NA	NA	Low
Hawken et al. (2016)[30]	Y	NA	NA	NA	Low
Kang et al. (2009)[31]	Y	NA	NA	NA	Low
Meek et al. (2021)[32]	PY	PN	NA	NA	Low
Pelissolo et al. (2016)[29]	Y	NA	NA	NA	Low
Prasko et al. (2006)[33]	PY	NA	NA	NA	Low
Seo et al. (2016)[34]	PY	NA	NA	NA	Low

Abbreviations: N = no; NA = not applicable; NI = no information; OCD = obsessive-compulsive disorder; PN = probably no; PY = probably yes; Y = yes.

Table E-9. Risk of Bias for Randomized Controlled Trials for OCD—Measurement of the Outcome

Author (Year)	Was the method of measuring the outcome inappropriate?	Could measurement or ascertainment of the outcome have differed between intervention groups?	Were outcome assessors aware of the intervention received by study participants?	Could assessment of the outcome have been influenced by knowledge of intervention received?	Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Risk of bias arising from measurement of the outcome
Carmi et al. (2018)[27]	N	N	N	NA	NA	Low
Carmi et al. (2019)[26]	N	PN	N	NA	NA	Low
Harika-Germaneau et al. (2019)[28]	N	PN	N	NA	NA	Low
Hawken et al. (2016)[30]	N	PN	N	NA	NA	Low
Kang et al. (2009)[31]	N	PN	N	NA	NA	Low
Meek et al. (2021)[32]	N	PN	N	NA	NA	Low
Pelissolo et al. (2016)[29]	N	PN	N	NA	NA	Low
Prasko et al. (2006)[33]	N	PN	N	NA	NA	Low
Seo et al. (2016)[34]	N	PN	N	NA	NA	Low

Abbreviations: N = no; NA = not applicable; NI = no information; OCD = obsessive-compulsive disorder; PN = probably no; PY = probably yes; Y = yes.

Table E-10. Risk of Bias for Randomized Controlled Trials for OCD—Selection of the Reported Result and Overall Risk of Bias Rating

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Carmi et al. (2018)[27]	PY	PN	PN	Low	High	High risk of bias due to postrandomization exclusions of noncompleters and high overall and differential attrition at both 1 week and 1-month follow-up.
Carmi et al. (2019)[26]	PY	PN	PN	Low	Some concerns	Primary endpoint was mITT analysis, other analyses were based on a completer's analysis
Harika-Germaneau et al. (2019)[28]	NI	PN	PY	Some concerns	Some concerns	Some concerns in reporting of selected outcomes domain. No published study protocol or registry.
Hawken et al. (2016)[30]	Y	PN	PN	Low	Some concerns	Some concerns regarding randomization and treatment allocation and very little information on group differences at baseline; TMS administrators not blinded to treatment group.
Kang et al. (2009)[31]	Y	N	N	Low	Some concerns	Some concerns because TMS administrators were not blinded to treatment group; completers analysis (1 postrandomization exclusion)
Meek et al. (2021)[32]	PY	PN	PN	Low	Some concerns	Method of allocation concealment NR; unclear whether TMS administrators were blinded; primary analysis excluded 3 participants who did not complete treatment, though authors state ITT analysis produced similar results.

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Pelissolo et al. (2016)[29]	NI	PN	PN	Some concerns	Some concerns	Some concerns for bias because no blinding of TMS administrators to treatment assignment and no trial registry or study protocol for assessment of reporting bias.
Prasko et al. (2006)[33]	NI	PN	PN	Some concerns	High	High risk of bias in randomization domain because of few details coupled with baseline imbalances between groups; high risk of bias in deviation from intended treatment domain because of postrandomization exclusions.
Seo et al. (2016)[34]	NI	PN	PN	Some concerns	Some concerns	Method of allocation concealment NR; TMS administrators not blinded; no trial registry or published study protocol mentioned.

Abbreviations: ITT = intention-to-treat; mITT = modified intention-to-treat; N = no; NA = not applicable; NI = no information; NR = not reported; OCD = obsessive-compulsive disorder; PN = probably no; PY = probably yes; TMS = transcranial magnetic stimulation; Y = yes.

Table E-11. Risk-of-Bias Ratings for Randomized Controlled Trials for MDD—Randomization Process

Author (Year)	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Did baseline differences between intervention groups suggest a problem with the randomization process?	Risk of bias arising from the randomization process
Anderson et al. (2007)[58]	Y	Y	N	Low
Avery et al. (2006)[68]	Y	NI	N	Some concerns
Blumberger et al. (2012)[43]	Y	Y	Y	Some concerns
Blumberger et al. (2016)[42]	Y	NI	PY	Some concerns
Bretlau et al. (2008)[65]	NI	NI	N	Some concerns
Chou et al. (2020)[52]	NI	NI	N	Some concerns
Cole et al. (2022)[51]	Y	Y	PN	Low
Concerto et al. (2015)[67]	NI	NI	PN	Some concerns
Croarkin et al. (2021)[36]	NI	NI	N	Some concerns
Duprat et al. (2016)[56]	Y	NI	NI	Some concerns
Fitzgerald et al. (2012)[57]	NI	NI	N	Some concerns
Garcia-Toro et al. (2001)[71]	NI	NI	N	Some concerns
Garcia-Toro et al. (2001)[62]	NI	NI	N	Some concerns
Garcia-Toro et al. (2006)[69]	NI	Y	N	Low
George et al. (2010)[39]	PY	NI	N	Some concerns
Hausmann et al. (2004)[70]	NI	NI	N	Some concerns
Herwig et al. (2003)[60]	NI	NI	PN	Some concerns
Hoppner et al. (2003)[61]	NI	NI	NI	High
Januel et al. (2006)[46]	Y	NI	N	Some concerns
Kaster et al. (2018)[54]	Y	Y	PN	Low
Kim et al. (2019)[40]	NI	NI	PY	High
Koerselman et al. (2004)[66]	NI	NI	N	Some concerns
Lee et al. (2018)[63]	NI	NI	PN	Some concerns
Levkovitz et al. (2015)[53]	Y	Y	N	Low
Li et al. (2014)[55]	NI	NI	PN	Some concerns
Li et al. (2020)[50]	Y	NI	N	Some concerns

Author (Year)	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Did baseline differences between intervention groups suggest a problem with the randomization process?	Risk of bias arising from the randomization process
O'Reardon et al. (2007)[37]	NI	NI	N	Some concerns
Padberg et al. (2002)[48]	NI	NI	N	Some concerns
Pallanti et al. (2010)[44]	Y	Y	N	Low
Rossini et al. (2005)[45]	Y	NI	N	Some concerns
Schutter et al. (2009)[59]	Y	Y	N	Low
Stern et al. (2007)[47]	NI	NI	N	Some concerns
Taylor et al. (2018)[49]	PY	PY	PY	Some concerns
Theleritis et al. (2017)[64]	Y	Y	N	Low
van Eijndhoven et al. (2020)[41]	NI	NI	PY	High
Yesavage et al. (2018)[38]	Y	Y	N	Low

Abbreviations: MDD = major depressive disorder; N = no; NI = no information; PN = probably no; PY = probably yes; Y = yes.

Table E-12. Risk of Bias for Randomized Controlled Trials for MDD—Deviations From Intended Interventions

Author (Year)	Were the participants aware of their assigned intervention during the trial?	Were carers and people delivering the interventions aware of participants' assigned intervention during the trials?	Were there deviations from the intended intervention that arose because of the experimental process?	Were these deviations from intended intervention balanced between groups?	Were these deviations likely to have affected the outcome?	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Was there potential for a substantial impact of the failure to analyze participants in the group to which they were randomized?	Risk of bias arising from deviations from intended interventions
Anderson et al. (2007)[58]	PY	NI	PN	NA	NA	Y	NA	Low
Avery et al. (2006)[68]	PN	Y	PN	NA	NA	Y	NA	Low
Blumberger et al. (2012)[43]	PY	Y	Y	Y	Y	Y	NA	High
Blumberger et al. (2016)[42]	PN	Y	Y	PN	PY	Y	NA	High
Bretlau et al. (2008)[65]	PN	PY	PN	NA	NA	PN	N	Some concerns
Chou et al. (2020)[52]	PN	NI	PN	NA	NA	PN	Y	High
Cole et al. (2022)[51]	N	N	NA	NA	NA	Y	NA	Low
Concerto et al. (2015)[67]	PN	Y	PN	NA	NA	Y	NA	Some concerns
Croarkin et al. (2021)[36]	PN	N	NA	NA	NA	Y	NA	Low
Duprat et al. (2016)[56]	PN	Y	PN	NA	NA	PY	NA	Low
Fitzgerald et al. (2012)[57]	N	Y	PN	NA	NA	PN	PN	Some concerns
Garcia-Toro et al. (2001)[71]	N	Y	N	NA	NA	PN	PN	Some concerns
Garcia-Toro et al. (2001)[62]	PN	PY	PN	NA	NA	N	PN	Some concerns
Garcia-Toro et al. (2006)[69]	N	Y	PN	NA	NA	Y	NA	Low

Author (Year)	Were the participants aware of their assigned intervention during the trial?	Were carers and people delivering the interventions aware of participants' assigned intervention during the trials?	Were there deviations from the intended intervention that arose because of the experimental process?	Were these deviations from intended intervention balanced between groups?	Were these deviations likely to have affected the outcome?	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Was there potential for a substantial impact of the failure to analyze participants in the group to which they were randomized?	Risk of bias arising from deviations from intended interventions
George et al. (2010)[39]	N	NI	PN	NA	NA	Y	PN	Some concerns
Hausmann et al. (2004)[70]	PN	Y	PN	NA	NA	N	PN	Some concerns
Herwig et al. (2003)[60]	PN	Y	N	NA	NA	Y	NA	Low
Hoppner et al. (2003)[61]	PN	PY	N	NA	NA	NI	PY	Some concerns
Januel et al. (2006)[46]	PN	NI	N	NA	NA	Y	NA	Low
Kaster et al. (2018)[54]	PN	N	Y	PN	PN	PN	NA	Some concerns
Kim et al. (2019)[40]	N	N	NA	NA	NA	PY	NA	Some concerns
Koerselman et al. (2004)[66]	PN	Y	PN	NA	NA	N	PN	Some concerns
Lee et al. (2018)[63]	N	NI	PN	NA	NA	PY	NA	Some concerns
Levkovitz et al. (2015)[53]	N	N	NA	NA	NA	PY	NA	Low
Li et al. (2014)[55]	N	Y	N	NA	NA	Y	NA	Low
Li et al. (2020)[50]	N	Y	N	NA	NA	Y	NA	Low
O'Reardon et al. (2007)[37]	N	N	Y	PN	Y	Y	NA	Low
Padberg et al. (2002)[48]	PN	PY	N	NA	NA	PY	NA	Low
Pallanti et al. (2010)[44]	N	N	PN	NA	NA	Y	NA	Low

Author (Year)	Were the participants aware of their assigned intervention during the trial?	Were carers and people delivering the interventions aware of participants' assigned intervention during the trials?	Were there deviations from the intended intervention that arose because of the experimental process?	Were these deviations from intended intervention balanced between groups?	Were these deviations likely to have affected the outcome?	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Was there potential for a substantial impact of the failure to analyze participants in the group to which they were randomized?	Risk of bias arising from deviations from intended interventions
Rossini et al. (2005)[45]	N	PY	PN	NA	NA	PY	NA	Low
Schutter et al. (2009)[59]	N	Y	N	NA	NA	PY	NA	Low
Stern et al. (2007)[47]	PN	Y	PN	NA	NA	Y	NA	Low
Taylor et al. (2018)[49]	PN	Y	PN	NA	NA	N	PN	Some concerns
Theleritis et al. (2017)[64]	N	N	N	NA	NA	Y	NA	Low
van Eijndhoven et al. (2020)[41]	N	Y	PN	NA	NA	NI	NI	Some concerns
Yesavage et al. (2018)[38]	N	N	NA	NA	NA	Y	NA	Low

Abbreviations: MDD = major depressive disorder; N = no; NA = not applicable; NI = no information; PN = probably no; PY = probably yes; Y = yes.

Table E-13. Risk of Bias for Randomized Controlled Trials for MDD—Missing Outcome Data

Author (Year)	Were outcome data available for all, or nearly all, participants randomized?	Is there evidence that result was not biased by missing outcome data?	Could missingness in the outcome depend on its true value?	Is it likely that missingness in the outcome depended on its true value?	Risk of bias arising from missing outcome data
Anderson et al. (2007)[58]	Y	NA	NA	NA	Low
Avery et al. (2006)[68]	Y	NA	NA	NA	Low
Blumberger et al. (2012)[43]	N	N	PY	PY	High
Blumberger et al. (2016)[42]	Y	NA	NA	NA	Low
Bretlau et al. (2008)[65]	Y	NA	NA	NA	Low
Chou et al. (2020)[52]	PY	NA	NA	NA	Low
Cole et al. (2022)[51]	PY	Y	NA	NA	Low
Concerto et al. (2015)[67]	Y	NA	NA	NA	Low
Croarkin et al. (2021)[36]	N	Y	NA	NA	Low
Duprat et al. (2016)[56]	PY	NA	NA	NA	Low
Fitzgerald et al. (2012)[57]	PN	PY	NA	NA	Low
Garcia-Toro et al. (2001)[71]	Y	NA	NA	NA	Low
Garcia-Toro et al. (2001)[62]	N	PY	PY	PY	Some concerns
Garcia-Toro et al. (2006)[69]	Y	NA	NA	NA	Low
George et al. (2010)[39]	PY	NA	NA	NA	Low
Hausmann et al. (2004)[70]	Y	NA	NA	NA	Low
Herwig et al. (2003)[60]	Y	NA	NA	NA	Low

Author (Year)	Were outcome data available for all, or nearly all, participants randomized?	Is there evidence that result was not biased by missing outcome data?	Could missingness in the outcome depend on its true value?	Is it likely that missingness in the outcome depended on its true value?	Risk of bias arising from missing outcome data
Hoppner et al. (2003)[61]	Y	NA	NA	NA	Low
Januel et al. (2006)[46]	PN	NI	PY	PY	High
Kaster et al. (2018)[54]	PN	PN	PY	PN	Some concerns
Kim et al. (2019)[40]	Y	NA	NA	NA	Low
Koerselman et al. (2004)[66]	PY	NA	NA	NA	Low
Lee et al. (2018)[63]	N	NI	NI	NI	High
Levkovitz et al. (2015)[53]	Y	NA	NA	NA	Low
Li et al. (2014)[55]	Y	NA	NA	NA	Low
Li et al. (2020)[50]	Y	NA	NA	NA	Low
O'Reardon et al. (2007)[37]	Y	NA	NA	NA	Low
Padberg et al. (2002)[48]	Y	NA	NA	NA	Low
Pallanti et al. (2010)[44]	Y	NA	NA	NA	Low
Rossini et al. (2005)[45]	PY	NA	NA	NA	Low
Schutter et al. (2009)[59]	Y	NA	NA	NA	Low
Stern et al. (2007)[47]	Y	NA	NA	NA	Low
Taylor et al. (2018)[49]	N	N	PN	NA	Some concerns
Theleritis et al. (2017)[64]	Y	NA	NA	NA	Low
van Eijndhoven et al. (2020)[41]	Y	NA	NA	NA	Low
Yesavage et al. (2018)[38]	Y	Y	NA	NA	Low

Abbreviations: MDD = major depressive disorder; N = no; NA = not applicable; NI = no information; PN = probably no; PY = probably yes; Y = yes.

Table E-14. Risk of Bias for Randomized Controlled Trials for MDD—Measurement of the Outcome

Author (Year)	Was the method of measuring the outcome inappropriate?	Could measurement or ascertainment of the outcome have differed between intervention groups?	Were outcome assessors aware of the intervention received by study participants?	Could assessment of the outcome have been influenced by knowledge of intervention received?	Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Risk of bias arising from measurement of the outcome
Anderson et al. (2007)[58]	N	Y	PY	PY	PY	Some concerns
Avery et al. (2006)[68]	N	N	N	NA	NA	Low
Blumberger et al. (2012)[43]	N	Y	N	NA	NA	Some concerns
Blumberger et al. (2016)[42]	N	PN	N	NA	NA	Low
Bretlau et al. (2008)[65]	N	PN	NI	NI	PN	Some concerns
Chou et al. (2020)[52]	N	N	N	NA	NA	Low
Cole et al. (2022)[51]	Y	N	N	NA	NA	Low
Concerto et al. (2015)[67]	N	PN	NI	Y	NI	High
Croarkin et al. (2021)[36]	N	PN	N	NA	NA	Low
Duprat et al. (2016)[56]	N	PN	N	NA	NA	Low
Fitzgerald et al. (2012)[57]	N	N	N	NA	NA	Low
Garcia-Toro et al. (2001)[71]	Y	N	NA	NA	NA	Low
Garcia-Toro et al. (2001)[62]	N	N	N	NA	NA	Low

Author (Year)	Was the method of measuring the outcome inappropriate?	Could measurement or ascertainment of the outcome have differed between intervention groups?	Were outcome assessors aware of the intervention received by study participants?	Could assessment of the outcome have been influenced by knowledge of intervention received?	Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Risk of bias arising from measurement of the outcome
Garcia-Toro et al. (2006)[69]	N	PN	NI	NI	PN	Some concerns
George et al. (2010)[39]	N	N	N	NA	NA	Low
Hausmann et al. (2004)[70]	N	N	N	NA	NA	Low
Herwig et al. (2003)[60]	N	N	N	NA	NA	Low
Hoppner et al. (2003)[61]	N	N	N	NA	NA	Low
Januel et al. (2006)[46]	N	N	N	NA	NA	Low
Kaster et al. (2018)[54]	PN	PN	PN	NA	NA	Low
Kim et al. (2019)[40]	N	N	N	NA	NA	Low
Koerselman et al. (2004)[66]	N	PN	N	NA	NA	Low
Lee et al. (2018)[63]	N	N	N	NA	NA	Low
Levkovitz et al. (2015)[53]	N	N	N	NA	NA	Low
Li et al. (2014)[55]	N	N	N	NA	NA	Low
Li et al. (2020)[50]	N	N	N	NA	NA	Low
O'Reardon et al. (2007)[37]	N	N	N	NA	NA	Low
Padberg et al. (2002)[48]	N	N	NA	NA	NA	Low

Author (Year)	Was the method of measuring the outcome inappropriate?	Could measurement or ascertainment of the outcome have differed between intervention groups?	Were outcome assessors aware of the intervention received by study participants?	Could assessment of the outcome have been influenced by knowledge of intervention received?	Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Risk of bias arising from measurement of the outcome
Pallanti et al. (2010)[44]	N	PN	N	NA	NA	Low
Rossini et al. (2005)[45]	N	N	N	NA	NA	Low
Schutter et al. (2009)[59]	Y	N	NA	NA	NA	Low
Stern et al. (2007)[47]	N	N	N	NA	NA	Low
Taylor et al. (2018)[49]	N	N	N	NA	NA	Low
Theleritis et al. (2017)[64]	Y	PN	N	NA	PN	Low
van Eijndhoven et al. (2020)[41]	N	N	N	NA	NA	Low
Yesavage et al. (2018)[38]	N	N	N	NA	NA	Low

Abbreviations: MDD = major depressive disorder; N = no; NA = not applicable; NI = no information; PN = probably no; PY = probably yes; Y = yes.

Table E-15. Risk of Bias for Randomized Controlled Trials for MDD—Selection of the Reported Results and Overall Risk-of-Bias Rating

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Anderson et al. (2007)[58]	NI	NI	NI	Some concerns	Some concerns	No clinical trial registration or published protocol is available. Also, partial responders (all in the active treatment group) received 2 additional weeks of treatment, potentially breaking the blind.
Avery et al. (2006)[68]	NI	PN	PN	Some concerns	Some concerns	Method of allocation concealment NR; no trial registration or published protocol available.
Blumberger et al. (2012)[43]	N	PY	PY	High	High	Missing data domain. High-differential attrition (unilateral group ~ 50%), measurement domains (differential measurement between groups), reporting domain (primary outcome and time point not reported). Some concerns for randomization domain (baseline differences).
Blumberger et al. (2016)[42]	NI	PN	PN	Some concerns	High	High risk of bias because additional intervention was provided to nonremitters at 3 weeks, while remitters only received treatment for 3 weeks.

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Bretlau et al. (2008)[65]	NI	NI	PY	Some concerns	Some concerns	Unclear whether outcome assessors were blinded; method of randomization and allocation concealment NR; no published protocol or trial registry; postrandomization exclusions for noncompliance though 1 patient, unlikely to affect results.
Chou et al. (2020)[52]	PY	PN	PN	Low	High	Some concerns because method of randomization and allcoation concealment NR and TMS administrators not blinded; high risk of bias because unclear whether ITT was used; postrandomization exclusions including 1 for adverse effects. Authors stated that the 20-week follow-up period was “open-label” and antidepressant use was allowed, but it is unclear whether the blind was broken during this time.
Cole et al. (2022)[51]	Y	PN	PN	Low	Low	

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Concerto et al. (2015)[67]	NI	PN	PN	Some concerns	High	Some concerns for bias in randomization, deviations from intended interventions, and selective reporting domains; high concerns for bias in outcome assessment domain because no information about whether outcome assessment was blinded and use of patient-reported outcomes with possibly inadequate sham control.
Croarkin et al. (2021)[36]	PY	PN	PN	Low	Some concerns	For randomization domain: No information but baseline characteristics balanced.
Duprat et al. (2016)[56]	PY	PN	PN	Low	Some concerns	Unclear methods of allocation concealment, no mention of whether randomized groups were balanced at baseline, TMS administrators not blinded.
Fitzgerald et al. (2012)[57]	NI	NI	NI	Some concerns	Some concerns	Some concerns for bias because method of randomization and allocation concealment NR, postrandomization exclusions from analysis; no trial registration or published protocol available.

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Garcia-Toro et al. (2001)[71]	NI	N	N	Some concerns	Some concerns	No information on prespecified analysis plan, no information about randomization for allocation sequence or concealment, postrandomization, posttreatment exclusions.
Garcia-Toro et al. (2001)[62]	NI	PN	PN	Some concerns	Some concerns	Lack of information for allocation sequence generation and concealment, completers analysis, missing data, and no trial registration.
Garcia-Toro et al. (2006)[69]	NI	PY	PN	Some concerns	Some concerns	No information on outcome assessment blinding and no trial protocol.
George et al. (2010)[39]	Y	N	N	Low	Some concerns	Method of allocation concealment NR; 9 postrandomization exclusions (2 withdrew before treatment, 7 were excluded by investigators from the first year of treatment while the sham was being developed), though small number with respect to total sample so unlikely to affect results

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Hausmann et al. (2004)[70]	NI	PN	PN	Some concerns	Some concerns	No information regarding allocation concealment or randomization process is given. Completer analyses. though few noncompleters. which likely does not affect results. No trial protocol. While there are some concerns in multiple domains, these do not seem to have substantially lowered the confidence in the results.
Herwig et al. (2003)[60]	NI	PN	NI	Some concerns	Some concerns	Lack of information on allocation sequence generation and concealment. No trial registration or protocol is available.
Hoppner et al. (2003)[61]	NI	PN	PN	Some concerns	High	High risk of bias in the randomization domain (methods NR and unable to compare baseline characteristics); some concerns in deviations domain and selective outcome reporting domain.
Januel et al. (2006)[46]	NI	N	N	Some concerns	High	Missing outcome data: 50% dropout in sham group due to lack of efficacy vs. 72% dropout in TMS group; no information on prespecified analysis plan; no information on allocation sequence concealment.

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Kaster et al. (2018)[54]	Y	N	PN	Low	Some concerns	Postrandomization exclusions because of revised protocol and missing data domains.
Kim et al. (2019)[40]	PY	PY	N	Some concerns	High	High risk of bias in randomization and selective reporting domains; some concerns in the deviations from intended intervention domain.
Koerselman et al. (2004)[66]	NI	PY	PY	Some concerns	Some concerns	Some concerns for randomization and allocation concealment NR; small number of postrandomization exclusions likely to bias toward the null; no trial registry/published protocol with concern for selective outcome reporting.
Lee et al. (2018)[63]	NI	N	N	Low	High	High risk of bias from missing data; some risk of bias from no information about randomization method or method of allocation concealment and deviations from intervention (some postrandomization exclusions of eligible participants for EEG artifact).
Levkovitz et al. (2015)[53]	PY	PY	PY	Some concerns	Some concerns	Some concerns for bias due to selective outcome reporting.

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Li et al. (2014)[55]	NI	N	N	Some concerns	Some concerns	No clinical trial registration is reported. No information about randomization procedures or allocation reported.
Li et al. (2020)[50]	Y	N	N	Some concerns	Low	
O'Reardon et al. (2007)[37]	PY	PN	PY	Some concerns	Some concerns	No information about method of randomization or allocation concealment, baseline imbalance in MADRS score and supplemental analyses not prespecified to exclude persons with low baseline MADRS scores. Although study allowed crossovers after 4 weeks for insufficient clinical response, we primarily relied on data collected before crossover.
Padberg et al. (2002)[48]	NI	PN	PN	Some concerns	Some concerns	No information on randomization/allocation sequence or prespecified analysis plan.
Pallanti et al. (2010)[44]	PY	PN	PN	Some concerns	Some concerns	Study did not include secondary outcome measure (CGI) as reported in its trial registry.
Rossini et al. (2005)[45]	NI	PN	PN	Some concerns	Some concerns	Some concerns for bias, method of allocation concealment NR; some concerns for selective outcome reporting because no designated primary study endpoint and no prespecified analysis plan.

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Schutter et al. (2009)[59]	PN	PN	N	Some concerns	Some concerns	Some concerns for deviations from prespecified outcomes.
Stern et al. (2007)[47]	NI	PN	PN	Some concerns	Some concerns	Lack of information on allocation sequence generation and concealment. No trial protocol.
Taylor et al. (2018)[49]	Y	PN	PN	Low	Some concerns	Baseline differences in disease severity, completers analysis, missing data domain.
Theleritis et al. (2017)[64]	Y	N	PY	Some concerns	Some concerns	Reporting domain: Multiple analyses of data
van Eijndhoven et al. (2020)[41]	PN	PN	PN	Some concerns	High	Method of randomization and allocation concealment NR and baseline imbalances present; some concerns because TMS administrators not blinded and unclear whether ITT used (no CONSORT); some concerns about retrospective trial registration; however, trial was stopped for futility.
Yesavage et al. (2018)[38]	Y	N	N	Low	Low	

Abbreviations: CG = control group; CONSORT = Consolidated Standards of Reporting Trials; EEG = electroencephalogram; ITT = intention-to-treat; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; N = no; NI = no information; NR = not reported; PN = probably no; PY = probably yes; TMS = transcranial magnetic stimulation; Y = yes.

Table E-16. Risk-of-Bias Ratings for Randomized Controlled Trials for PTSD—Randomization Process

Author (Year)	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Did baseline differences between intervention groups suggest a problem with the randomization process?	Risk of bias arising from the randomization process
Isserles et al. (2021)[75]	Y	Y	N	Low
Kozel et al. (2018)[76]	Y	Y	PN	Low
Philip et al. (2019)[78]	PY	PY	N	Low
Watts et al. (2012)[77]	NI	NI	PY	High

Abbreviations: N = no; NI = no information; PN = probably no; PTSD = posttraumatic stress disorder; PY = probably yes; Y = yes.

Table E-17. Risk of Bias for Randomized Controlled Trials for PTSD—Deviations From Intended Interventions

Author (Year)	Were the participants aware of their assigned intervention during the trial?	Were carers and people delivering the interventions aware of participants' assigned intervention during the trials?	Were there deviations from the intended intervention that arose because of the experimental process?	Were these deviations from intended intervention balanced between groups?	Were these deviations likely to have affected the outcome?	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Was there potential for a substantial impact of the failure to analyze participants in the group to which they were randomized?	Risk of bias arising from deviations from intended interventions
Isserles et al. (2021)[75]	N	N	NA	NA	NA	Y	NA	Low
Kozel et al. (2018)[76]	PN	Y	PN	NA	NA	Y	NA	Some concerns
Philip et al. (2019)[78]	N	N	NA	NA	NA	Y	NA	Low
Watts et al. (2012)[77]	N	NI	N	NA	NA	Y	NA	Low

Abbreviations: N = no; NA = not applicable; PN = probably no; PTSD = posttraumatic stress disorder Y = yes.

Table E-18. Risk of Bias for Randomized Controlled Trials for PTSD—Missing Outcome Data

Author (Year)	Were outcome data available for all, or nearly all, participants randomized?	Is there evidence that result was not biased by missing outcome data?	Could missingness in the outcome depend on its true value?	Is it likely that missingness in the outcome depended on its true value?	Risk of bias arising from missing outcome data
Isserles et al. (2021)[75]	PY	NA	NA	NA	Some concerns
Kozel et al. (2018)[76]	PN	N	PY	NI	Some concerns
Philip et al. (2019)[78]	Y	NA	NA	NA	Low
Watts et al. (2012)[77]	Y	NA	NA	NA	Low

Abbreviations: N = no; NA = not applicable; PN = probably no; PTSD = posttraumatic stress disorder; PY = probably yes; Y = yes.

Table E-19. Risk of Bias for Randomized Controlled Trials for PTSD—Measurement of the Outcome

Author (Year)	Was the method of measuring the outcome inappropriate?	Could measurement or ascertainment of the outcome have differed between intervention groups?	Were outcome assessors aware of the intervention received by study participants?	Could assessment of the outcome have been influenced by knowledge of intervention received?	Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Risk of bias arising from measurement of the outcome
Isserles et al. (2021)[75]	N	N	N	NA	NA	Low
Kozel et al. (2018)[76]	Y	N	N	NA	NA	Low
Philip et al. (2019)[78]	N	N	N	NA	NA	Low
Watts et al. (2012)[77]	N	N	N	NA	NA	Low

Abbreviations: N = no; NA = not applicable; PTSD = posttraumatic stress disorder; Y = yes.

Table E-20. Risk of Bias for Randomized Controlled Trials for PTSD—Selection of the Reported Result and Overall Risk of Bias Rating

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Isserles et al. (2021)[75]	Y	N	PN	Low	Some concerns	While the study highlighted the per-protocol analysis dataset for the main efficacy outcomes, it also included the mITT analysis for some of the outcomes, though not for all. Safety data are ITT. Unclear whether the reported results for "response" outcome represent the mITT or per-protocol analysis dataset. Not clear how missing data were handled despite modest levels of attrition by end of follow-up.
Kozel et al. (2018)[76]	Y	N	N	Low	Some concerns	Moderate levels of attrition and unclear how missing data were handled.
Philip et al. (2019)[78]	Y	N	N	Low	Low	
Watts et al. (2012)[77]	NI	Y	N	High	High	No information about randomization or allocation concealment and baseline imbalances in PTSD symptom scores; selected outcome reporting (only reported favorable results from end of treatment; did not fully report other time points).

Abbreviations: ITT = intention-to-treat; mITT = modified intention-to-treat; N = no; NI = no information; PTSD = posttraumatic stress disorder; Y = yes.

Table E-21. Risk-of-Bias Ratings for Randomized Controlled Trials for Smoking Cessation—Randomization Process

Author (Year)	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Did baseline differences between intervention groups suggest a problem with the randomization process?	Risk of bias arising from the randomization process
Dieler et al. (2014)[82]	NI	NI	N	Some concerns
Li et al. (2020)[80]	NI	Y	N	Low
Sheffer et al. (2018)[79]	Y	Y	PY	Some concerns
Trojak et al. (2015)[81]	Y	Y	N	Low
Zangen et al. (2021)[83]	Y	Y	N	Low

Abbreviations: N = no; NI = no information; PY = probably yes; Y = yes.

Table E-22. Risk of Bias for Randomized Controlled Trials for Smoking Cessation—Deviations From Intended Interventions

Author (Year)	Were the participants aware of their assigned intervention during the trial?	Were carers and people delivering the interventions aware of participants' assigned intervention during the trials?	Were there deviations from the intended intervention that arose because of the experimental process?	Were these deviations from intended intervention balanced between groups?	Were these deviations likely to have affected the outcome?	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Was there potential for a substantial impact of the failure to analyze participants in the group to which they were randomized?	Risk of bias arising from deviations from intended interventions
Dieler et al. (2014)[82]	N	PY	PN	PN	N	Y	NA	Low
Li et al. (2020)[80]	N	N	NA	NA	NA	N	Y	High
Sheffer et al. (2018)[79]	PN	N	NA	NA	NA	Y	NA	Low
Trojak et al. (2015)[81]	N	N	NA	NA	NA	N	NI	High
Zangen et al. (2021)[83]	N	N	NA	NA	NA	Y	NA	Low

Abbreviations: N = no; NA = not applicable; PN = probably no; PY = probably yes; Y = yes.

Table E-23. Risk of Bias for Randomized Controlled Trials for Smoking Cessation—Missing Outcome Data

Author (Year)	Were outcome data available for all, or nearly all, participants randomized?	Is there evidence that result was not biased by missing outcome data?	Could missingness in the outcome depend on its true value?	Is it likely that missingness in the outcome depended on its true value?	Risk of bias arising from missing outcome data
Dieler et al. (2014)[82]	N	PN	PY	PY	High
Li et al. (2020)[80]	N	PN	PY	Y	High
Sheffer et al. (2018)[79]	N	PY	NA	NA	Low
Trojak et al. (2015)[81]	N	PN	Y	PY	High
Zangen et al. (2021)[83]	N	PY	NA	NA	Low

Abbreviations: N = no; NA = not applicable; PN = probably no; PY = probably yes; Y = yes.

Table E-24. Risk of Bias for Randomized Controlled Trials for Smoking Cessation—Measurement of the Outcome

Author (Year)	Was the method of measuring the outcome inappropriate?	Could measurement or ascertainment of the outcome have differed between intervention groups?	Were outcome assessors aware of the intervention received by study participants?	Could assessment of the outcome have been influenced by knowledge of intervention received?	Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Risk of bias arising from measurement of the outcome
Dieler et al. (2014)[82]	PN	N	NI	PN	NA	Low
Li et al. (2020)[80]	N	N	NI	PN	NA	Low
Sheffer et al. (2018)[79]	N	N	N	NA	NA	Low
Trojak et al. (2015)[81]	N	N	N	NA	NA	Low
Zangen et al. (2021)[83]	N	N	N	NA	NA	Low

Abbreviations: N = no; NA = not applicable; NI = no information; PN = probably no; Y = yes.

Table E-25. Risk of Bias for Randomized Controlled Trials for Smoking Cessation—Selection of the Reported Result and Overall Risk-of-Bias Rating

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Dieler et al. (2014)[82]	PY	N	PN	Low	High	Large amount of missing data: 25% to 69%. Single imputation for all follow-up data points, assuming all missing values were equal to relapse. Possible that some in treatment group did not relapse, though authors did make most conservative assumptions to bias to the null.
Li et al. (2020)[80]	Y	PN	PY	Some concerns	High	Completers analysis and concerns about missing data.
Sheffer et al. (2018)[79]	NI	PN	PY	Some concerns	Some concerns	Baseline imbalance in FTND and willingness to engage in treatment, statistically significant; performed non a priori analyses for abstinence measures, no information on prespecified analysis plan

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Trojak et al. (2015)[81]	NI	PN	N	Some concerns	High	Concerns about complete case analysis, missing data, and reporting domain. Over 1/3 of participants dropped out by end of study, not clear how many participants lost at each step or reasons why they were lost to follow-up
Zangen et al. (2021)[83]	Y	PN	PN	Low	Low	

Abbreviations: FTND = Fagerstrom Test For Nicotine Dependence; N = no; NI = no information; PN = probably no; PY = probably yes; Y = yes.

Table E-26. Risk-of-Bias Ratings for Randomized Controlled Trials for SUD—Randomization Process

Author (Year)	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Did baseline differences between intervention groups suggest a problem with the randomization process?	Risk of bias arising from the randomization process
Belgers et al. (2022)[84]	Y	PN	N	Some concerns
Harel et al. (2021)[86]	NI	NI	N	Some concerns
Lolli et al. (2021)[88]	Y	Y	PN	Low
Martinotti et al. (2022)[85]	Y	Y	PN	Low
Perini et al. (2020)[87]	Y	Y	PY	Low
Schluter et al. (2019)[89]	Y	Y	PN	Low

Abbreviations: N = no; NI = no information; PN = probably no; PY = probably yes; SUD = substance use disorder; Y = yes.

Table E-27. Risk of Bias for Randomized Controlled Trials for SUD—Deviations From Intended Interventions

Author (Year)	Were the participants aware of their assigned intervention during the trial?	Were carers and people delivering the interventions aware of participants' assigned intervention during the trials?	Were there deviations from the intended intervention that arose because of the experimental process?	Were these deviations from intended intervention balanced between groups?	Were these deviations likely to have affected the outcome?	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Was there potential for a substantial impact of the failure to analyze participants in the group to which they were randomized?	Risk of bias arising from deviations from intended interventions
Belgers et al. (2022)[84]	N	Y	N	NA	NA	PY	NA	Low
Harel et al. (2021)[86]	N	N	NA	NA	NA	Y	NA	Low
Lolli et al. (2021)[88]	N	Y	N	NA	NA	NI	PN	Some concerns
Martinotti et al. (2022)[85]	N	Y	PN	NA	NA	N	PY	High
Perini et al. (2020)[87]	N	N	NA	NA	NA	PN	N	Some concerns
Schluter et al. (2019)[89]	PY	PY	PN	NA	NA	PY	NA	Some concerns

Abbreviations: N = no; NA = not applicable; PN = probably no; PY = probably yes; SUD = substance use disorder; Y = yes.

Table E-28. Risk of Bias for Randomized Controlled Trials for SUD—Missing Outcome Data

Author (Year)	Were outcome data available for all, or nearly all, participants randomized?	Is there evidence that result was not biased by missing outcome data?	Could missingness in the outcome depend on its true value?	Is it likely that missingness in the outcome depended on its true value?	Risk of bias arising from missing outcome data
Belgers et al. (2022)[84]	Y	NA	NA	NA	Low
Harel et al. (2021)[86]	N	PN	PY	PN	Some concerns
Lolli et al. (2021)[88]	N	PN	PY	PY	Some concerns
Martinotti et al. (2022)[85]	N	PN	NI	NI	High
Perini et al. (2020)[87]	PN	PN	PY	PN	Some concerns
Schluter et al. (2019)[89]	Y	NA	NA	NA	Low

Abbreviations: N = no; NA = not applicable; NI = no information; PN = probably no; PY = probably yes; SUD = substance use disorder; Y = yes.

Table E-29. Risk of Bias for Randomized Controlled Trials for SUD—Measurement of the Outcome

Author (Year)	Was the method of measuring the outcome inappropriate?	Could measurement or ascertainment of the outcome have differed between intervention groups?	Were outcome assessors aware of the intervention received by study participants?	Could assessment of the outcome have been influenced by knowledge of intervention received?	Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Risk of bias arising from measurement of the outcome
Belgers et al. (2022)[84]	N	N	Y	NI	PN	Some concerns
Harel et al. (2021)[86]	N	N	N	NA	NA	Low
Lolli et al. (2021)[88]	PN	N	N	NA	NA	Low
Martinotti et al. (2022)[85]	N	N	N	NA	NA	Low
Perini et al. (2020)[87]	N	N	N	NA	NA	Low
Schluter et al. (2019)[89]	N	PN	PY	PY	PN	Some concerns

Abbreviations: N = no; NA = not applicable; NI = no information; PN = probably no; PY = probably yes; SUD = substance use disorder.

Table E-30. Risk of Bias for Randomized Controlled Trials for SUD—Selection of the Reported Result and Overall Risk-of-Bias Rating

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Belgers et al. (2022)[84]	PY	Y	PN	High	High	Paper only reports data from 1-year follow-up, did not analzye and report interim time points when data were collected for alcohol outcome measurements
Harel et al. (2021)[86]	PY	PY	PN	Some concerns	Some concerns	Some concerns due to lack of information on allocation sequence randomization and concealment, missing data, and reporting domains.
Lolli et al. (2021)[88]	PY	N	N	Low	Some concerns	Some concerns for deviation from intervention domain: No information about method used for urine data from patients who dropped out but describes how urine sample collections were extremely erratic throughout the study in both arms. Some concerns for missing data domain: high dropout rate, patients with greater severity craving tended to dropout.
Martinotti et al. (2022)[85]	Y	N	N	Low	High	High attrition, no ITT analysis, no mention of analysis methods to correct for bias or sensitivity analyses, incomplete information on reasons for dropout

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall rating	Rationale/comments
Perini et al. (2020)[87]	Y	PN	PY	Some concerns	Some concerns	Some concerns for missing data, dropouts had higher AUDIT scores, no ITT or mITT analysis though unlikely to signficantly affect results, did not report all outcomes described in methods (CGI)
Schluter et al. (2019)[89]	PY	N	N	Low	Some concerns	Some concerns due to individuals guessing their treatment allocation correctly, significantly higher than the expected chance level. Self-reported outcome.

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test; CGI = Clinical Global Impression; ITT = intention-to-treat; mITT = modified intention-to-treat; N = no; PN = probably no; PY = probably yes; SUD = substance use disorder.

Table E-31. Quality of Health Economic Studies—Part I

Author (Year)	Was the study objective presented in a clear, specific, and measurable manner?	Were the perspective of the analysis (societal, third-party payer, and so on) and reasons for its selection stated?	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial-best, expert opinion-worst)?	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	Was uncertainty handled by (i) statistical analysis to address random events; (ii) sensitivity analysis to cover a range of assumptions?	Was incremental analysis performed between alternatives for resources and costs?	Was the methodology for data abstraction (including value health states and other benefits) stated?
Gregory et al. (2022)[35]	Yes	Yes	Yes	NA	Yes	Yes	Yes
Simpson et al. (2009)[73]	Yes	Yes	Yes	NA	Yes	Yes	Yes
Voigt et al. (2017)[74]	Yes	No	Yes	NA	Yes	Yes	Yes

Abbreviations: NA = not applicable.

Table E-32. Quality of Health Economic Studies—Part 2

Author (Year)	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 yr. discounted (3–5%) and justification given for the discount rate?	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	Was the primary outcome measure(s) for the economic evaluation clearly stated and were the major short-term, long-term, and negative outcomes included?	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear transparent manner?	Were the choice of economic model, main assumptions and limitations of the study stated and justified?
Gregory et al. (2022)[35]	No	Cannot determine	Yes	Yes	Yes	Yes
Simpson et al. (2009)[73]	Yes	Yes	Yes	Yes	Yes	No
Voigt et al. (2017)[74]	Yes	Yes	Yes	Yes	Yes	Yes

Table E-33. Quality of Health Economic Studies—Part 3

Author (Year)	Did the author(s) explicitly discuss direction and magnitude of potential biases?	Were the conclusions/recommendations of the study justified and based on the study results?	Was there a statement disclosing the source of funding for the study?	Total Score[a]/Total Modified Score
Gregory et al. (2022)[35]	Yes	Yes	Yes	84/85
Simpson et al. (2009)[73]	Yes	Yes	Yes	92/93
Voigt et al. (2017)[74]	Yes	Yes	Yes	95/96

Notes:
[a] Based on scale of 0 (worst quality) to 100 (best quality).