

02.01.46 Transcranial Magnetic Stimulation*



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Related Policies:

Summary

Description

Transcranial magnetic stimulation (TMS) is a noninvasive method of delivering electrical stimulation to the brain. The technique involves the placement of a small coil over the scalp and passing a rapidly alternating current through the coil wire. The electrical current produces a magnetic field that passes unimpeded through the scalp and bone and stimulates neuronal function. TMS is proposed for the treatment of treatment-resistant depression (TRD) and other psychiatric and neurologic disorders.

Summary of Evidence

Migraine Headaches

For individuals who have migraine headaches who receive transcranial magnetic stimulation (TMS), the evidence includes a systematic review (n=8 trials) and a sham controlled RCT of 201 patients conducted

for submission to the U.S. Food and Drug Administration (FDA) for clearance in 2013. Relevant outcomes are symptoms, functional outcomes, and quality of life. The systematic review found that TMS reduced migraine pain intensity and frequency compared to sham; it was unclear whether patients were receiving background pharmacotherapy. The trial results were limited by the 46% dropout rate and the use of a post hoc analysis. No recent studies have been identified with these devices. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Obsessive-Compulsive Disorder (OCD)

For individuals who have obsessive-compulsive disorder (OCD) who receive TMS, the evidence includes a number of small-to-moderate sized, sham-controlled, double-blind RCTs and meta-analyses of these studies. Relevant outcomes are symptoms, functional outcomes, and quality of life. A meta-analysis of 15 RCTs (N=483 patients, range 18 to 65 patients) conducted in 2016 found a benefit of TMS on patient-reported OCD symptom severity at time points ranging from 2 to 6 weeks, but there was substantial variability in the stimulation parameters, including the cortical region that was stimulated and the frequency of stimulation. A meta-analysis conducted in 2021 included 26 RCTs. The primary analysis found a significant effect of TMS compared to sham on OCD symptoms, but the effect seemed to last only until 4 weeks after the last treatment. The RCT that was the basis of FDA clearance of deep TMS for treatment of OCD compared deep TMS to sham in 99 patients for 6 weeks, with an additional 4 weeks of follow-up as a secondary outcome. Using a modified intention-to-treat (ITT) analysis (n=94), there was a larger mean decrease from baseline (improvement) on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) score (the primary efficacy outcome) in the active treatment group (-6.0 points) than the sham group (-2.8 points), translating to a moderate effect size of 0.69. At 6 weeks, the response rate was 38.1% in the active treatment group compared to 11.1% in the sham group ($p=.003$), as measured by a 30% or greater increase in the YBOCS. The difference in the primary outcome measure between active and sham groups was not statistically significant in the ITT analysis. There was a benefit for TMS on clinician-reported measures of improvement, but no significant difference between groups on patient-reported disability and impairment. Additional trials with sufficient sample size and follow-up duration are needed to confirm these results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Schizophrenia

For individuals who have schizophrenia who receive TMS, the evidence includes a number of sham controlled, double-blind RCTs and meta-analyses of these studies. Relevant outcomes are symptoms, functional outcomes, and quality of life. Although some evidence suggests that applying TMS to the temporoparietal cortex may help with auditory hallucination and positive symptoms, there is insufficient evidence to support or disprove TMS use in the treatment of schizophrenia. In most instances, TMS was used as adjunctive therapy to conventional pharmacotherapy. In these studies, the number of enrolled individuals was small, and placebo effect could be a confounding factor. Larger sample sizes and homogeneous clinical variables have not been established. Additionally, studies did not show long term effects and have also shown high frequency TMS appears to be effective in auditory hallucinations. TMS at any frequency may be effective for negative symptoms of schizophrenia. The 2020 and 2021 meta-analyses were unable to support or refute the use of TMS for the treatment of auditory hallucinations (AH) in schizophrenia. Further randomized controlled studies with adequate power are needed to confirm the efficacy of TMS for the treatment of AH in schizophrenia. However, TMS appears to be associated with worsening of overall positive symptoms of schizophrenia. Further testing of this hypothesis is needed to refine the use, and parameters of TMS in individuals with psychosis. A 2019 meta-analysis that reviewed high frequency TMS as treatment for cognitive deficit in schizophrenia noted individuals who received high frequency TMS showed acute improvement in specific areas of cognition, specifically executive function and working memory in the short-term; and in working memory and language function in long-term, as compared to the sham. Due to limitations of this analysis, such as small sample size,

heterogeneity, a large number of different assessment scales, and the inclusion of a wide range of cognitive domain, there remains limited evidence of the efficacy of TMS on cognition. Further research is needed using larger sample sizes and rigorous study designs on the use of TMS for auditory hallucinations or negative symptoms of schizophrenia. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Miscellaneous Other Conditions

For individuals who have psychiatric, neurological disorders, or other conditions outside of depression, migraine, or obsessive-compulsive disorder including but not limited to chronic pain, fibromyalgia, generalized anxiety disorder, post-traumatic stress disorder, schizophrenia who receive TMS the evidence includes numerous small RCTs and meta-analyses of these randomized trials. Relevant outcomes are symptoms, functional outcomes, and quality of life. The trials included in the meta-analyses are typically small and of low methodologic quality. In addition, stimulation parameters have not been established, and trial results are heterogeneous. There are no large, high-quality trials for any of these conditions demonstrating efficacy or the durability of any treatment effects. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Newer Protocols of Transcranial Magnetic Stimulation (TMS)

For individuals who receive TMS outside of conventional and deep TMS protocols including but not limited to accelerated, high-dose additional courses of treatment, MRI-guided theta burst TMS, and the simultaneous/combination utilization of esketamine for the treatment of depression, the evidence includes RCTs, systematic reviews and meta-analyses. Relevant outcomes are symptoms, functional outcomes, and quality of life. There are no large, high-quality trials which have evaluated its simultaneous/combination utilization with TMS. Additional, well powered, high-quality studies are needed to support the durability, potential benefits, and the long-term effects of this therapy. Stimulation parameters have not been established and varied greatly in identified eligible studies, and trial results are often heterogeneous. There are no large, high-quality trials for any of these protocols demonstrating efficacy or the durability of any treatment effects. The evidence is insufficient in determining the effects of the technology on net health outcomes.

Additional Information

None

OBJECTIVE

The objective of this evidence review is to evaluate whether the use of transcranial magnetic stimulation (TMS) of the brain improves the net health outcome for individuals with various conditions.

PRIOR APPROVAL

Prior approval is required.

POLICY

Note: For medical necessity clinical coverage criteria using InterQual® criteria related to Transcranial Magnetic Stimulation, refer to the [Wellmark Authorization Table](#).

Transcranial Magnetic Stimulation (TMS) for Conditions Outside of Major Depression

Transcranial magnetic stimulation (TMS) is considered **investigational** for all conditions outside of major depressive disorder (MDD) including, but not limited to the following because the evidence is insufficient to determine the technology results in an improvement in the net health outcomes:

- Anxiety
- Bipolar disorder
- Chronic pain
- Fibromyalgia
- Migraine headaches
- Obsessive-compulsive disorder
- Posttraumatic stress disorder
- Schizophrenia

Investigational Types/Protocols of Transcranial Magnetic Stimulation (TMS)

The following types and protocols of transcranial magnetic stimulation (TMS) are considered **investigational** including, but not limited to the following because the evidence is insufficient to determine the technology results in an improvement in the net health outcomes:

- Accelerated TMS
- Accelerated Theta Burst TMS (i.e. SNT Protocol)
- High dose TMS
- MRI-guided theta burst TMS
- Simultaneous/Combination utilization of esketamine with TMS (see [Policy Guidelines](#))

POLICY GUIDELINES

Transcranial magnetic stimulation (TMS) should be performed using a U.S. Food and Drug Administration cleared device in appropriately selected individuals, by health care professionals who are adequately trained and experienced in the specific techniques used.

A variety of TMS modalities have been developed, which differ on parameters including stimulation intensity, frequency, pattern, and site of the brain stimulation.

Conventional TMS

In conventional TMS, high frequency stimulation is delivered over the left dorsolateral prefrontal cortex (DLPFC) or low frequency stimulation over the right DLPFC. In bilateral TMS, both procedures are performed in the same session.

A treatment course of conventional TMS usually does not exceed 5 days a week for 6 weeks (total of 30 sessions), or a treatment course of conventional TMS for 5 days a week for 6 weeks (total of 30 sessions), followed by a 3-week taper of 3 TMS treatments in week 1, 2 TMS treatments the next week, and 1 TMS treatment in the last week. The treatment plan can be individualized depending on the type of device used, safety and side effect considerations and response to treatment.

Deep TMS

Deep TMS employs an H-coil helmet designed to encompass a broader surface area and stimulate deeper brain structures than conventional TMS. An example of a typical course of a deep TMS *planning* and *treatment* sessions could be a total of 44 sessions.

Simultaneous/Combination Treatment with TMS + Esketamine

The policy does not currently include administration specific to simultaneous/combo treatment with TMS + esketamine. However, as the simultaneous/combo treatment with TMS + esketamine does not currently meet Wellmark technology assessment criteria, nor is there any definitive guidance on the optimum regimen for this combination therapy or is it widely recognized as a generally accepted standard of medical practice, it is considered investigational.

Theta Burst

Theta burst stimulation is administered at lower intensities and at shorter intervals than conventional TMS.

Theta burst stimulation may be administered using an accelerated protocol. One example of an accelerated theta burst protocol, described by Cole et al., is the Stanford Neuromodulation Therapy (SNT) protocol.

- *“Our protocol, previously referred to as Stanford accelerated intelligent neuromodulation therapy (SAINT) and now entitled Stanford neuromodulation therapy (SNT), includes 1) an efficient form of rTMS, termed intermittent theta-burst stimulation (iTBS) (14); 2) treatment with multiple iTBS sessions per day at optimally spaced intervals (15–18); 3) application of a higher overall pulse dose of stimulation (19, 20); and 4) personalized targeting for application of the stimulation of the left DLPFC to subgenual anterior cingulate cortex (sgACC) circuit.”*

Coding

See the [Codes table](#) for details.

BACKGROUND

Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS), introduced in 1985 as a new method of noninvasive stimulation of the brain, involves placement of a small coil over the scalp, passing a rapidly alternating current through the coil wire, which produces a magnetic field that passes unimpeded through the scalp and bone, resulting in electrical stimulation of the cortex. Transcranial magnetic stimulation was initially used to investigate nerve conduction (e.g., TMS over the motor cortex will produce a contralateral muscular-evoked potential). The motor threshold, which is the minimum intensity of stimulation required to induce a motor response, is empirically determined for each person by localizing the site on the scalp for optimal stimulation of a hand muscle, then gradually increasing the intensity of stimulation. Interest in the use of TMS as a treatment for depression was augmented by the development of a device that could deliver rapid, repetitive stimulation. Imaging studies had shown a decrease in the activity of the left dorsolateral prefrontal cortex in depressed patients, and early studies suggested that high-frequency (e.g., 5 to 10 Hz) TMS of the left dorsolateral prefrontal cortex had antidepressant effects. In contrast to electroconvulsive therapy (ECT), TMS does not require general anesthesia and does not generally induce a convulsion. Repetitive TMS (rTMS) is also being tested as a treatment for a variety of other psychiatric and neurologic disorders.

Conventional TMS delivers repeated electromagnetic pulses to induce prolonged modulation of neural activity, typically applied over the dorsolateral prefrontal cortex. High-frequency rTMS (usually ≥ 10 Hz) induces an increase in neural activity whereas low-frequency TMS (usually ≤ 1 Hz) has the opposite effect. If both procedures are performed in the same session, the intervention is described as bilateral rTMS.

A variety of TMS modalities have been developed, which differ on parameters including stimulation intensity, frequency, pattern, and site of the brain stimulation. Deep TMS employs an H-coil helmet design to encompass a broader surface area and stimulate deeper brain structures than conventional TMS. Theta burst stimulation is administered at lower intensities and shorter intervals than conventional rTMS.

Table 1. Transcranial Magnetic Stimulation (TMS) Types

Type	Definition
Accelerated	Proposes an accelerated treatment schedule, using multiple sessions per day for fewer weeks duration.
Bilateral	Combines high frequency stimulation of the left dorsolateral prefrontal cortex (DLPC) with low frequency stimulation of the right DLPC (either simultaneously or sequentially) each session.
Conventional (Repetitive)	High frequency stimulation is delivered over the left dorsolateral prefrontal cortex (DLPFC) or low frequency stimulation over the right DLPFC. A treatment course of conventional TMS should not exceed 5 days a week for 6 weeks (total of 30 sessions), followed by a 3-week taper of 3 TMS treatments in week 1, 2 TMS treatments the next week, and 1 TMS treatment in the last week.
Deep	Deep TMS employs an H-coil helmet designed to encompass a broader surface area and stimulate deeper brain structures than conventional TMS.
High dose	Delivers more pulses than usual over the same treatment time frame (e.g., 6000 pulses per session instead of 3000).
MRI-Guided Theta Bust	MRI-Guided Theta burst stimulation differs from standard theta burst stimulation because it utilizes MRI scans to pinpoint and precisely target specific areas of the brain to stimulate thus theorized to maximize the efficacy of treatment. MRI-guided theta burst stimulation or TMS is also called connectivity-guided theta burst stimulation or TMS.
Theta	Theta burst stimulation is administered at lower intensities and at shorter intervals than conventional TMS. Theta burst stimulation may be administered using an accelerated protocol. One example of an accelerated theta burst protocol is the Stanford Neuromodulation Therapy (SNT) protocol, consisting of multiple high pulse dose applications per day that is personalized for the stimulation of the left DLPFC to subgenual anterior cingulate cortex (sgACC) circuit.

Regulatory Status

Devices for transcranial stimulation have been cleared for marketing by the U.S. Food and Drug Administration (FDA) receiving clearance (FDA Product Code: GWF).

Indications were expanded to include treating pain associated with certain migraine headaches in 2013, and obsessive-compulsive disorder in 2018.

In 2014, eNeura Therapeutics received 510(k) marketing clearance for the SpringTMS® for the treatment of migraine headaches. The device differs from the predicate Cerena™ TMS device with the addition of an LCD screen, a use authorization feature, a lithium battery pack, and a smaller size. The stimulation parameters are unchanged. The sTMS Mini (eNeura Therapeutics) received marketing clearance by the FDA in 2016. FDA product code: OKP.

In August 2018, the Deep TMS System (Brainsway) was granted a de novo 510(k) classification by the FDA as an adjunct for the treatment of adult patients with obsessive-compulsive disorder. The new classification applies to this device and substantially equivalent devices of this generic type.

The NeoPulse, now known as NeuroStar® TMS, was granted a de novo 510(k) classification by the FDA in 2008. The de novo 510(k) review process allows novel products with moderate or low-risk profiles and without predicates, which would ordinarily require premarket approval as a class III device, to be down-classified in an expedited manner and brought to market with a special control as a class II device.

In March 2024, the FDA approved the NeuroStar Advanced Therapy “as an adjunct for the treatment of Major Depressive Disorder (MDD) in adolescent patients (15-21)”. The approval was based on a noncomparative retrospective pre-post analysis of data from 1,169 adolescents (age 12-21) from the TrakStar registry, all of whom received standard NeuroStar treatment.

In 2014, the Cerena™ TMS device (eNeura Therapeutics) was granted a de novo 510(k) classification by the FDA for the acute treatment of pain associated with migraine headache with aura. Warnings, precautions, and contraindications include the following:

- The device is only intended for patients experiencing the onset of pain associated with a migraine headache with aura.
- The device should not be used:
 - on headaches due to underlying pathology or trauma.
 - for medication overuse headaches.
- The device has not been demonstrated as safe and/or effective:
 - when treating cluster headache or a chronic migraine headache.
 - when treating during the aura phase.
 - in relieving the associated symptoms of a migraine (photophobia, phonophobia, and nausea).
 - in pregnant women, children under the age of 18, and adults over the age of 65.

The FDA has cleared multiple rTMS systems for adjunctive treatment of major depressive disorder in adolescents aged 15 to 21, including the NeuroStar Advanced Therapy System (K231926), the Magstim Horizon (K243869), and the MagVenture (K251125) stimulators.

The Table below lists some devices that are FDA cleared for migraine headache pain (Product Code: OKP) and obsessive-compulsive disorder (Product Code: QCI). Please note that the table below is not intended to be a comprehensive list.

Table 2. FDA Approved TMS Devices for Migraine Headaches and Obsessive-Compulsive Disorder

Device	Manufacturer	Indication	FDA Clearance No.	FDA Clearance Date
MagVenture TMS Therapy System	Tonica Elektronik	Major depressive disorder and obsessive-compulsive disorder	K193006	08/09/2020
Ultimate rTMS for OCD (M-series)	Brain Ultimate, Inc.	Major depressive disorder and obsessive-compulsive disorder	K230735	09/13/2023
CloudTMS Edge for OCD	TeleEMG, LLC	Obsessive-Compulsive Disorder	K233742	12/22/2023
Savi Dual™ Migraine Therapy	ENeura	Migraine (acute and prophylactic treatment in individuals ≥ 12 years of age)	K230358	05/16/2023
Horizon 3.0 TMS Therapy System	Magstim	Major depressive disorder and obsessive-compulsive disorder	K222171	01/13/2023
ALTMS Magnetic Stimulation Therapy System	REMEDI Co., Ltd	Major depressive disorder	K220625	04/06/2022
Neurostar	Neuronetics	Major Depressive Disorder	K083538	12/16/2008
		Obsessive-Compulsive Disorder	K212289	05/06/2022
Brainsway Deep TMS System	Brainsway	Major Depressive Disorder	K122288	01/07/2013
		Obsessive-Compulsive Disorder	K183303	03/08/2019
Springtms Total Migraine System	Eneura	Migraine headache with aura	K140094	05/21/2014

Device	Manufacturer	Indication	FDA Clearance No.	FDA Clearance Date
Rapid Therapy System	Magstim	Major Depressive Disorder	K143531	05/08/2015
Magvita	Tonica Elektronik	Major Depressive Disorder	K150641	07/31/2015
Mag Vita TMS Therapy System w/Theta Burst Stimulation	Tonica Elektronik	Major Depressive Disorder	K173620	8/14/2018
Neurosoft	TeleEMG	Major Depressive Disorder	K160309	12/22/2016
Horizon	Magstim	Major Depressive Disorder	K171051	09/13/2017
Horizon TMS Therapy System (Theta Burst Protocol)	Magstim	Major Depressive Disorder	K182853	03/15/2019
Nexstim	Nexstim	Major Depressive Disorder	K171902	11/10/2017
Apollo	Mag & More	Major Depressive Disorder	K180313	05/04/2018

RATIONALE

This evidence review was created in January 2012 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through December 2025.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will

be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Migraine Headache

Clinical Context and Therapy Purpose

The purpose of TMS is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with migraine headache pain.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with migraine headaches.

Interventions

The therapy being considered is transcranial magnetic stimulation (TMS).

Comparators

The following therapies are currently being used to treat migraine headache pain: pharmacotherapy (e.g., triptans, ibuprofen, combination analgesics)

Outcomes

The general outcomes of interest are reductions in symptoms and improvements in quality of life and functional outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Saltychev et al (2022) conducted a systematic review and meta-analysis of 8 RCTs that compared rTMS to sham stimulation in patients with migraine. All RCTs used high frequency rTMS to the left dorsolateral prefrontal cortex and all studies except 1 included patients with chronic migraine. All studies except 1 had a low risk of bias and the risk of publication bias was nonsignificant. Results for the frequency of migraine days per month and the intensity of migraine pain both favored rTMS; however, the authors stated that the difference in migraine pain intensity was clinically insignificant. The analysis is summarized in the tables below.

Table 3. Systematic Review & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Saltychev et al (2022)	2004-2021	8	Adults with migraine	339 (11 to 100)	RCTs	3 to 12 rTMS sessions over 3 days to 8 weeks

Table 4. Systematic Review & Meta-Analysis Results

Study	Migraine days per month	Migraine pain (scale of 0 to 100)
Saltychev et al (2022)		
N=339	N=339	N=257
Difference (95% CI)	-8.09 (-11.4 to -4.79)	-13.56 (-21.8 to -5.32)
I^2	$I^2=87\%$	$I^2=86\%$

CI: confidence interval

Randomized Controlled Trial

A pivotal randomized, double-blind, multicenter, sham-controlled trial was performed with the Cerena TMS device to demonstrate the safety and effectiveness of a de novo application. Enrolled in the trial were 201 patients with a history of an aura preceding more than 30% of headaches of moderate or severe severity for approximately 90% of migraine attacks. Following a month-long baseline phase to establish the frequency and severity of the migraine, patients were randomized to a treatment phase consisting of 3 treatments or 3 months, whichever occurred first. Patients were instructed to treat their migraine headache during the aura phase and to record their pain severity (0 to 3), severity of associated migraine symptoms (photophobia, phonophobia, nausea), presence of vomiting, and use of rescue medications at the time of treatment and at 1, 2, 24, and 48 hours after treatment. The primary endpoint was the proportion of patients who were pain-free 2 hours after treatment. Of the 201 patients enrolled, 164 recorded at least 1 treatment and 113 recorded at least 1 treatment when there was pain. Post hoc analysis of these 113 patients showed a benefit of the device for the primary endpoint (37.74% pain free after 2 hours for Cerena vs. 16.67% for sham; $p=.018$) and for the proportion of subjects who were pain free after 24 hours (33.96% for Cerena vs. 10% for sham; $p=.002$). Active treatment was not inferior to sham for the proportion of subjects free of photophobia, suggesting that the device does not worsen photophobia. However, the device was not inferior to sham for the proportion of subjects free of nausea and phonophobia.

Section Summary: Migraine Headache

The available evidence on the use of TMS devices to treat migraine include a systematic review and a pivotal RCT. The systematic review found that TMS reduced migraine pain and intensity compared to sham. The results of the pivotal trial were limited by the 46% dropout rate and post hoc analysis. According to the FDA labeling, the device has not been demonstrated as safe or effective when treating cluster headache, chronic migraine headache, or migraine headache during the aura phase. The device has not been demonstrated to be as effective in relieving the associated symptoms of migraine (photophobia, phonophobia, nausea).

Obsessive-Compulsive Disorder (OCD)

Clinical Context and Therapy Purpose

The purpose of TMS is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with obsessive-compulsive disorder (OCD).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with OCD.

OCD is characterized by the inability to suppress intrusive thoughts, impulses, images, and repetitive motor responses.

Interventions

The therapy being considered is transcranial magnetic stimulation (TMS).

The use of TMS for individuals with OCD is based on the observation that OCD symptoms are associated with excessive activity in certain cortical areas. Transcranial magnetic stimulation is proposed as a treatment to modulate these brain areas.

Comparators

The following therapies are currently being used to treat OCD: pharmacotherapy, psychological, and behavioral therapy.

Outcomes

The general outcomes of interest are reductions in symptoms and improvements in quality of life and functional outcomes.

The Yale-Brown Obsessive-Compulsive Scale (YBOCS) is a clinician-rated, 10-item scale commonly used to assess the severity of symptoms in OCD. Each item is rated from 0 (no symptoms) to 4 (extreme symptoms) (total range, 0 to 40), with separate subtotals for the severity of obsessions and compulsions.

YBOCS scores of 0 to 13 correspond to 'mild symptoms' on the Clinical Global Impression of Severity (CGI-Severity=0 to 2), 14 to 25 with 'moderate symptoms' (CGI-Severity=3), 26 to 34 with 'moderate-severe symptoms' (CGI-Severity=4) and 35 to 40 with 'severe symptoms' (CGI-Severity=5 to 6). An improvement of $\geq 35\%$ on the YBOCS is most predictive of treatment response.

Follow-up over months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Hayes Inc. published a Health Technology Assessment in 2019, that was last reviewed in 2022 for transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder in the adult population. Hayes provided two different ratings.

1. Hayes gave a “C” rating for the use of repetitive transcranial magnetic stimulation (rTMS) as an add-on therapy for obsessive-compulsive disorder (OCD) in adult individuals with an inadequate response to ≥ 1 prior treatments without contraindications to rTMS. According to Hayes a C rating indicates, “This Rating reflects a low-quality body of evidence that rTMS may improve clinical outcomes in patients with OCD. Considerable uncertainty remains regarding the effectiveness of rTMS versus sham or alternative treatments, the clinical significance of improvement with rTMS treatment, durability of benefit, optimal treatment parameters (i.e., high- versus low-frequency stimulation and choice of cortical target), and patient selection criteria.”
2. Hayes gave a “D²” rating for the second was for the use of rTMS as monotherapy for OCD in adults with inadequate response to ≥ 1 prior treatments without contraindications to rTMS which. a D² rating indicates, “the paucity of evidence related to this indication.”

A systematic review by Trevizol et al (2016) included 15 RCTs (N=483) that compared active with sham rTMS for OCD. All studies were sham-controlled and double-blind. The sample sizes in the trials ranged from 18 to 65 patients. Seven studies used low-frequency stimulation, and 8 studies used high-frequency stimulation. The cortical regions varied among the studies, targeting the supplementary motor area, orbitofrontal cortex, or left, right, or bilateral DLPFC. The researchers calculated the SMD for the primary outcome (YBOCS score). Response rates were not reported.

The pooled mean difference between groups on the YBOCS was 2.94 (95% CI, 1.26 to 4.62), translating to a small to moderate effect size for active stimulation of 0.45 (95% CI, 0.20 to 0.71). Individual adverse effects were not assessed due to a lack of reporting in the primary studies, but there was no difference between groups in the dropout rate. Intervention protocols were heterogeneous across the studies, but regression analysis did not identify any treatment protocol or other variables as predictors of TMS response.

More recently, Liang et al (2021) conducted a systematic review and meta-analysis of different TMS modalities for the treatment of OCD. Three of the 5 protocols assessed were significantly more efficacious than sham TMS, and all treatment strategies were similar to sham TMS regarding tolerability (Table 6). Transcranial magnetic stimulation was not more effective than sham TMS, but there was direct evidence from only 1 RCT for this comparison (Carmi et al, 2019, discussed in the next section). The overall quality of the evidence was rated very low for efficacy and low for tolerability, and the reviewers concluded that high quality RCTs with low selection and performance bias are needed to further verify the efficacy of specific rTMS strategies for OCD treatment.

Perera et al (2021) conducted a systematic review and meta-analysis of rTMS in the treatment of OCD. All RCTs in the analysis (n=26) had a low risk of bias. A random effects model was used to compare pre- and post-stimulation YBOCS scores, with effect sizes reported as Hedges' *g*. The analysis found that rTMS had a significant effect on YBOCS scores compared to sham (effect size, 0.64; 95% CI, 0.39 to 0.89; $p < .0001$). Raw mean difference in YBOCS score between treatments was 4.04 (95% CI, 2.54 to 5.54; $p < .001$). The effect size was still significant when 2 dominant trials were removed. Effect sizes with rTMS appeared to be significant until 4 weeks after treatment, and low- and high-frequency rTMS had similar efficacy to each other. The authors performed several subgroup analyses (cortical target,

stimulation frequency, total pulses per session, total duration of treatment) but none of the effect sizes were significant between rTMS and sham.

Table 5. Systematic Review of Transcranial Magnetic Stimulation in Patients with Obsessive-Compulsive Disorder: Characteristics

Study	Dates	Trials Included	Participants	N (Range)	Design	Duration
Perera et al (2021)	Up to October 2020	26	Mean age, 33 years	781	RCT, sham-controlled	1 week to 6 weeks
Liang et al (2021)	Up to March 2020	22	Mean age, 34.1 years	698	RCT, sham- or active-controlled	1 week to 10 weeks
Trevizol et al (2016)	Up to March 2016	15	Mean age, 31.9 (SD, 7.6) years, 44.1% women	483 (18 to 65); mean, 16.1 (SD, 8.45)	RCT, sham-controlled	1 week to 6 weeks

OCD: obsessive-compulsive disorder; RCT: randomized controlled trial; SD: standard deviation.

Table 6. Systematic Review and Meta-Analysis: Results

Study	YBOCS Score	Dropouts
Perera et al (2021)		
Total N	781	781
	Mean difference (95% CI)	
Active rTMS	4.04 (2.54 to 5.54)	NR
	$I^2=62.06\%$; $p<.0001$	
Liang et al (2021)		
	Mean Difference (95% CrI)	OR (95% CrI)
Low frequency rTMS applied over the dorsolateral prefrontal cortex	6.34 (2.12 to 10.42)	0.81 (0.08 to 8.17)
High-frequency rTMS applied over the dorsolateral prefrontal cortex	3.75 (1.04 to 6.81)	1.08 (0.37 to 3.19)
Low-frequency rTMS applied over the supplementary motor area	4.18 (0.83 to 7.62)	0.98 (0.37 to 2.67)

Study	YBOCS Score	Dropouts
Low-frequency rTMS applied over the orbitofrontal cortex	4.43 (-2.57 to 11.31)	0.59 (0.06 to 5.68)
High-frequency rTMS applied over the anterior cingulate cortex/medial prefrontal cortex (deep TMS)	4.25 (-1.16 to 9.59)	1.62 (0.26 to 15.98)
Trevizol et al (2016)		
Total N	483	483
	SMD: 0.45 (0.20 to 0.71)	OR: 1.02 (0.76 to 1.36)
	$I^2=43\%$; $p=.039$	
	Mean Difference: 2.94 (1.26 to 4.62)	
	$I^2=58\%$; $p=.002$	

CI: confidence interval; CrI: credible interval; NR: not reported; OR: odds ratio; rTMS: repetitive transcranial magnetic stimulation; SMD: standardized mean difference; YBOCS: Yale-Brown Obsessive-Compulsive Scale.

Randomized Controlled Trials

This section discusses in detail the sham-controlled RCT of deep TMS for OCD conducted by Carmi et al (2019). The trial was submitted to the FDA as part of the de novo classification request, to establish a reasonable assurance of safety and effectiveness of the device. Study characteristics, results, and limitations are summarized in the tables below. A total of 99 patients were randomized to active treatment or sham. The primary outcome was the difference between groups in the mean change from baseline to 6 weeks on the YBOCS. Secondary outcomes included the response rate (defined as a 30% or greater improvement from baseline on the YBOCS), the Clinical Global Impression of Improvement (CGI-I), the Clinical Global Impression of Severity (CGI-S), and the Sheehan Disability Scale, a patient-reported measure of disability and impairment. Results at 10 weeks were also reported as secondary outcomes.

The primary efficacy analysis used a modified ITT analysis ($n=94$), excluding 5 patients who were found to not meet eligibility criteria following randomization. There was a greater decrease from baseline in the active treatment group (-6.0 points) than the sham group (-2.8 points), translating to a moderate effect size of 0.69. At 6 weeks, the response rate was 38.1% in the active treatment group compared to 11.1% in the sham group ($p=.003$). The FDA review provides data from the ITT analysis of the mean change in the YBOCS score ($n=99$). In the ITT data set, the YBOCS score decreased by -6.0 points (95% CI, -3.8 to -8.2) in the active group and by -4.1 points (95% CI, -1.9 to -6.2) in the sham group. Although the decreases were both statistically significant from baseline, the difference of 1.9 points between the treatment arms was not statistically significant ($p=.0988$). Results on the secondary outcomes were mixed. More patients in the active treatment group were considered improved based on the CGI-I and the CGI-S at 6 weeks, but there was no significant difference between groups on the Sheehan Disability Scale.

Table 7. Summary of Key Randomized Controlled Trial Characteristics - Transcranial Magnetic Stimulation for Individuals with Obsessive-Compulsive Disorder

Study; Trial	Countries	Sites	Dates	Participants	Interventions		Duration of follow-up
Carmi et al (2019) NCT02229903	U.S., Israel, Canada	11	2014-2017	N=99 adults ages 22 to 68 years, diagnosis of OCD as a primary disorder, receiving treatment in an outpatient setting, and having a YBOCS score ≥ 20 ; in maintenance treatment with a therapeutic dosage of a SRI for at least 2 months before randomization or, if they were not on an SRI, in maintenance treatment on CBT and have failed to respond adequately to at least 1 past trial of an SRI. Exclusions: primary axis I diagnosis other than OCD, severe neurological impairment, any condition associated with an increased risk of seizures.	Deep TMS 6-week treatment phase (consisting of 5 weeks of daily treatments 5 days a week and 4 treatments during the 6th week)	Sham	6 weeks (primary) 10 weeks (secondary)

CBT: cognitive behavioral therapy; OCD: obsessive-compulsive disorder; SRI: serotonin reuptake inhibitor; TMS: transcranial magnetic stimulation; YBOCS: Yale-Brown Obsessive-Compulsive Scale.

Study	YBOCS (Primary Outcome)	YBOCS Response	CGI-I	CGI-S (modified)	Sheehan Disability Scale	Adverse events (all)	Dropouts
Carmi et al (2019), NCT02229903	Mean change from baseline at 6 weeks	($\geq 30\%$ change from baseline to 6 weeks)	Moderate to very much improved from baseline				

Study	YBOCS (Primary Outcome)	YBOCS Response	CGI-I	CGI-S (modified)	Sheehan Disability Scale	Adverse events (all)	Dropouts
			at 6 weeks				
N analyzed	94	94	94	94			
TMS	-6.0 points (95% CI, 4.0 to 8.1)	38.1% (16/42)	20/41 (49%)	25/41 (61%)	-3.8 points (95% CI, -1.5 to -6.1)	73%	6/48 (12.5%)
Sham	-3.3 points (95% CI, 1.2 to 5.3)	11.1% (5/45)	9/43 (21%)	14/43 (32.6%)	-3.0 points (95% CI, -0.8 to -5.3)	69%	6/51 (12.0%)
Difference; P-value	2.8 points; p=.01 Effect size: 0.69	p=.003	p=.011	p=.022	NS (p-value not reported)	p=.639	NS (p-value not reported)

CGI-I: Clinical Global Impression of Improvement; CGI-S: Clinical Global Impression of Severity; CI: confidence interval; NS: non-significant; TMS: transcranial magnetic stimulation; YBOCS: Yale-Brown Obsessive-Compulsive Scale.

Table 8. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Carmi et al (2019) NCT02229903					1,2. 6 weeks (primary)

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 9. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Carmi et al (2019) NCT02229903				6. Modified ITT analysis of 94/100 patients who were enrolled. The difference in the primary outcome was not statistically significant in the ITT data set (n=99)		

ITT: intention-to-treat.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Obsessive-Compulsive Disorder

The evidence on rTMS for OCD includes a number of small-to-moderate sized, sham-controlled, double-blind randomized trials and meta-analyses of these RCTs. A meta-analysis of 15 RCTs (N=483 patients, range 18 to 65 patients) conducted in 2016 found a benefit of rTMS on patient-reported OCD symptom severity at time points ranging from 2 to 6 weeks, but there was substantial variability in the stimulation parameters, including the cortical region that was stimulated and the frequency of stimulation. The largest meta-analysis conducted in 2021 included 26 RCTs. Differences in pre- and posttreatment YBOCS scores were significantly improved with rTMS compared to sham, but the evidence was only sufficient to conclude that the effects lasted until 4 weeks after the last treatment. In a network meta-analysis that included both direct and indirect evidence, the authors did not find that deep TMS was more effective than sham rTMS. The RCT that was the basis of FDA clearance of deep TMS for treatment of OCD compared deep rTMS to sham in 99 patients for 6 weeks, with an additional 4 weeks of follow-up as a secondary outcome. Using a modified ITT analysis (n=94), there was a larger mean decrease from baseline (improvement) on the YBOCS score (the primary efficacy outcome) in the active treatment group (-6.0 points) than the sham group (-2.8 points), translating to a moderate effect size of 0.69. At 6 weeks, the response rate was 38.1% in the active treatment group compared to 11.1% in the sham group (p=.003), as measured by a 30% or greater increase in the YBOCS. The difference in the primary outcome measure between active and sham groups was not statistically significant in the ITT analysis. There was a benefit for rTMS on clinician-reported measures of improvement, but no significant difference between groups on patient-reported disability and impairment. Additional trials with sufficient sample size and follow-up duration are needed to confirm these results.

Miscellaneous Other Conditions

Clinical Context and Therapy Purpose

The purpose of TMS is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with psychiatric, neurologic disorders, or other conditions outside of migraine or OCD.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with psychiatric, neurologic disorders, or other conditions outside of migraine or OCD.

Interventions

The therapy being considered is transcranial magnetic stimulation (TMS).

Comparators

The following therapies are currently being used to treat psychiatric disorders other than depression or OCD: pharmacotherapy or psychological and behavioral therapy. The following therapies are currently being used to treat neurologic disorders other than migraine: pharmacotherapy and therapy as appropriate including either physical or occupational therapy.

Outcomes

The general outcomes of interest are reductions in symptoms and improvements in quality of life and functional outcomes.

Follow-up over months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Bipolar Disorder (BD)

Systematic Reviews

Hayes Inc. published a Health Technology Assessment on March 10, 2023, on repetitive transcranial magnetic stimulation for the treatment of bipolar disorder that was again reviewed in April 2025. The assessment provided a Hayes rating of D² indicating published evidence is insufficient to assess the safety and/or impact on health outcomes or patient management for the use of repetitive transcranial magnetic stimulation (rTMS) in adult patients with bipolar depression.

Konstantinou et al (2022) conducted a systematic review of 31 RCTs of rTMS for the treatment of bipolar disorder; meta-analysis was not performed. Most included studies were in the setting of bipolar depression (n=24). Only 8 studies had a low risk of bias. Overall, rTMS seems safe and well-tolerated but efficacy results are mixed and there is no consensus about the optimal rTMS regimen. The authors noted

limitations of the available literature including heterogeneity among studies, differences in sham treatments, and small sample sizes. They also stated that adequately powered sham-controlled studies are needed to verify the efficacy of rTMS in patients with bipolar disorder.

Tee et al (2020) conducted a systematic review and meta-analysis of sham controlled RCTs of rTMS for the treatment of bipolar disorder. Eight trials of rTMS in bipolar depression showed small but statistically significant improvements in depression scores compared to sham control (SMD, 0.302; $p < .05$). However, most studies had a high risk of bias, which could have exaggerated the treatment effects. The effect of rTMS was inconclusive in bipolar mania due to the high heterogeneity and limited number of controlled trials.

Chronic Pain

Systematic Reviews

A Cochrane review by O'Connell et al (2018) evaluating noninvasive brain stimulation techniques was first published in 2010 and was updated in 2014 and 2018. The reviewers identified 42 RCTs (range, 4 to 70 participants) on TMS for chronic pain. Meta-analysis of 27 rTMS studies versus sham (N=655 participants) for pain intensity at short-term follow-up (0 to < 1-week postintervention) demonstrated a small effect with heterogeneity (SMD, -0.22; 95% CI, -0.29 to -0.16, low-quality evidence). This equates to a 7% (95% CI, 5% to 9%) reduction in pain, or a 0.40 (95% CI, 0.53 to 0.32) point reduction on a 0 to 10 pain intensity scale, which did not meet the minimum clinically important difference threshold of 15% or greater. There is very low-quality evidence that single doses of high frequency rTMS of the motor cortex may have short-term effects on chronic pain and quality of life, but multiple sources of bias exist that may have influenced the observed effects. We did not find evidence that low frequency rTMS, rTMS applied to the DLPFC, and cranial electrotherapy stimulation are effective for reducing pain intensity in chronic pain.

Jiang et al (2022) conducted a systematic review and meta-analysis of 38 RCTs that assessed the analgesic effect of rTMS in 1338 patients with neuropathic pain. A single rTMS session was used in 13 studies and multiple sessions were used in the remaining 25 studies. The overall risk of bias in most studies was low or uncertain. According to a random effects analysis, rTMS was superior to sham therapy in reducing pain scores (effect size, -0.66; 95% CI, -0.87 to -0.46; $p < .001$; $I^2 = 78\%$). Beneficial effects of rTMS on pain were observed at 1 month ($p < .001$) and 2 months ($p = .01$). Low frequency rTMS (≤ 1 Hz) did not effectively reduce pain compared to higher frequency stimulation. The analysis did not find an increased risk of adverse events with rTMS compared to sham therapy. The authors concluded that larger, well-designed trials are needed to determine the long-term effect of rTMS in this setting. The broad conclusions of this review have not changed substantially for this update. There remains a need for substantially larger, rigorously designed studies, particularly of longer courses of stimulation. Future evidence may substantially impact upon the presented results. (First published in 2010 and was updated in 2014 and 2018.)

Fibromyalgia

Systematic Reviews

Ahmed et al (2025) included 43 RCTs (N=2120) in a network meta-analysis evaluating noninvasive brain stimulation for fibromyalgia. Low-frequency rTMS reduced pain intensity more than sham (SMD, -1.20; 95% CI -1.82 to -0.58), with high-frequency rTMS showing a smaller effect (SMD, -0.58; 95% CI -1.00 to -0.17). Low-frequency rTMS over the right dorsolateral prefrontal cortex (DLPFC) produced the most pronounced effects (SMD, -1.42; 95% CI -2.69 to -0.15) and maintained short-term improvements. High-frequency rTMS over the left primary motor cortex (M1) also reduced pain (SMD, -0.78; 95% CI -1.39 to -0.18). rTMS was well tolerated and achieved clinically meaningful pain reductions.

Su et al (2021) conducted a meta-analysis of 18 RCTs (N=643) with rTMS in patients with fibromyalgia. Reduction in disease influence according to the Fibromyalgia Impact Questionnaire showed a significant effect of rTMS (SMD, -0.7; 95% CI, -1.173 to -0.228). The effect of rTMS on disease influence, pain, depression, and anxiety lasted for at least 2 weeks after the last session. Older patients were most likely to experience reduced Fibromyalgia Impact Questionnaire scores. The authors concluded that larger RCTs are needed to confirm these findings.

Saltychev and Laimi (2017) published a meta-analysis of rTMS for the treatment of patients with fibromyalgia. The meta-analysis included 7 sham-controlled, double-blind trials with a low risk of bias. Trial sample sizes ranged from 18 to 54 patients. Five studies provided high-frequency stimulation to the left primary motor cortex, and the others were to the right or left DLPFC. The number of sessions ranged from 10 to 24, and follow-up ranged from immediately after treatment to 3 months posttreatment. In the pooled analysis, pain severity decreased after the last simulation by 1.2 points (95% CI, -1.7 to -0.8 points) on a 10-point numeric rating scale, while pain severity measured at 1 week to 1 month after the last simulation decreased by 0.7 points (95% CI, -1.0 to -0.3 points). Both were statistically significant, but not considered clinically significant, based on a minimal clinically important difference of 1.5 points.

Generalized Anxiety Disorder

Systematic Review

Qi et al (2024) included 7 RCTs (N=298) of rTMS for the treatment of generalized anxiety disorder in a systematic review and meta-analysis. Results showed that rTMS significantly reduced anxiety symptoms as measured by the Hamilton Anxiety Rating Scale (SMD, -1.17; 95% CI, -2.19 to -0.15). Response rates were higher in rTMS groups (RR, 0.61; 95% CI, 0.39 to 0.96), although remission did not reach statistical significance (RR, 0.73; 95% CI, 0.50 to 1.07). Headaches were more common in the intervention groups, but no differences in discontinuation were observed. The conclusions were limited by sample sizes and significant heterogeneity.

Cui et al (2019) included 21 studies (N=1481 patients) in a meta-analysis of rTMS plus drug therapy compared to drug therapy alone for the treatment of generalized anxiety disorder. Results of the analysis showed that rTMS improved anxiety symptoms as measured by the Hamilton Anxiety Scale (SMD, -0.68; 95% CI, -0.89 to -0.46). The conclusions that could be drawn from the body of evidence were limited by significant heterogeneity across studies, and the authors concluded that additional high-quality studies are needed to confirm the results.

Posttraumatic Stress Disorder (PTSD)

Systematic Review

Trevizol et al (2016) published a systematic review on the efficacy of low- and high-frequency rTMS for posttraumatic stress disorder. Five sham-controlled randomized trials (N=118 patients) were included. Most trials used stimulation of the right DLPFC, though some delivered rTMS to the left DLPFC or bilaterally. Three trials used high-frequency stimulation while 1 used low-frequency stimulation and another compared high- with low-frequency stimulation; the percent motor threshold ranged from 80% to 120%. Some trials provided rTMS in combination with a scripted narrative of the traumatic event, and different posttraumatic stress disorder scales were used. In a meta-analysis, active rTMS was found to be superior to sham (SMD, 0.74; 95% CI, 0.06 to 1.42), although heterogeneity across the trials was high.

Brown et al (2024) published a Cochrane systematic review of rTMS for posttraumatic stress disorder. The search was conducted through January 2023, and the authors identified 13 RCTs (N=577). Notably, 5 studies were conducted in the US, primarily enrolling white, male veterans. The authors found that rTMS

probably makes little to no difference on posttraumatic stress disorder severity immediately following treatment (SMD, -0.14; 95% CI, -0.54 to 0.27; 3 studies, 99 participants; moderate-certainty evidence); however, there was significant heterogeneity amongst the studies.

Schizophrenia (SZs)

Systematic Reviews

Blyth et al (2025) included 126 studies (N=4122 participants) in a meta-analysis of rTMS safety in schizophrenia. Results showed that active rTMS was associated with higher rates of headache or scalp pain, dizziness or syncope, facial twitching, and nausea compared to sham (p<.05). The prevalence of seizure was low (1.39 per 1000) and not different from sham or from the general population. No increased risk of cognitive impairment, worsening psychosis, depression, or mania was observed.

He et al (2017) published a meta-analysis of the effects of 1-Hz (low frequency) and 10-Hz (high frequency) rTMS for auditory hallucinations and negative symptoms of schizophrenia, respectively. For 1-Hz rTMS, 13 studies were included. Compared with sham, the rTMS group showed greater improvement in auditory hallucinations (SMD, -0.29; 95% CI, -0.57 to -0.01). However, significant heterogeneity across the studies was found (p=.06). In the 7 studies using 10-Hz rTMS, the overall effect size for improvement in negative symptoms was -0.41 (95% CI, -1.16 to -0.35); again, there was significant heterogeneity across studies (p<.001). The review was further limited by the small number of articles included and by the lack of original data for some studies.

A Cochrane review by Dougall et al (2015) selected 41 studies (N=1473 participants). Based on very low-quality evidence, there was a significant benefit of low- and high-frequency temporoparietal TMS compared with sham for the global state (7 RCTs) and positive symptoms (5 RCTs). For prefrontal rTMS compared with sham, the evidence on global and cognitive state was of very low-quality and equivocal. Reviewers concluded that the evidence was insufficient to support or refute the use of TMS to treat symptoms of schizophrenia and, although some evidence suggested that temporoparietal TMS might improve certain symptoms (e.g., auditory hallucinations, positive symptoms of schizophrenia), the results were not sufficiently robust to provide certainty.

Randomized Controlled Trials

Several additional small, single center RCTs of rTMS for the treatment of schizophrenia have been published since the systematic reviews described above. These studies were limited by their small sample sizes, very high loss to follow-up, and inadequate duration of follow-up (see tables below). Due to these limitations, these studies do not provide sufficient evidence to draw conclusions about the effectiveness of the technology in patients with schizophrenia.

Table 10. Summary of Key Randomized Controlled Trial Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions ¹		Duration of follow- up
					Active	Comparator	

Study; Trial	Countries	Sites	Dates	Participants	Interventions ¹		Duration of follow- up
Ye et al (2024)	China	1	2016- 2019	Inpatient male veterans diagnosed with schizophrenia per DSM-V criteria who were clinically stable on antipsychotic therapy ≥ 24 weeks (N=84 randomized)	Neuronavigation-guided high-frequency rTMS over left DLPFC: 10 Hz (1200 pulses per session) or 20 Hz (1600 pulses per session) administered 5 times a week (Monday to Friday) for 6 weeks (n=56 total; 28 per group)	Sham rTMS (n=28)	24 weeks
Hua et al (2024)	China	1	2016- 2021	Adults ages 18 to 60 diagnosed with schizophrenia per DSM-IV criteria and medication-resistant auditory verbal hallucinations who were clinically stable on antipsychotic therapy ≥ 2 weeks (N=66 randomized; 62 completed)	Imaging-navigated rTMS over left temporoparietal junction administered as 3 sessions per day for 14 consecutive days (n=32)	Sham rTMS (n=30)	6 weeks
Xiu et al (2024)	China	1	Not reported	Adults diagnosed with schizophrenia per DSM-IV criteria and persistent daily auditory verbal hallucinations despite ≥ 2 antipsychotics	Neuronavigation-guided high-frequency rTMS over left DLPFC: 10 Hz (1,200 pulses per session) or 20 Hz (1,600 pulses per session) administered 5	Sham rTMS (n=25)	32 weeks

Study; Trial	Countries	Sites	Dates	Participants	Interventions ¹		Duration of follow- up
				(N=120 randomized; 89 completed)	times a week (Monday–Friday) for 8 weeks. (n=80; 40 in each group)		
Zhu et al (2021)	China	7	2017- 2018	Inpatients ages 18 to 50 years with a diagnosis of schizophrenia per ICD-10 criteria who were right- handed and clinically stable for the past 3 months (N=32)	Intermittent theta burst stimulation over the cerebellum (3 pulses at 50 Hz repeated at a rate of 5 Hz for a total of 600 pulses administered 5 times a week (Monday to Friday) for 2 weeks (N=32)	Sham intermittent theta burst stimulation (N=	24 weeks
Guan et al (2020)	China	1	Not reported	Male patients ages 20 to 60 years with a DSM-IV diagnosis of schizophrenia and ≥5-year duration of illness.	20 Hz stimulus on left DLPFC 40 sessions, administered 5 times a week (Monday to Friday) for 8 weeks (N=28)	Sham rTMS (N=28)	8 weeks
Kumar et al (2020)	India	1	Not reported	Patients who were right- handed, clinically diagnosed as having schizophrenia as per ICD-10 criteria for at least 1 year; on stable doses of medicines (if	Active rTMS: 20 sessions of high frequency rTMS per day (5 consecutive sessions per week for 4 weeks) at 20 Hz frequency (N=50)	Sham rTMS (N=50)	4 months

Study; Trial	Countries	Sites	Dates	Participants	Interventions ¹		Duration of follow- up
				receiving) for the last 4 weeks, but continued to have significant negative symptoms. Excluded patients who had received rTMS treatment in the past for a similar condition, comorbid ICD-10 Axis I diagnosis, or Axis II Personality Disorder or any other exclusion criteria common to every TMS protocol.			
Zhuo et al (2019)	China	1	2013-2014	Adults ages 20 to 60 years with a DSM-IV diagnosis of schizophrenia; on a stable dose of antipsychotic medication for at least 1 month before study enrollment. Exclusions: DSM-IV-TR axis I disorder other than schizophrenia;	Active rTMS: 20 treatment sessions on consecutive weekdays. 20 Hz rTMS applied to the left DLPFC (N=35)	Sham rTMS (N=35)	4 weeks

Study; Trial	Countries	Sites	Dates	Participants	Interventions ¹		Duration of follow- up
				history of epilepsy or seizure; significant or unstable neurologic disorder; cardiac pacemaker; previous brain injury or surgery; any metal clips, plates, or other metal items in the head; or substance dependency; or ECT within 3 months.			

DLPFC: dorsolateral prefrontal cortex; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ECT: electroconvulsive therapy; ICD-10: International Classification of Disease, 10th edition; rTMS: repetitive transcranial magnetic stimulation.

Table 11. Summary of Key Randomized Controlled Trial Results

Study	Main Results
Ye et al (2024)	During the 6-week treatment, 20 Hz rTMS, but not 10 Hz, produced greater gains in immediate memory compared with the sham group ($p < .05$). By 24 weeks, both 10 Hz and 20 Hz rTMS showed benefits on immediate memory and RBANS total score ($p < .05$).
Hua et al (2024)	At 2 weeks, rTMS significantly reduced AHRS scores compared with sham (MD, 5.96; $p < .001$), and this effect was sustained through week 6 (MD, 7.89; $p < .001$). Individuals in the rTMS group also reported significantly better response rates, PANSS scores, and HAMD scores at both the 2-week and 6-week assessments ($p < .05$).
Xiu et al (2024)	Significant differences were observed in favor of the 20Hz and 10Hz groups for immediate memory, delayed memory, language, and RBANS total score

	compared to the sham control at 6-month follow-up ($p < .05$).
Zhu et al (2021)	At 2, 6, 12, and 24 weeks after the end of treatment, PANSS negative symptom scores were significantly lower in the rTMS group compared to the sham group ($p < .05$). The effect of treatment on positive symptoms and PANSS total scores was not significant.
Guan et al (2020)	At 2 weeks, 4 weeks, and 6 weeks, no significant differences in PANSS total score and sub scores between the sham and treatment groups. Immediate memory performance was higher in the rTMS group compared with the sham group at week 8 after covarying for education, age, and dose of drug. The improvement in immediate memory score was correlated with a decrease in the excitement factor score.
Kumar et al (2020)	Total SANS score was reduced significantly after the intervention in both the active (60.6 ± 11.75 to 43.9 ± 12.67 ; $p < .01$) and sham (61.5 ± 13.69 to 50.5 ± 14.11 ; $p < .01$) groups. Post-intervention scores were significantly lower among the subjects who received active rTMS as compared to those who received sham.
Zhuo et al (2019)	Significant decrease in negative symptoms but no significant improvement in cognition.

PANSS: Positive and Negative Syndrome Scale; rTMS: repetitive transcranial magnetic stimulation. SANS: Scale for Assessing Negative Symptoms in Schizophrenia.

Table 12. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Ye et al (2024)	4. Included inpatient men only				
Hua et al (2024)					1. 6 weeks not sufficient to show durability of effects
Xiu et al (2024)					

Zhu et al (2021)	4. Included inpatients only				
Guan et al (2020)	4. Included men only				1. 8 weeks not sufficient to show durability of effects
Kumar et al (2020)					
Zhuo et al (2019)					1. 4 weeks not sufficient to show durability of effects

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 13. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Ye et al (2024)				1. 25% of patients were lost to follow-up by 24 weeks	1. power calculation not reported	
Hua et al (2024)				1. 4 discontinued in active vs 12 in sham by follow-up (26% dropout differential)		
Xiu et al (2024)				1. 26% of patients were lost to follow-up by 32 weeks	1. power calculation not reported	
Zhu et al (2021)					1. power calculation not reported	

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Ye et al (2024)				1. 25% of patients were lost to follow-up by 24 weeks	1. power calculation not reported	
Hua et al (2024)				1. 4 discontinued in active vs 12 in sham by follow-up (26% dropout differential)		
Xiu et al (2024)				1. 26% of patients were lost to follow-up by 32 weeks	1. power calculation not reported	
Guan et al (2020)				1. 15/56 (26.8%) patients discontinued	1. power calculation not reported	
Kumar et al (2020)				1. 33% attrition (32% active and 38% sham)		
Zhuo et al (2019)				1. 10/70 discontinued (14.3%)	1. power calculation not reported	

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Miscellaneous Other Conditions

For individuals who have psychiatric disorders other than depression or OCD (e.g., anxiety disorder, posttraumatic stress disorder, schizophrenia) who receive rTMS, the evidence includes numerous small RCTs and meta-analyses of these studies. The trials included in the meta-analyses are typically small and of low methodologic quality. In addition, stimulation parameters have not been established, and trial results are heterogeneous. There are no large, high-quality trials for any of these conditions demonstrating efficacy or the durability of any treatment effects.

For individuals who have neurological conditions other than migraine (e.g., chronic pain, fibromyalgia and stroke) who receive rTMS, the evidence includes numerous small RCTs and meta-analyses of these

randomized trials. The trials included in the meta-analyses are typically small and of low methodologic quality. In addition, stimulation parameters have not been established, and trial results are heterogeneous. There are no large, high-quality trials for any of these conditions demonstrating efficacy or the durability of any treatment effects.

Newer Protocols of Transcranial Magnetic Stimulation (TMS)

Clinical Context and Therapy Purpose

The purpose of transcranial magnetic stimulation (TMS) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations

The relevant population of interest are individuals being treated with transcranial magnetic stimulation (TMS).

Individuals with TRD are actively managed by psychiatrists and other mental health professionals in an outpatient clinical setting.

Interventions

The therapy being considered is miscellaneous newer transcranial magnetic stimulation (TMS) (e.g., accelerated, high-dose, combination esketamine and TMS).

Conventional TMS

In conventional TMS, high frequency stimulation is delivered over the left dorsolateral prefrontal cortex (DLPFC) or low frequency stimulation over the right DLPFC. In bilateral TMS, both procedures are performed in the same session.

A treatment course of conventional TMS usually does not exceed 5 days a week for 6 weeks (total of 30 sessions), or a treatment course of conventional TMS for 5 days a week for 6 weeks (total of 30 sessions), followed by a 3-week taper of 3 TMS treatments in week 1, 2 TMS treatments the next week, and 1 TMS treatment in the last week. The treatment plan can be individualized depending on the type of device used, safety and side effect considerations and response to treatment.

Deep TMS

Deep TMS employs an H-coil helmet designed to encompass a broader surface area and stimulate deeper brain structures than conventional TMS. An example of a typical course of a deep TMS *planning* and *treatment* sessions could be a total of 44 sessions.

Comparators

The following therapies are currently being used to treat major depressive disorder: pharmacotherapy, psychological therapy, behavioral therapy, electroconvulsive therapy (ECT), conventional, repetitive and deep TMS.

Outcomes

The general outcomes of interest are reductions in symptoms and improvements in quality of life and functional outcomes. Follow-up over months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Accelerated Transcranial Magnetic Stimulation in the Treatment of Major Depressive Disorder

Systematic Reviews & Meta-Analysis

Shi et al (2024) included 10 reviews in their systematic review and meta-analysis on accelerated transcranial magnetic stimulation (aTMS) evaluating the efficacy and maintained long-term effects on individuals with MDD. The results did show reduced depression scores post aTMS “(SMD = 1.80, 95% CI (1.31, 2.30), $p < 0.00001$)”. Although there was a positive effect on depression scores directly after aTMS, scores at follow-up were lower based on the depression rating scale “(SMD = 0.22, 95% CI (0.06, 0.37), $p = 0.006$)” which raises questions about the long-term maintenance of aTMS. “At the end of treatment with the accelerated repetitive transcranial magnetic stimulation (arTMS) mode, depressive symptoms may continue to improve (SMD = 0.29, 95% CI (0.10, 0.49), $I^2 = 22\%$, $p = 0.003$), while the accelerated intermittent theta burst stimulation (aiTBS) mode only maintains posttreatment effects (SMD = 0.01, 95% CI (-0.45, 0.47), $I^2 = 66\%$, $p = 0.98$).” No remarkable difference in therapeutic effectiveness between aTMS and standard TMS (SMD = -0.67, 95% CI (-1.62, 0.27), $p = 0.16$). The studies included in this meta-analysis have short and inconsistent follow-up durations. Additional studies that include long-term outcomes are indicated.

Hayes published an Evolving Evidence Review in September 2022 for Accelerated Repetitive Transcranial Magnetic Stimulation for Treatment of Depression that was last reviewed in November of 2023. Their October 2022 search of PubMed and Embase identified 4 systematic reviews (Brunoni et al., 2017, Mutz et al., 2019, Sonmez et al., 2019 and Chen et al., 2020) and 5 clinical studies (Baeken et al., 2013; Fitzgerald et al., 2018; Modirrousta et al., 2018; Schulze et al., 2018; Kim et al., 2021). Of the systematic reviews 3 included meta-analysis that did not find a clear benefit utilizing accelerated rTMS over sham or rTMS treatment on depression severity, response, remission and safety. There was 1 systematic review with meta-analysis that reported accelerated rTMS reduced depression severity when compared to baseline. One systematic review with meta-analysis did not find that accelerated rTMS was superior when compared to TBS, electroconvulsive therapy (ECT), direct current stimulation (DCS), or magnetic seizure therapy (MST). For the 5 clinical studies 3 were considered RCTs; 1 good- and 2 poor-quality; 1 poor quality crossover RCT and 1 retrospective cohort study. These 5 studies did not provide statistically significant benefit for accelerated rTMS when compared to conventional rTMS or sham treatment. Depression severity decreased in comparison to baseline in 2 studies. Additionally, the rates for response and remission varied greatly (20.3% - 41.5% and 11.9% to 64.7). Lastly, the treatment protocols for accelerated TMS varied greatly (i.e., number of pulses and sessions daily, number of treatments per week and number of weeks total the treatment was given.) Ultimately Hayes concluded, “Evidence from clinical studies, systematic reviews, and policies and guidelines addressing accelerated repetitive transcranial magnetic stimulation (rTMS) suggest that the protocol is safe; however, there is not enough evidence to support it as a recommended treatment. Treatment parameters varied greatly in the eligible clinical studies, which may ultimately impact proponents’ claims that an accelerated treatment protocol would reduce patient burden.”

High - Dose Transcranial Magnetic Stimulation in the Treatment of Major Depressive Disorder

Meta-Analysis

Yu et al (2024) completed a random-effects meta-analysis and dose-response meta-analysis (DRMA) to examine antidepressant efficacy of rTMS and association with total pulses. It included 50 RCTs with 1280 individuals in the rTMS arms and 1214 in the sham groups. The DRMA model was bell-shaped ($R^2 = 0.42$) suggesting that > 26,660 total pulses (high dose) was not linked with additional improvement of depressive symptoms. When combining doses, “15-20 Hz rTMS was superior to 10 Hz rTMS (0.61, 0.15-1.10)”. Additional studies are indicated to investigate dosing parameters for high-dose TMS in the treatment of MDD.

Randomized Controlled Trials (RCTs)

Fitzgerald et al (2020) published a pragmatic RCT that explored the relationship between pulse number and response to repetitive transcranial magnetic stimulation treatment in depression. There were 300 individuals with TRD followed across 4-weeks who were treated with 50 trains of 10 Hz stimulation for a total of 125 trains per day. Response rates did not have any significant differences (standard right = 49.1%, high right = 48.4%; standard left = 52.5%, high left = 47.3%). QOL improvements were noted in all treatment groups. When illness duration was controlled, there was improved remission rates in the high left sided group compared to the moderate left sided group. Authors noted that the “de facto standard in clinical practice” since the FDA pivotal trial is 75 trains. This study cannot definitively validate that the 50 and 125 train protocols are not inferior to providing the de facto standard stimulation at 75 trains. Additionally, the dropout rate reduced the analytic power. Lastly there was no identified sham/placebo-controlled group. In this study, for all TMS doses provided, there was no consistent difference in the effect of rTMS and high dose rTMS.

Stanford Neuromodulation Therapy (SNT) (formerly Stanford accelerated intelligent neuromodulation therapy [SAINT])

Systematic Review

Lan et al (2023) published a systematic review evaluating studies of Stanford Neuromodulation Therapy (SNT) that used resting-state functional connectivity Magnetic Resonance Imaging (fcMRI) to target high-dose iTBS (10 sessions of iTBS daily, 18,000 pulses/day, 5 consecutive days, and 90,000 total pulses) for treatment-resistant depression. Reviewers reported conducting a “systematic search” through September 25, 2023, but did not describe their search strategy (e.g., details about which databases were searched or what search terms were used.) The RCT by Cole et al (2021) (n=29) and three single-arm noncomparative studies (n=34) were included. No meta-analyses were conducted. In the RCT, significantly higher rates of antidepressant response (71.4% versus 13.3%) and remission (57.1% versus 0%) were reported for active SNT compared with sham. Antidepressant response rates ranged from 83.3% to 90.5% in the single-arm prospective studies, while remission rates ranged from 66.7% to 90.5%. No severe adverse events were reported. Significant limitations noted by the authors included the small number of studies, limited sample sizes, lack of long-term follow-up data, and the absence of head-to-head comparisons with established treatments for treatment-resistant depression.

Randomized Controlled Trial

Cole et al (2021) published a randomized, double-blind, sham-controlled, single-center clinical trial evaluating an accelerated, high-dose, fcMRI-guided intermittent theta-burst stimulation protocol (Stanford Neuromodulation Therapy, SNT) for treatment-resistant major depressive disorder. At a planned interim analysis, 29 individuals met criteria and were randomized to active SNT (N=14) or sham stimulation (N=15). The mean age of participants ranged from 52 years in the sham group to 49 years in the active group, and all participants had persistent depressive symptoms despite prior adequate antidepressant treatment. The baseline mean Montgomery-Åsberg Depression Rating Scale (MADRS) score was 31 in

the active SNT group and 35 in the sham SNT group ($p=0.06$). The primary outcome was the MADRS score at 4 weeks, for which individuals receiving active SNT had a significantly greater reduction in depression severity compared to the sham group (52.5% mean improvement versus 11.1%, $p<.05$). Response was defined as a reduction of $\geq 50\%$ in the MADRS score, and remission was defined as MADRS score ≤ 10 . Rather than using the standard fixed-timepoint approach of measuring Response and Remission at the 4-week endpoint, participants were identified as responders or remitters if they met these specific criteria *at any point* during the 4-week follow-up. Using this method, 85.7% in the active SNT group and 26.7% in the sham group met response criteria at some point during the 4-week follow-up and 78.6% versus 13.3% met remission criteria. Adverse events were generally mild and not meaningfully different between groups. While this RCT provides an initial signal of potential benefit, important limitations raise caution in its interpretation, including the small sample size, the short-term follow-up, potential for response and remission effect overestimation from their use of a best-case outcome assessment approach, and use of a single center setting that may limit generalizability in routine clinical practice. Larger, fully powered trials with longer follow-up are needed to establish durability, reproducibility, and comparative effectiveness.

Single-Arm Open-Label Study

Cole et al (2020) conducted a single-arm, open-label study examining the preliminary efficacy and safety of SNT in individuals for treatment-resistant depression. In this study, the baseline mean MADRS was 34.86, and in the intent-to-treat analysis of all 22 enrolled participants, the remission rate (MADRS < 11) was 90.5% immediately following treatment (50 iTBS sessions at 1,800 pulses per session, 50-minute intersession intervals delivered as 10 daily sessions over 5 consecutive days at 90% resting motor threshold) and 60% maintained remission one-month following treatment.

Additionally, a retrospective exploratory analysis by Geoly et al (2025) that included 46 total participants from the 2021 RCT by Cole et al and the 2020 single-group, open-label study by Cole et al, found that of the overall 70% of participants who entered remission the week following treatment, only 47% remained in remission after 12 weeks.

MRI / Connectivity-Guided Transcranial Magnetic Stimulation in the Treatment of Miscellaneous Conditions

For MRI/connectivity-guided TMS there were no systematic reviews and only 1 published randomized controlled trial for major depressive disorder by Morriss was identified which is discussed below which was also the only RCT identified by Hayes, Inc.

Randomized Controlled Trial

Morriss et al (2024) published an RCT on the use of connectivity-guided intermittent theta burst versus repetitive transcranial magnetic stimulation for treatment-resistant depression. There were 128 individuals in the functional magnetic resonance imaging neuronavigated connectivity-guided intermittent theta burst stimulation (cgtTBS) group and 127 individuals in the rTMS group, all of whom were randomly assigned. Each participant had 20 sessions over 4-6 weeks. At baseline and at 16 weeks a functional resting-state MRI was completed. Results showed no difference in efficacy or safety between cgtTBS and rTMS in the Depression Rating Scale 17-item score ("intention-to-treat adjusted mean, -0.31 , 95% confidence interval (CI) -1.87 , 1.24 , $P = 0.689$ "). Limitations included TMS treatments were different in frequency and "intensity of stimulation (80% resting motor threshold (RMT) or 120% RMT) and approach to selection of treatment location (resting state effective connectivity versus structural MRI even though they" "were well matched for number of pulses per treatment session, session duration and number of sessions". Additional trials with sufficient sample size and longer-term follow-up duration are needed.

Simultaneous/Combination Utilization of Esketamine with Transcranial Magnetic Stimulation in the Treatment of Major Depressive Disorder

There were no RCTs that directly evaluated utilizing TMS used in combination with esketamine were identified that would determine improved long-term health outcomes such as change in disease status and morbid events.

Section Summary: Miscellaneous Newer Transcranial Magnetic Stimulation (TMS)

Protocols

For individuals who have MDD that receive miscellaneous newer TMS protocols the evidence includes RCTs, systematic reviews and meta-analyses. Stimulation parameters have not been established and varied greatly in identified studies, and trial results are often heterogeneous. There are no large, high-quality trials for any of these conditions demonstrating long-term efficacy or durability of treatment effects.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Psychiatric Association (APA)

Obsessive-Compulsive Disorder

The American Psychiatric Association's (2007, reaffirmed in 2012) guidelines on the Treatment of Patients with Obsessive-Compulsive Disorder indicated that "findings of the four published trials of rTMS are inconsistent, perhaps because the studies differed in design, stimulation sites, duration, and stimulation parameters. The available results and the technique's non-invasiveness and good tolerability should encourage future research, but the need for daily treatment may limit the use of TMS in practice."

Schizophrenia

The APA released practice guideline for the *Treatment of Patients with Schizophrenia* in 2020 that states, "Although studies have also been done with TMS for treatment of hallucinations and for treatment of negative symptoms, at present there is insufficient evidence of benefit to suggest use of TMS in individuals with schizophrenia."

International Neuromodulation Society/North American Neuromodulation Society

In 2020, an expert consensus panel from the International Neuromodulation Society-North American Neuromodulation Society performed a literature review and published recommendations for transcranial magnetic stimulation in the treatment of pain and headache. For neuropathic pain, the panel recommended transcranial magnetic stimulation to the primary motor cortex (high level evidence) or the left dorsolateral prefrontal cortex (F3 location) (at least moderate level evidence). For postoperative pain, the panel recommended that transcranial magnetic stimulation to the F3 location be only selectively offered due to at least moderate certainty that the net benefit is small. For primary headache, the panel only based 2 recommendations on moderate certainty evidence: single transcranial magnetic stimulation

for acute migraine and high frequency rTMS to the primary motor cortex for migraine prevention. For posttraumatic brain injury, high level evidence supported a recommendation for high-frequency transcranial magnetic stimulation to the primary motor cortex or the F3 location.

National Institute for Health and Care Excellence (NICE)

Auditory Hallucinations

In 2020 NICE provided guidance on the use of TMS stating for auditory hallucinations, the “evidence on the safety of transcranial magnetic stimulation for auditory hallucinations is adequate and 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.”

Migraine

In 2014, the NICE provided guidance on the use of rTMS for treating and preventing migraine. The guidance stated that evidence on the efficacy of TMS for the treatment of migraine was limited in quantity and for the prevention of migraine was limited in both quality and quantity. Evidence on its safety in the short- and medium-term was adequate, but there was uncertainty about the safety of long-term or frequent use of TMS.

Obsessive-Compulsive Disorder

In 2020, the NICE stated that rTMS has not demonstrated any major safety concerns for management of obsessive-compulsive disorder or auditory hallucinations, but evidence for both uses is lacking; therefore, NICE recommends that rTMS be used in patients with these conditions only in the context of research.

Veteran's Affairs/Department of Defense

The 2023 VA/DoD guideline for management of bipolar disorder states "for individuals with bipolar disorder who have demonstrated partial or no response to pharmacologic treatment for depressive symptoms, we suggest offering repetitive transcranial magnetic stimulation [rTMS] as an adjunctive treatment." However, the recommendation was rated as "weak" and the confidence in the evidence was very low. For the management of PTSD, the 2023 guideline found insufficient evidence for or against rTMS.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

REFERENCES

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcranial magnetic stimulation for depression. TEC Assessments. 2009;Volume 24:Tab 5.
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcranial magnetic stimulation for depression. TEC Assessments. 2011;Volume 26:Tab 3.
3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcranial magnetic stimulation for depression. TEC Assessments. 2013;Volume 28:Tab 9.
4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcranial magnetic stimulation for the treatment of schizophrenia. TEC Assessments. 2011;Volume 26:Tab 6.

5. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol Med* 2009; 39(1):65-75.
6. Picht T, Schulz J, Hama M, Schmidt S, Suess O, Vajkoczy P. Assessment of the influence of navigated transcranial magnetic stimulation on surgical planning for tumors in or near the motor cortex. *Neurosurgery*. 2012 May;70(5):1248-56.
7. Pollak TA, Nicholson TR, Edwards MJ, David AS. A systematic review of transcranial magnetic stimulation in the treatment of functional (conversion) neurological symptoms. *J Neurol Neurosurg Psychiatry*. 2013 Jan 8. [Epub ahead of print]
8. Marlow NM, Bonilha HS, Short EB. Efficacy of transcranial direct current stimulation and repetitive transcranial magnetic stimulation for treating fibromyalgia syndrome: A systematic review. *Pain PRact*. 2012 May 28. [Epub ahead of print]
9. Canadian Agency for Drugs and Technologies in Health. January 15, 2013. Repetitive Transcranial Magnetic Stimulation for Specific Patient Populations: Clinical and Cost Effectiveness and Safety
10. Kavirajan HC, Lueck K, Chuang K. Alternating current cranial electrotherapy stimulation (CES) for depression. *Cochrane Database Syst Rev*. Jul 8 2014;7:CD010521. PMID 25000907.
11. Barclay TH, Barclay RD. A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression. *J Affect Disord*. Aug 2014;164:171-177. PMID 24856571.
12. O'Connell NE, Wand BM, Marston L, et al. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev*. 2014;4:CD008208. PMID 24729198
13. Transcranial Magnetic Stimulation for the Treatment of Adults with PTSD, GAD or Depression: A Review of Clinical Effectiveness and Guidelines," *Canadian Agency for Drugs and Technologies in Health*, 2014; Rapid Response Report: Summary with Critical Appraisal.
14. Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: A systematic review and meta-analysis of randomized trials. *Depression and Anxiety*, 2013; 30:614-623.
15. B. Micallef-Trigona, "Comparing the Effects of Repetitive Transcranial Magnetic Stimulation and Electroconvulsive Therapy in the Treatment of Depression: A Systematic Review and Meta-Analysis," *Depression Research and Treatment*, Volume 2014, Article ID 135049, 8 pages, <http://dx.doi.org/10.1155/2014/135049>. Accessed November 26, 2025.
16. A. Sarker, R.C. Kadosh, "Transcranial Electrical Stimulation and Numerical Conditioning," *Can J Exp Psychol*. 2016 Mar;70(1):41-58. doi: 10.1037/cep0000064.
17. G. Grammer, A. Kuhle, C. Clark, M. Dretsch, K. Williams, J. Cole, "Severity of depression predicts remission rates using transcranial magnetic stimulation," *Frontiers in Psychiatry*, 2015; Volume 6 Article 114.
18. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials," *Health Quality Ontario*, Ontario Health Technology Assessment Series, 2016; Vol. 16, No. 5.
19. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: An Economic Analysis," *Health Quality Ontario*, Ontario Health Technology Assessment Series, 2016; Vol. 16, No. 6.

20. A. Mantovani, M. Pavlicova, D. Avery, A. et al., "Long-Term Efficacy of Repeated Daily Prefrontal Transcranial Magnetic Stimulation (TMS) In Treatment-Resistant Depression," *PsychiatryOnline*, Depression: Challenges and Treatments, 2016; Volume 14 Issue 2, pp. 277-282.
21. Mantovani, A, Pavlicova, M, Avery, D, et al. Long-Term Efficacy of Repeated Daily Prefrontal Transcranial Magnetic Stimulation (TMS) in Treatment-Resistant Depression. (2012) Depression and Anxiety, 00:1-8
22. Trevizol AP, Shiozawa P, Cook IA, et al. Transcranial magnetic stimulation for obsessive-compulsive disorder: an updated systematic review and meta-analysis. J ECT. Dec 2016;32(4):262-266. PMID 27327557
23. FDA clears brain stimulation device for OCD, Medscape FDA Approvals August 17, 2018. <https://www.medscape.com/viewarticle/900889>. Accessed November 26, 2025.
24. Butler M, Urosevic S, Desai P, et al. Treatment for bipolar disorder in adults: a systematic review. Comparative Effectiveness Review No. 208. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ). August 2018. Available at: [https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-208-bipolar_November 26, 2025.report.pdf](https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-208-bipolar_November%2026%2C%2025.report.pdf)
25. Trevizol AP, Barros MD, Silva PO, et al. (2016) Transcranial magnetic stimulation for posttraumatic stress disorder: an updated systematic review and meta-analysis. Trends Psychiatry Psychother. Jan-Mar 2016;38(1):50-55. PMID 27074341
26. Saltychev M, Laimi K.(2017) Effectiveness of repetitive transcranial magnetic stimulation in patients with fibromyalgia: a meta-analysis. Int J Rehabil Res. Mar 2017;40(1):11-18. PMID 27977465
27. Jahangard, L, Tayebi, M, Haghighi, M, Ahmadpanah, M, Holsboer-Trachsler, E, Sadeghi Bahmani, D, and Brand, S. Does rTMS on brain areas of mirror neurons lead to higher improvements on symptom severity and empathy compared to the rTMS standard procedure? – Results from a double-blind interventional study in individuals with major depressive disorders. Journal of Affective Disorders. 2019;257:527-535
28. Kito, S, Miyazi, M, Nakatani, H, et al. Effectiveness of high-frequency left prefrontal repetitive transcranial magnetic stimulation in patients with treatment-resistant depression: A randomized clinical trial of 37.5-minute vs 18.75-minute protocol. Neuropsychopharmacology Reports. 2019;39(3):203-208.
29. Tee MMK, Au CH. A Systematic Review and Meta-Analysis of Randomized Sham-Controlled Trials of Repetitive Transcranial Magnetic Stimulation for Bipolar Disorder. Psychiatr Q. Aug 29 2020. PMID 32860557
30. Kan, RLD., Zhang, BBB., Zhang, JJQ. et al. Non-invasive brain stimulation for posttraumatic stress disorder: a systematic review and meta-analysis. Transl Psychiatry 10, 168 (2020). <https://doi.org/10.1038/s41398-020-0851-5> Accessed November 26, 2025.
31. Berlim MT, Van Den Eynde F. Repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex for treating posttraumatic stress disorder: an exploratory meta-analysis of randomized, double-blind and sham-controlled trials. Can J Psychiatry. 2014 Sep;59(9):487-96. doi: 10.1177/070674371405900905. PMID: 25565694; PMCID: PMC4168811.

32. Jiang Y, Guo Z, Xing G, et al. Effects of High-Frequency Transcranial Magnetic Stimulation for Cognitive Deficit in Schizophrenia: A Meta-Analysis. *Front Psychiatry*. 2019 Mar 29;10:135. doi: 10.3389/fpsy.2019.00135. PMID: 30984036; PMCID: PMC6450172.
33. Kennedy NI, Lee WH, Frangou S. Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: A meta-analysis of randomized controlled trials. *Eur Psychiatry*. 2018 Mar;49:69-77. doi: 10.1016/j.eurpsy.2017.12.025. Epub 2018 Feb 3. PMID: 29413808.
34. Goudra B, Shah D, Balu G, Gouda G, Balu A, Borle A, Singh PM. Repetitive Transcranial Magnetic Stimulation in Chronic Pain: A Meta-analysis. *Anesth Essays Res*. 2017 Jul-Sep;11(3):751-757. doi: 10.4103/aer.AER_10_17. PMID: 28928582; PMCID: PMC5594801.
35. Lefaucheur JP, Aleman A, Baeken C, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clin Neurophysiol*. 2020 Feb;131(2):474-528. doi: 10.1016/j.clinph.2019.11.002. Epub 2020 Jan 1. Erratum in: *Clin Neurophysiol*. 2020 May;131(5):1168-1169. doi: 10.1016/j.clinph.2020.02.003. PMID: 31901449.
36. InterQual Criteria: Transcranial Magnetic Stimulation (TMS). Current moderate or severe major depressive episode confirmed with a self-report rating scale and no psychotic symptoms informational note. 2020
37. McGirr A, Vila-Rodriguez F, Cole J, et al. Efficacy of Active vs Sham Intermittent Theta Burst Transcranial Magnetic Stimulation for Patients With Bipolar Depression: A Randomized Clinical Trial. *JAMA Netw Open*. 2021;4(3):e210963. doi:10.1001/jamanetworkopen.2021.0963
38. Kedzior KK, Reitz SK, Azorina V, et al. Durability of the antidepressant effect of the high-frequency repetitive transcranial magnetic stimulation (rTMS) In the absence of maintenance treatment in major depression: a systematic review and meta-analysis of 16 double-blind, randomized, sham-controlled trials. *Depress Anxiety*. Mar 2015;32(3):193-203. PMID 25683231
39. Berlim MT, Van den Eynde F, Daskalakis ZJ. Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. *Depress Anxiety*. Jul 2013;30(7):614-623.
40. Blumberger DM, Vila-Rodriguez F, Thorpe KE, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet*. Apr 28 2018;391(10131):1683-1692. PMID 29726344
41. Food and Drug Administration. De Novo classification request for cerena transcranial magnetic stimulator (TMS) device. 2013; https://www.accessdata.fda.gov/cdrh_docs/reviews/K130556.pdf Accessed November 26, 2025.
42. Food and Drug Administration. 510(k) Summary: Brainsway deep TMS System (K122288). 2013; https://www.accessdata.fda.gov/cdrh_docs/pdf12/k122288.pdf. Accessed November 26, 2025.
43. Storch EA, De Nadai AS, Conceicao do Rosario M, et al. Defining clinical severity in adults with obsessive-compulsive disorder. *Compr Psychiatry*. Nov 2015; 63: 30-5. PMID 26555489

44. Farris SG, McLean CP, Van Meter PE, et al. Treatment response, symptom remission, and wellness in obsessive-compulsive disorder. *J Clin Psychiatry*. Jul 2013; 74(7): 685-90. PMID 23945445
45. Carmi L, Tendler A, Bystritsky A, et al. Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Prospective Multicenter Randomized Double-Blind Placebo-Controlled Trial. *Am J Psychiatry*. Nov 01 2019; 176(11): 931-938. PMID 31109199
46. U.S. Food and Drug Administration. De novo classification request for Brainsway Deep Transcranial Magnetic Stimulation System. 2018; https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170078.pdf Accessed November 26, 2025.
47. Cui H, Jiang L, Wei Y, et al. Efficacy and safety of repetitive transcranial magnetic stimulation for generalized anxiety disorder: A meta-analysis. *Gen Psychiatr*. 2019; 32(5): e100051. PMID 31673675
48. He H, Lu J, Yang L, et al. Repetitive transcranial magnetic stimulation for treating the symptoms of schizophrenia: A PRISMA compliant meta-analysis. *Clin Neurophysiol*. May 2017; 128(5): 716-724. PMID 28315614
49. Dougall N, Maayan N, Soares-Weiser K, et al. Transcranial magnetic stimulation (TMS) for schizophrenia. *Cochrane Database Syst Rev*. Aug 20 2015; (8): CD006081. PMID 26289586
50. Kumar N, Vishnubhatla S, Wadhawan AN, et al. A randomized, double blind, sham-controlled trial of repetitive transcranial magnetic stimulation (rTMS) in the treatment of negative symptoms in schizophrenia. *Brain Stimul*. May 2020; 13(3): 840-849. PMID 32289715
51. Zhuo K, Tang Y, Song Z, et al. Repetitive transcranial magnetic stimulation as an adjunctive treatment for negative symptoms and cognitive impairment in patients with schizophrenia: a randomized, double-blind, sham-controlled trial. *Neuropsychiatr Dis Treat*. 2019; 15: 1141-1150. PMID 31190822
52. Rachid F. (2019). Accelerated transcranial magnetic stimulation for the treatment of Patients with depression: A review. *Asian journal of psychiatry*, 40, 71–75. <https://doi.org/10.1016/j.ajp.2019.02.003> Accessed November 26, 2025.
53. Rapinesi, C., Kotzalidis, G. D., Ferracuti, S., et al. (2019). Brain Stimulation in Obsessive-Compulsive Disorder (OCD): A Systematic Review. *Current neuropharmacology*, 17(8), 787–807. <https://doi.org/10.2174/1570159X17666190409142555> Accessed November 26, 2025.
54. Zhou, D. D., Wang, W., Wang, G. M., et al. (2017). An updated meta-analysis: Short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder. *Journal of affective disorders*, 215, 187–196. <https://doi.org/10.1016/j.jad.2017.03.033> Accessed November 26, 2025.
55. Rehn, S., Eslick, G. D., & Brakoulias, V. (2018). A Meta-Analysis of the Effectiveness of Different Cortical Targets Used in Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Obsessive-Compulsive Disorder (OCD). *The Psychiatric quarterly*, 89(3), 645–665. <https://doi.org/10.1007/s11126-018-9566-7> Accessed November 26, 2025

56. Lusicic A., Schruers K.R., Pallanti S., et al. Transcranial magnetic stimulation in the treatment of obsessive-compulsive disorder: current perspectives. *Neuropsychiatr Dis Treat* 2018. 14:1721-36
57. Acevedo, N., Bosanac, P., Pikoos, T., et al. (2021). Therapeutic Neurostimulation in Obsessive-Compulsive and Related Disorders: A Systematic Review. *Brain sciences*, 11(7), 948. <https://doi.org/10.3390/brainsci11070948> Accessed November 26, 2025.
58. Fineberg, N. A., Hollander, E., Pallanti, S., et al. (2020). Clinical advances in obsessive-compulsive disorder: a position statement by the International College of Obsessive-Compulsive Spectrum Disorders. *International clinical psychopharmacology*, 35(4), 173–193. <https://doi.org/10.1097/YIC.0000000000000314> Accessed November 26, 2025.
59. Gan, H., Zhu, J., Zhuo, K., et al. (2021). High frequency repetitive transcranial magnetic stimulation of dorsomedial prefrontal cortex for negative symptoms in patients with schizophrenia: A double-blind, randomized controlled trial. *Psychiatry research*, 299, 113876. <https://doi.org/10.1016/j.psychres.2021.113876> Accessed November 26, 2025.
60. Guttesen, L. L., Albert, N., Nordentoft, M., et al. (2021). Repetitive transcranial magnetic stimulation and transcranial direct current stimulation for auditory hallucinations in schizophrenia: Systematic review and meta-analysis. *Journal of psychiatric research*, 143, 163–175. <https://doi.org/10.1016/j.jpsychires.2021.09.001> November 26, 2025.
61. Li, J., Cao, X., Liu, S., Li, X., & Xu, Y. (2020). Efficacy of repetitive transcranial magnetic stimulation on auditory hallucinations in schizophrenia: A meta-analysis. *Psychiatry research*, 290, 113141. <https://doi.org/10.1016/j.psychres.2020.113141> November 26, 2025.
62. Kennedy, N. I., Lee, W. H., & Frangou, S. (2018). Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: A meta-analysis of randomized controlled trials. *European psychiatry: the journal of the Association of European Psychiatrists*, 49, 69–77. <https://doi.org/10.1016/j.eurpsy.2017.12.025> November 26, 2025.
63. Goldwaser EL, Daddario K, Aaronson ST. A retrospective analysis of bipolar depression treated with transcranial magnetic stimulation. *Brain Behav.* 2020;10(12):e01805. doi:10.1002/brb3.1805
64. Guan HY, Zhao JM, Wang KQ, et al. High-frequency neuronavigated rTMS effect on clinical symptoms and cognitive dysfunction: a pilot double-blind, randomized controlled study in Veterans with schizophrenia. *Transl Psychiatry*. Feb 25 2020; 10(1): 79. PMID 32098946
65. Kazemi R, Rostami R, Khomami S, et al. Bilateral transcranial magnetic stimulation on DLPFC changes resting state networks and cognitive function in patients with bipolar depression. *Front Hum Neurosci.* 2018;12:356. doi:10.3389/fnhum.2018.00356
66. Phillips AL, Burr RL, Dunner DL. Repetitive transcranial magnetic stimulation in the treatment of bipolar depression: experience from a clinical setting. *J Psychiatr Pract.* 2020;26(1):37-45. doi:10.1097/PRA.0000000000000447
67. McGirr A, Vila-Rodriguez F, Cole J, et al. Efficacy of Active vs Sham Intermittent Theta Burst Transcranial Magnetic Stimulation for Patients With Bipolar Depression: A Randomized Clinical Trial. *JAMA Netw Open.* 2021;4(3):e210963. doi:10.1001/jamanetworkopen.2021.0963

68. Saltychev M, Laimi K. Effectiveness of repetitive transcranial magnetic stimulation in patients with fibromyalgia: a meta-analysis. *Int J Rehabil Res*. Mar 2017; 40(1): 11-18. PMID 27977465
69. Tseng P, Zeng B, Hung C, et al. Assessment of Noninvasive Brain Stimulation Interventions for Negative Symptoms of Schizophrenia: A Systematic Review and Network Meta-analysis. *JAMA Psychiatry*. 2022;79(8):770–779. doi:10.1001/jamapsychiatry.2022.1513
70. Saltychev M, Juhola J. Effectiveness of high-frequency repetitive transcranial magnetic stimulation (rTMS) in migraine - a systematic review and meta-analysis. *Am J Phys Med Rehabil*. Jan 14 2022. PMID 35034064
71. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry*. Nov 1989; 46(11): 1006-11. PMID 2684084
72. Liang K, Li H, Bu X, et al. Efficacy and tolerability of repetitive transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. *Transl Psychiatry*. May 28 2021; 11(1): 332. PMID 34050130
73. Perera MPN, Mallawaarachchi S, Miljevic A, et al. Repetitive Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Meta-analysis of Randomized, Sham-Controlled Trials. *Biol Psychiatry Cogn Neurosci Neuroimaging*. Oct 2021; 6(10): 947-960. PMID 33775927
74. Konstantinou G, Hui J, Ortiz A, et al. Repetitive transcranial magnetic stimulation (rTMS) in bipolar disorder: A systematic review. *Bipolar Disord*. Feb 2022; 24(1): 10-26. PMID 33949063
75. Hao et al. Repetitive transcranial magnetic stimulation for improving function after stroke. *Cochrane Database Syst Rev* 2013(5):CD008862
76. Nguyen, T. D., Hieronymus, F., Lorentzen, R., et al. (2021). The efficacy of repetitive transcranial magnetic stimulation (rTMS) for bipolar depression: A systematic review and meta-analysis. *Journal of affective disorders*, 279, 250–255.
<https://doi.org/10.1016/j.jad.2020.10.013> November 26, 2025.
77. Tavares D.F., Myczkowski M.L., Alberto R.L., et al., Treatment of Bipolar Depression with Deep TMS: Results from a Double Blind, Randomized, Parallel Group, Sham-Controlled Clinical Trial. *Neuropsychopharmacology* 2017, 42: 2593-2601. Available at: www.neuropsychopharmacology.org Accessed November 26, 2025.
78. Ma et al. A randomized double-blinded sham-controlled trial of alpha electroencephalogram-guided transcranial magnetic stimulation for obsessive-compulsive disorder. *Chin Med J (Engl)* 2014. 127(4):601-6.
79. Fitzsimmons, S. M. D. D., van der Werf, Y. D., van Campen, A. D et al. (2022). Repetitive transcranial magnetic stimulation for obsessive-compulsive disorder: A systematic review and pairwise/network meta-analysis. *Journal of affective disorders*, 302, 302–312.
<https://doi.org/10.1016/j.jad.2022.01.048> Accessed November 26, 2025.
80. Gao, T., Du, J., Tian, S., et al. (2022). A meta-analysis of the effects of non-invasive brain stimulation on obsessive-compulsive disorder. *Psychiatry research*, 312, 114530.
<https://doi.org/10.1016/j.psychres.2022.114530> Accessed November 26, 2025.

81. Kammen, A., Cavaleri, J., Lam, J., et al. (2022). Neuromodulation of OCD: A review of invasive and non-invasive methods. *Frontiers in neurology*, 13, 909264. <https://doi.org/10.3389/fneur.2022.909264> Accessed November 26, 2025.
82. Rosson, S., de Filippis, R., Croatto, G., et al. (2022). Brain stimulation and other biological non-pharmacological interventions in mental disorders: An umbrella review. *Neuroscience and biobehavioral reviews*, 139, 104743. <https://doi.org/10.1016/j.neubiorev.2022.104743> Accessed November 26, 2025.
83. Edinoff, A. N., Hegefeld, T. L., Petersen, M., et al. (2022). Transcranial Magnetic Stimulation for Post-traumatic stress disorder. *Frontiers in psychiatry*, 13, 701348. <https://doi.org/10.3389/fpsyt.2022.701348> Accessed November 26, 2025.
84. Boggio, P. S., Rocha, M., Oliveira, M. O., et al. (2010). Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. *The Journal of clinical psychiatry*, 71(8), 992–999. <https://doi.org/10.4088/JCP.08m04638blu> Accessed November 26, 2025.
85. Cheng, P., Zhou, Y., Xu, L. Z., et al. (2021). Clinical application of repetitive transcranial magnetic stimulation for post-traumatic stress disorder: A literature review. *World journal of clinical cases*, 9(29), 8658–8665. <https://doi.org/10.12998/wjcc.v9.i29.8658> Accessed November 26, 2025.
86. Cirillo, P., Gold, A. K., Nardi, A. E., et al. (2019). Transcranial magnetic stimulation in anxiety and trauma-related disorders: A systematic review and meta-analysis. *Brain and behavior*, 9(6), e01284. <https://doi.org/10.1002/brb3.1284> Accessed November 26, 2025.
87. Wagner, E., Honer, W. G., Sommer, I. E., et al. (2021). Repetitive transcranial magnetic stimulation (rTMS) for schizophrenia patients treated with clozapine. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*, 22(1), 14–26. <https://doi.org/10.1080/15622975.2020.1733080> Accessed November 26, 2025.
88. Dollfus, S., Lecardeur, L., Morello, R., et al. (2016). Placebo Response in Repetitive Transcranial Magnetic Stimulation Trials of Treatment of Auditory Hallucinations in Schizophrenia: A Meta-Analysis. *Schizophrenia bulletin*, 42(2), 301–308. <https://doi.org/10.1093/schbul/sbv076> Accessed November 26, 2025.
89. Dougall, N., Maayan, N., Soares-Weiser, K. et al. (2015). Transcranial magnetic stimulation (TMS) for schizophrenia. *The Cochrane database of systematic reviews*, 2015(8), CD006081. <https://doi.org/10.1002/14651858.CD006081.pub2> Accessed November 26, 2025.
90. Rachid F. (2018). Maintenance repetitive transcranial magnetic stimulation (rTMS) for relapse prevention in with depression: A review. *Psychiatry research*, 262, 363–372. <https://doi.org/10.1016/j.psychres.2017.09.009>
91. Wilson, S., Croarkin, P. E., Aaronson, S. T., Carpenter, L. L., Cochran, M., Stultz, D. J., & Kozel, F. A. (2022). Systematic review of preservation TMS that includes continuation, maintenance, relapse-prevention, and rescue TMS. *Journal of affective disorders*, 296, 79–88. <https://doi.org/10.1016/j.jad.2021.09.040> Accessed November 26, 2025
92. Zhu L, Zhang W, Zhu Y, et al. Cerebellar theta burst stimulation for the treatment of negative symptoms of schizophrenia: A multicenter, double-blind, randomized controlled trial. *Psychiatry Res*. Nov 2021; 305: 114204. PMID 34587567

93. O'Connell NE, Marston L, Spencer S, et al. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev*. Apr 13 2018; 4: CD008208. PMID 29652088
94. Jiang X, Yan W, Wan R, et al. Effects of repetitive transcranial magnetic stimulation on neuropathic pain: A systematic review and meta-analysis. *Neurosci Biobehav Rev*. Jan 2022; 132: 130-141. PMID 34826512
95. Su YC, Guo YH, Hsieh PC, et al. Efficacy of Repetitive Transcranial Magnetic Stimulation in Fibromyalgia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Clin Med*. Oct 12 2021; 10(20). PMID 34682790
96. Bulteau S, Sébille V, Fayet G. et al. Efficacy of intermittent Theta Burst Stimulation (iTBS) and 10-Hz high-frequency repetitive transcranial magnetic stimulation (rTMS) in treatment-resistant unipolar depression: study protocol for a randomised controlled trial. *Trials*. 2017 Jan 13;18(1):17. doi: 10.1186/s13063-016-1764-8. PMID: 28086851; PMCID: PMC5237321.
97. Leung A, Shirvalkar P, Chen R, et al. Transcranial Magnetic Stimulation for Pain, Headache, and Comorbid Depression: INS-NANS Expert Consensus Panel Review and Recommendation. *Neuromodulation*. Apr 2020; 23(3): 267-290. PMID 32212288
98. Zengin G, Topak OZ, Atesci O, Culha Atesci F. The efficacy and safety of transcranial magnetic stimulation in treatment-resistant bipolar depression. *Psychiatr Danub*. 2022;34(2):236-244. doi:10.24869/psyd.2022.236
99. Mak AD, Neggers SF, Leung ON, et al. Antidepressant efficacy of low-frequency repetitive transcranial magnetic stimulation in antidepressant-nonresponding bipolar depression: a single-blind randomized sham-controlled trial. *Int J Bipolar Disord*. 2021;9(1):40. doi:10.1186/s40345-021-00245-1
100. Cole E.J, Stimpson K.H, Bentzley B.S., et al. Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. *The American Journal of Psychiatry*. August 2020. Available at: https://psychiatryonline.org/doi/10.1176/appi.ajp.2019.19070720?url_ver=Z39.88-2003&rft_id=ori:rid:crossref.org&rft_dat=cr_pub%20%20pubmed Accessed December 8, 2025.
101. Shi R, Wang Z, Yang D, et al. Short-term and long-term efficacy of accelerated transcranial magnetic stimulation for depression: a systematic review and meta-analysis. *BMC Psychiatry*. 2024 Feb 7;24(1):109. doi: 10.1186/s12888-024-05545-1. PMID: 38326789; PMCID: PMC10851556.
102. Fitzgerald PB, Hoy KE, Reynolds J, et al. A pragmatic randomized controlled trial exploring the relationship between pulse number and response to repetitive transcranial magnetic stimulation treatment in depression. *Brain Stimul*. 2020 Jan-Feb;13(1):145-152. doi: 10.1016/j.brs.2019.09.001. Epub 2019 Sep 6. PMID: 31521543.
103. American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder (3rd ed.). 2010. Available at: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed November 26, 2025.
104. American Psychiatric Association (APA). Depressive disorders: Major Depressive Disorder. In: *Diagnostic and statistical manual of mental disorders (5th ed.)*. Washington, DC: American Psychiatric Press; 2013. <https://doi.org/10.1176/appi.books.9780890425596> . Available at:

https://doi.org/10.1176/appi.books.9780890425787.x04_Depressive_Disorders. Accessed November 26, 2025.

105. Baeken C, Vanderhasselt MA, Remue J, et al. Intensive HF-rTMS treatment in refractory medication-resistant unipolar depressed patients. *J Affect Disord*. 2013;151(2):625-631. doi:[10.1016/j.jad.2013.07.008](https://doi.org/10.1016/j.jad.2013.07.008) Accessed November 26, 2025.
106. Brunoni AR, Chaimani A, Moffa AH, et al. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: a systematic review with network meta-analysis [published correction appears in *JAMA Psychiatry*. April 1, 2017;74(4):424]. *JAMA Psychiatry*. 2017;74(2):143-152. doi:[10.1001/jamapsychiatry.2016.3644](https://doi.org/10.1001/jamapsychiatry.2016.3644) Accessed November 26, 2025.
107. Chail A, Saini RK, Bhat PS, et al. Transcranial magnetic stimulation: a review of its evolution and current applications. *Ind Psychiatry J*. 2018;27(2):172-180. doi:[10.4103/ipj.ipj_88_18](https://doi.org/10.4103/ipj.ipj_88_18) Accessed November 26, 2025.
108. Fife D, Reps J, Cepeda MS, et al. Treatment resistant depression incidence estimates from studies of health insurance databases depend strongly on the details of the operating definition. *Heliyon*. 2018;4(7):e00707. doi:10.1016/j.heliyon.2018.e00707
109. Fitzgerald PB, Hoy KE, Elliot D, et al. Accelerated repetitive transcranial magnetic stimulation in the treatment of depression. *Neuropsychopharmacology*. 2018;43(7):1565-1572. doi:[10.1038/s41386-018-0009-9](https://doi.org/10.1038/s41386-018-0009-9) Accessed November 26, 2025.
110. Gaynes B. Assessing the risk factors for difficult-to-treat depression and treatment-resistant depression. *J Clin Psychiatry*. 2016;77 Suppl 1:4-8. doi:10.4088/JCP.14077su1c.01
111. Gaynes B, Asher G, Gartlehner G, et al. Definition of Treatment-Resistant Depression in the Medicare Population. Technology Assessment Program - Technical Assessment Project ID: PSYT0816. Rockville, MD: Agency for Healthcare Research and Quality; February 2018. Available at: <https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id105TA.pdf>. Accessed November 26, 2025.
112. Huang YZ, Lu MK, Antal A, et al. Plasticity induced by non-invasive transcranial brain stimulation: a position paper. *Clin Neurophysiol*. 2017;128(11):2318-2329. doi:[10.1016/j.clinph.2017.09.007](https://doi.org/10.1016/j.clinph.2017.09.007) Accessed November 26, 2025.
113. Kim SJ, Son SJ, Jang M, et al. Rapid symptom improvement in major depressive disorder using accelerated repetitive transcranial magnetic stimulation. *Clin Psychopharmacol Neurosci*. 2021;19(1):73-83. doi:[10.9758/cpn.2021.19.1.73](https://doi.org/10.9758/cpn.2021.19.1.73) Accessed November 26, 2025.
114. Chen L, Hudaib AR, Hoy KE, et al. Efficacy, efficiency and safety of high-frequency repetitive transcranial magnetic stimulation applied more than once a day in depression: A systematic review. *J Affect Disord*. 2020 Dec 1;277:986-996. doi:10.1016/j.jad.2020.09.035. Epub 2020 Sep 11. PMID: 33065843.
115. Mutz J, Vipulanathan V, Carter B., et al. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis *BMJ* 2019; 364 :l1079 doi:10.1136/bmj.l1079
116. Lefaucheur JP, André-Obadia N, Antal A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol*. 2014;125(11):2150-2206. doi:[10.1016/j.clinph.2014.05.021](https://doi.org/10.1016/j.clinph.2014.05.021) Accessed November 26, 2025.

117. Mayo Foundation for Medical Education and Research (MFMER). Depression (major depressive disorder). February 3, 2018. Available at: <https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007>. Accessed November 26, 2025.
118. McClintock SM, Reti IM, Carpenter LL, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. *J Clin Psychiatry*. 2018;79(1):16cs10905. doi:[10.4088/JCP.16cs10905](https://doi.org/10.4088/JCP.16cs10905) Accessed November 26, 2025.
119. Miron JP, Jodoin VD, Lespérance P, et al. Repetitive transcranial magnetic stimulation for major depressive disorder: basic principles and future directions. *Ther Adv Psychopharmacol*. 2021;11:20451253211042696. doi:[10.1177/20451253211042696](https://doi.org/10.1177/20451253211042696) Accessed November 26, 2025.
120. Modirrousta M, Meek BP, Wikstrom SL. Efficacy of twice-daily vs once-daily sessions of repetitive transcranial magnetic stimulation in the treatment of major depressive disorder: a retrospective study. *Neuropsychiatr Dis Treat*. 2018;14:309-316. doi:[10.2147/NDT.S151841](https://doi.org/10.2147/NDT.S151841) Accessed November 26, 2025.
121. Müller HH, Kornhuber J, Maler JM, et al. The effects of stimulation parameters on clinical outcomes in patients with vagus nerve stimulation implants with major depression. *J ECT*. 2013;29(3):e40-42. doi:10.1097/YCT.0b013e318290f7ed
122. National Institute of Mental Health (NIMH). Depression. Revised 2021. Bethesda, MD: National Institutes of Health. Available at: https://radarcart.boisestate.edu/library/files/2017/07/Depression_NIH-15-3561.pdf Accessed November 26, 2025.
123. Otte C, Gold SM, Penninx BW, et al. Major depressive disorder. *Nat Rev Dis Primers*. 2016;2(1):16065. doi:[10.1038/nrdp.2016.65](https://doi.org/10.1038/nrdp.2016.65) Accessed November 26, 2025.
124. Perera T, George MS, Grammer G, et al. The Clinical TMS Society consensus review and treatment recommendations for tms therapy for major depressive disorder. *Brain Stimul*. 2016;9(3):336-346. doi:[10.1016/j.brs.2016.03.010](https://doi.org/10.1016/j.brs.2016.03.010) Accessed November 26, 2025.
125. Rachid F. Accelerated transcranial magnetic stimulation for the treatment of patients with depression: a review. *Asian J Psychiatry*. 2019;40:71-75. doi:[10.1016/j.ajp.2019.02.003](https://doi.org/10.1016/j.ajp.2019.02.003) Accessed November 26, 2025.
126. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A star*d report. *Am J Psychiatry*. 2006;163(11):1905-1917. doi:10.1176/ajp.2006.163.11.1905
127. Schulze L, Feffer K, Lozano C, et al. Number of pulses or number of sessions? An open-label study of trajectories of improvement for once-vs. twice-daily dorsomedial prefrontal rTMS in major depression. *Brain Stimul*. 2018;11(2):327-336. doi:[10.1016/j.brs.2017.11.002](https://doi.org/10.1016/j.brs.2017.11.002) Accessed November 26, 2025.
128. Sonmez AI, Camsari DD, Nandakumar AL, et al. Accelerated TMS for depression: a systematic review and meta-analysis. *Psychiatry Res*. 2019;273:770-781. doi:[10.1016/j.psychres.2018.12.041](https://doi.org/10.1016/j.psychres.2018.12.041) Accessed November 26, 2025.
129. Yu CL, Kao YC, Thompson T, et al. The association of total pulses with the efficacy of repetitive transcranial magnetic stimulation for treatment-resistant major depression: A dose-response meta-analysis. *Asian J Psychiatry*. 2024 Feb;92:103891. doi:10.1016/j.ajp.2023.103891. Epub 2023 Dec 25. PMID: 38183740.

130. Brown R, Cherian K, Jones K, et al. Repetitive transcranial magnetic stimulation for post-traumatic stress disorder in adults. *Cochrane Database Syst Rev*. Aug 02 2024; 8(8): CD015040. PMID 39092744
131. Morriss R, Briley PM, Webster L, et al. Connectivity-guided intermittent theta burst versus repetitive transcranial magnetic stimulation for treatment-resistant depression: a randomized controlled trial. *Nat Med*. 2024 Feb;30(2):403-413. doi: 10.1038/s41591-023-02764-z. Epub 2024 Jan 16. PMID: 38228914; PMCID: PMC10878976
132. VA/DoD Clinical Practice Guideline. (2022). The Management of Major Depressive Disorder. Washington, DC: U.S. Government Printing Office.
<https://www.healthquality.va.gov/guidelines/MH/mdd/VADoDMDDCPGFinal508.pdf>. Accessed November 26, 2025
133. American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. Arlington, VA: American Psychiatric Association, 2007. Available online at
https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/ocd.pdf. Accessed November 26, 2025.
134. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Schizophrenia, Third Edition. Washington, D.C.: APA; 2020. Available at: [www.
https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841](https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841). Accessed November 26, 2025.
135. FDA Briefing Document Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting February 12, 2019. https://www.natap.org/2019/newsUpdates/PDAC_DSaRM-2122019-FDABackgrounder.pdf Accessed November 26, 2025.
136. National Institute for Health and Care Excellence (NICE). Transcranial magnetic stimulation for treating and preventing migraine [IPG477]. 2014;
<https://www.nice.org.uk/guidance/ipg477>. Accessed November 26, 2025
137. National Institute for Health and Care Excellence (NICE). Transcranial magnetic stimulation for obsessive-compulsive disorder [IPG676]. 2020;
<https://www.nice.org.uk/guidance/ipg676>. Accessed November 26, 2025.
138. National Institute for Health and Care Excellence (NICE). Transcranial magnetic stimulation for auditory hallucinations [IPG680]. 2020;
<https://www.nice.org.uk/guidance/ipg680/chapter/1-Recommendations>. Accessed November 26, 2025.
139. Hayes, a symplr company. . Health Technology Assessment: Repetitive Transcranial Magnetic Stimulation for Treatment of Bipolar Disorder. Published April 3, 2025. Annual Review March 2024. Available at www.hayesinc.com. Accessed November 26, 2025.
140. Hayes, a symplr company.. Health Technology Assessment: Transcranial Magnetic Stimulation For The Treatment Of Obsessive-Compulsive Disorder. Published Mar 5, 2019. Annual Review Feb 15, 2022. Available at www.hayesinc.com. Accessed November 26, 2025.
141. Hayes, a symplr company. . Health Technology Assessment: Maintenance Repetitive Transcranial Magnetic Stimulation for Prevention of Recurrent Depression in Adults. Published April 2023. Annual Review: June 3, 2025. Available at www.hayesinc.com. Accessed November 26, 2025.

142. Hayes a symplr company.. Evolving Evidence Review: Accelerated Repetitive Transcranial Magnetic Stimulation for Treatment of Depression. Published September 26, 2022. Annual Review; November 2023. Available at www.hayesinc.com. Accessed November 26, 2025.
143. UpToDate. Holtzheimer P.E., Keck P., Solomon D. Bipolar disorder in adults: Overview of neuromodulation procedures. Topic last updated July 21, 2025. Review current through September 2024 <https://www.uptodate.com>. Accessed November 26, 2025.
144. UpToDate. Kane J., Rubio J.M., Kishimoto T., et al. Treatment-resistant schizophrenia. Topic last updated August 2024. Review current through October 2025. Available at: www.uptodate.com. Accessed December 1, 2025.
145. UpToDate. Denys D., Koning P.P. Stein M.B., et al. Deep brain stimulation for treatment of obsessive-compulsive disorder. Last updated May 2024. Review current through October 2025. Available at: www.uptodate.com. Accessed December 1, 2025.
146. UpToDate. Schwedt T.J., Swanson J.W., Goddeau R.P., Acute treatment of migraine in adults. Last updated March 2024. Review current through May 22, 2025. Available at: www.uptodate.com. Accessed November 26, 2025.
147. UpToDate. Holtzheimer PE, Roy-Byrne PP, Solomon. Unipolar major depression: Administering transcranial magnetic stimulation (TMS). Review current through October 2025. Last updated July 21, 2025. Available at: www.uptodate.com. Accessed December 1, 2025.
148. VA/DoD Clinical Practice Guideline. (2023). VA/DoD Clinical Practice Guideline for Management of Bipolar Disorder. Washington, DC: U.S. Government Printing Office. <https://www.healthquality.va.gov/guidelines/MH/bd/VA-DoD-CPG-BD-Full-CPGFinal508.pdf>. Accessed November 26, 2025.
149. VA/DoD Clinical Practice Guideline. (2023). VA/DoD Clinical Practice Guideline for Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Washington, DC: U.S. Government Printing Office. <https://www.healthquality.va.gov/HEALTHQUALITY/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG-Edited-111624-V5-81825.pdf> Accessed November 26, 2025.
150. U.S. Food and Drug Administration. NeuroStar Advanced Therapy System. February 2024. https://www.accessdata.fda.gov/cdrh_docs/pdf23/K231926.pdf Accessed November 26, 2025.
151. Zimmerman M, Chelminski I, Posternak M. A review of studies of the Montgomery-Asberg Depression Rating Scale in controls: implications for the definition of remission in treatment studies of depression. *Int Clin Psychopharmacol*. Jan 2004; 19(1): 1-7. PMID 15101563
152. Center for Drug Evaluation and Research Application Number: 211243Orig1s000 Summary Review https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211243Orig1s000SumR.pdf. Accessed November 26,
153. Alphs L, Fu D-J, Williamson D, et al. Validation and mapping of the Suicidal Ideation and Behavior Assessment Tool (SIBAT). (abstract W88) *Neuropsychopharmacology*. 2018;43:S427S428.
154. Gross M, Nakamura L, Pascual-Leone A, et al. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-

- analysis comparing the recent vs. the earlier rTMS studies. *Acta Psychiatr Scand.* Sep 2007; 116(3): 165-73. PMID 17655557
155. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol Med.* Jan 2009; 39(1): 65-75. PMID 18447962
 156. Sehatzadeh Sh, Tu HA, Palimaka S, et al. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Ont Health Technol Assess Ser.* 2016; 16(5): 1-66. PMID 27099642
 157. Voigt JD, Leuchter AF, Carpenter LL. Theta burst stimulation for the acute treatment of major depressive disorder: A systematic review and meta-analysis. *Transl Psychiatry.* May 28 2021; 11(1): 330. PMID 34050123
 158. Papakostas GI, Trivedi MH, Shelton RC, et al. Comparative effectiveness research trial for antidepressant incomplete and non-responders with treatment resistant depression (ASCERTAIN-TRD) a randomized clinical trial. *Mol Psychiatry.* Aug 2024; 29(8): 2287-2295. PMID 38454079
 159. Dunner DL, Aaronson ST, Sackeim HA, et al. A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. *J Clin Psychiatry.* Dec 2014; 75(12): 1394-401. PMID 25271871
 160. Richieri R, Guedj E, Michel P, et al. Maintenance transcranial magnetic stimulation reduces depression relapse: a propensity-adjusted analysis. *J Affect Disord.* Oct 2013; 151(1): 129-35. PMID 23790811
 161. Connolly KR, Helmer A, Cristancho MA, et al. Effectiveness of transcranial magnetic stimulation in clinical practice post-FDA approval in the United States: results observed with the first 100 consecutive cases of depression at an academic medical center. *J Clin Psychiatry.* Apr 2012; 73(4): e567-73. PMID 22579164
 162. Janicak PG, Nahas Z, Lisanby SH, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. *Brain Stimul.* Oct 2010; 3(4): 187-99. PMID 20965447
 163. Qi L, Wang S, Li X, et al. Non-invasive brain stimulation in the treatment of generalized anxiety disorder: A systematic review and meta-analysis. *J Psychiatr Res.* Oct 2024; 178: 378-387. PMID 39208534
 164. Li H, Wang J, Li C, et al. Repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults. *Cochrane Database Syst Rev.* Sep 17 2014; 2014(9): CD009083. PMID 25230088
 165. Mantovani A, Aly M, Dagan Y, et al. Randomized sham controlled trial of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for the treatment of panic disorder with comorbid major depression. *J Affect Disord.* Jan 10 2013; 144(1-2): 153-9. PMID 22858212
 166. Blyth SH, Cruz Bosch C, Raffoul JJ, et al. Safety of rTMS for Schizophrenia: A Systematic Review and Meta-analysis. *Schizophr Bull.* Mar 14 2025; 51(2): 392-400. PMID 39278637
 167. Ye S, Guan X, Xiu M, et al. Early efficacy of rTMS intervention at week 2 predicts subsequent responses at week 24 in schizophrenia in a randomized controlled trial. *Neurotherapeutics.* Sep 2024; 21(5): e00392. PMID 38944636

168. Hua Q, Wang L, He K, et al. Repetitive Transcranial Magnetic Stimulation for Auditory Verbal Hallucinations in Schizophrenia: A Randomized Clinical Trial. *JAMA Netw Open*. Nov 04 2024; 7(11): e2444215. PMID 39527055
169. Xiu MH, Guan HY, Zhao JM, et al. Cognitive Enhancing Effect of High-Frequency Neuronavigated rTMS in Chronic Schizophrenia Patients With Predominant Negative Symptoms: A Double-Blind Controlled 32-Week Follow-up Study. *Schizophr Bull*. Sep 21 2020; 46(5): 1219-1230. PMID 32185388
170. Jansen JM, Daams JG, Koeter MW, et al. Effects of non-invasive neurostimulation on craving: a meta-analysis. *Neurosci Biobehav Rev*. Dec 2013; 37(10 Pt 2): 2472-80. PMID 23916527
171. Chang CH, Liou MF, Liu CY, et al. Efficacy of Repetitive Transcranial Magnetic Stimulation in Patients With Methamphetamine Use Disorder: A Systematic Review and Meta-Analysis of Double-Blind Randomized Controlled Trials. *Front Psychiatry*. 2022; 13: 904252. PMID 35711590
172. Ahmed I, Mustafaoglu R, Memon AR, et al. Comparative Effectiveness of Noninvasive Brain Stimulation for the Treatment of Pain, Fatigue, and Sleep Quality in Fibromyalgia. A Systematic Review With Network Meta-Analysis. *Clin J Pain*. May 01 2025; 41(5). PMID 40091857
173. Le Q, Qu Y, Tao Y, et al. Effects of repetitive transcranial magnetic stimulation on hand function recovery and excitability of the motor cortex after stroke: a meta-analysis. *Am J Phys Med Rehabil*. May 2014; 93(5): 422-30. PMID 24429509
174. Li Y, Qu Y, Yuan M, et al. Low-frequency repetitive transcranial magnetic stimulation for patients with aphasia after stroke: A meta-analysis. *J Rehabil Med*. Sep 2015; 47(8): 675-81. PMID 26181486
175. Qiao J, Ye QP, Wu ZM, et al. The Effect and Optimal Parameters of Repetitive Transcranial Magnetic Stimulation on Poststroke Dysphagia: A Meta-Analysis of Randomized Controlled Trials. *Front Neurosci*. 2022; 16: 845737. PMID 35573312
176. Zhang L, Xing G, Fan Y, et al. Short- and Long-term Effects of Repetitive Transcranial Magnetic Stimulation on Upper Limb Motor Function after Stroke: a Systematic Review and Meta-Analysis. *Clin Rehabil*. Sep 2017; 31(9): 1137-1153. PMID 28786336
177. Graef P, Dadalt MLR, Rodríguez DAMDS, et al. Transcranial magnetic stimulation combined with upper-limb training for improving function after stroke: A systematic review and meta-analysis. *J Neurol Sci*. Oct 15 2016; 369: 149-158. PMID 27653882
178. Zhang JJY, Ang J, Saffari SE, et al. Repetitive Transcranial Magnetic Stimulation for Motor Recovery After Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials With Low Risk of Bias. *Neuromodulation*. Jan 2025; 28(1): 16-42. PMID 39320286
179. National Institute for Health and Care Excellence (NICE). Repetitive transcranial magnetic stimulation for depression [IPG542]. 2015; <https://www.nice.org.uk/guidance/ipg542> . Accessed November 26, 2025.
180. Cole EJ, Phillips AL, Bentzley BS, et al. Stanford Neuromodulation Therapy (SNT): a double-blind randomized controlled trial. *Am J Psychiatry*. 2021; 179(2): 132-141. doi:10.1176/appi.ajp.2021.20101429 Accessed December 8, 2025.
181. Hayes, a symplr company. Evidence Analysis Research Brief: Stanford Neuromodulation Therapy for Treatment Resistant Depression. Published December 8, 2025. Available at www.hayesinc.com. Accessed December 8, 2025.

182. Batail JM, Xiao X, Azeez A, Tischler C, Kratter IH, Bishop JH, Saggar M, Williams NR. Network effects of Stanford Neuromodulation Therapy (SNT) in treatment-resistant major depressive disorder: a randomized, controlled trial. *Transl Psychiatry*. 2023 Jul 3;13(1):240. doi: 10.1038/s41398-023-02537-9. PMID: 37400432; PMCID: PMC10318050.
183. Gajawelli N, Geoly AD, Batail JM, Xiao X, Maron-Katz A, Cole E, Azeez A, Kratter IH, Saggar M, Williams NR. Increased anti-correlation between the left dorsolateral prefrontal cortex and the default mode network following Stanford Neuromodulation Therapy (SNT): analysis of a double-blinded, randomized, sham-controlled trial. *Npj Ment Health Res*. 2024 Jul 6;3(1):35. doi: 10.1038/s44184-024-00073-y. PMID: 38971869; PMCID: PMC11227523.
184. Geoly AD, Stimpson KH, Espil FM, Bentzley BS, Williams NR. Durability of clinical benefit with Stanford Neuromodulation Therapy (SNT) in treatment-resistant depression. *Brain Stimul*. 2025 May-Jun;18(3):875-881. doi: 10.1016/j.brs.2025.04.006. Epub 2025 Apr 8. PMID: 40209894.
185. Lan XJ, Cai DB, Liu QM, Qin ZJ, Pridmore S, Zheng W, Xiang YT. Stanford neuromodulation therapy for treatment-resistant depression: a systematic review. *Front Psychiatry*. 2023 Dec 13;14:1290364. doi: 10.3389/fpsy.2023.1290364. PMID: 38161728; PMCID: PMC10756664.

CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	0889T	Personalized target development for accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation derived from a structural and resting-state functional MRI, including data preparation and transmission, generation of the target, motor threshold-starting location, neuronavigation files and target report, review and interpretation
	0890T	Accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation, including target assessment, initial motor threshold determination, neuronavigation, delivery and management, initial treatment day
	0891T	Accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation, including neuronavigation, delivery and management, subsequent treatment day
	0892T	Accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation, including neuronavigation, delivery and management, subsequent motor threshold redetermination with delivery and management, per treatment day

	90867	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management
	90868	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent delivery and management, per session
	90869	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold re-determination with delivery and management
HCPCS		
	No code(s)	
Type of Service	Medicine	
Place of Service	Outpatient	

POLICY HISTORY

Date	Reason	Action
December 2025	Annual Review	Policy Renewed
December 2024	Annual Review	Policy Revised
April 2024	Annual Review	Policy Revised
August 2023	Annual Review	Policy Revised
August 2022	Annual Review	Policy Revised
June 2022	Interim Review	Policy Revised
August 2021	Annual Review	Policy Revised
August 2020	Annual Review	Policy Revised
August 2019	Annual Review	Policy Revised
March 2019	Interim Review	Policy Revised
August 2018	Annual Review	Policy Revised

Date	Reason	Action
December 2017	Interim Review	Policy Revised
August 2017	Annual Review	Policy Revised
February 2017	Interim Review	Policy Revised
October 2016	Annual Review	Policy Revised
August 2016	Annual Review	Policy Revised
October 2015	Annual Review	Policy Revised
November 2014	Annual Review	Policy Revised
July 2014	Interim Review	Policy Renewed
January 2014	Annual Review	Policy Revised
January 2013	Annual Review	Policy Revised
January 2012	Literature Review	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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