Policy Number	**PSY301.015**
Policy Effective Date	**10/01/2024**
Policy End Date	**12/31/2025**

Transcranial Magnetic Stimulation as a Treatment for Psychiatric/Neurologic Disorders

Table of Contents

Related Policies (if applicable)
None

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Coverage

Initial Treatment
Transcranial magnetic stimulation (TMS), which can include but is not limited to, conventional TMS, deep TMS, and theta burst stimulation (See **NOTE 1**) **may be considered medically necessary** when ALL the following conditions are met:

1. Acute phase treatment (See **NOTE 2**) with confirmed diagnosis of:
   a. Moderate to severe major depressive disorder (MDD), either single episode or recurrent (non-psychotic) documented by standardized rating scales that reliably measure depressive symptoms:
      - In individuals ≥ 18 years old, or
      - As an augmentation agent for individuals 15-17 years old (as an augmentation agent along with antidepressant medications in individuals 15-17 years old, or
   b. Obsessive-Compulsive Disorder (OCD) per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria in adults; **AND**

2. Individual has tried and had an inadequate response to 2 antidepressant agents from 2 different antidepressant classes (i.e., selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, bupropion, or mirtazapine). An adequate trial of an antidepressant is defined by the following:
   a. The trial length was at least 4 weeks at generally accepted doses without significant improvement/response in symptoms; **AND**
3. Individual has failed a trial of a psychotherapy known to be effective in the treatment of major depressive disorder (i.e., cognitive behavioral therapy) of an adequate frequency and duration, without significant improvement in depressive symptoms, as documented by standardized rating scales that reliably measure depressive symptoms; AND
4. National standardized rating scales such as the Patient Health Questionnaire-9 (PHQ-9) and the Yale-Brown Obsessive-Compulsive Scale (YBOCS) are administered weekly during treatment; **AND**
5. The treatment is delivered by a device that is U.S. Food and Drug Administration FDA-approved for the indication being treated (see Table 1 in Description section) in a safe and effective manner. TMS treatment should generally follow the protocol and parameters specified in the manufacturer's user manual, with modifications only as supported by the published scientific evidence base; **AND**
6. TMS treatment (or retreatment) is prescribed by a psychiatrist (see **NOTE 3**) that has been trained in the use of the specific FDA-cleared device. TMS treatments are to be provided by or under the direct supervision of a psychiatrist (see **NOTE 3**) trained in the use of the specific FDA-cleared device.

   The TMS operator must be present at all times and must be trained, certified, and proficient to deliver TMS treatments, including but not limited to:
   a. Device operation and TMS coil targeting/repositioning, and
   b. Basic cardiac life support and the identification and management of any treatment complications (i.e., seizures), and
   c. Adequate resuscitation equipment (e.g., suction and oxygen), and
   d. The TMS operator must maintain awareness of response times of emergency services (either fire/ambulance or "code team"), which should be available within 5 minutes. These relationships should be reviewed on at least a 1-year basis and include mock drills; **AND**
7. None of the following conditions or contraindications are present:
   a. Seizure disorder or any history of seizure disorder (except those induced by electroconvulsive therapy (ECT) or isolated febrile seizures in infancy without subsequent treatment or recurrence); or
   b. Presence of acute or chronic psychotic symptoms or disorders (e.g., schizophrenia, schizophreniform or schizoaffective disorder) in the current depressive episode or within the last 6 months (whichever is longer); or
   c. Neurological conditions that include epilepsy, cerebrovascular disease, dementia, increased intracranial pressure, history of repetitive or severe head trauma, or primary or secondary tumors in the central nervous system; or
   d. Excessive use of alcohol or illicit substances within the last 30 days.

NOTE 1: The details in this policy relate to both TMS devices that have been approved or cleared by the FDA for the treatment of the approved indications therein.

NOTE 2: If the above conditions are met, 36 acute phase sessions may be authorized for the treatment of MDD. A treatment course should not exceed 5 days a week for 6 weeks (total of 30 sessions). TMS may be followed by a 3-week taper of 3 transcranial TMS treatments in week 1, 2 TMS treatments the next week, and 1 TMS treatment in the last week.

If the above conditions are met, 29 acute phase sessions of TMS may be approved for the treatment of OCD. TMS treatments are 20-30 minutes in duration on average for a period of 6 weeks.

NOTE 3: If, due to geographical access concerns or in accordance with state practice laws and regulations, a psychiatrist is not readily available, then a provider that has been trained in the use of the specific FDA-cleared device may prescribe and/or administer treatment using best practice guidelines.

- Direct supervision means the psychiatrist (or provider) must be present in the area, and immediately available for all TMS sessions.
- Additionally, it is expected that the psychiatrist (or provider) should perform the initial motor threshold determination and identify the appropriate coil location for subsequent treatments.

Subsequent Treatments

Subsequent acute phase treatments for TMS using an FDA-cleared device in accordance with the FDA labeled indications **may be considered medically necessary** if the patient meets ALL of the following conditions:

1. Individual has documented positive response to prior treatment, as defined by at least a 50% reduction in severity of scores for MDD on a standardized rating scale such as the PHQ-9 OR at least a 30% reduction in severity of scores for OCD on a standardized rating scale such as the YBOCS, by the end of acute phase treatment; **AND**
2. Individual has not received a separate acute phase TMS treatment within the last 6 months; **AND**
3. None of the following conditions or contraindications are present:
    a. Seizure disorder or any history of seizure disorder (except those induced by ECT or isolated febrile seizures in infancy without subsequent treatment or recurrence); or
    b. Presence of acute or chronic psychotic symptoms or disorders (e.g., schizophrenia, schizophreniform or schizoaffective disorder) in the current depressive episode, or within the last 6 months (whichever is longer); or
    c. Neurological conditions that include epilepsy, cerebrovascular disease, dementia, increased intracranial pressure, history of repetitive or severe head trauma, or primary or secondary tumors in the central nervous system; or
    d. Excessive use of alcohol or illicit substances within the last 30 days; or
    e. The individual did not respond to a prior course of TMS treatments as defined by:

- Not achieving at least, a 50% reduction in severity of scores for depression in a standardized rating scale such as the PHQ-9 by the end of acute phase treatment (i.e., 36 sessions); or
- Not achieving at least, a 30% reduction in severity of scores for OCD in a standardized rating scale such as the YBOCS by the end of acute phase treatment (i.e., 29 sessions).

Subsequent TMS **is considered experimental, investigational, and/or unproven** for:

1. An individual who did not respond to a prior episode of repetitive transcranial magnetic stimulation (rTMS) or deep tanscranial magnetic stimulation (dTMS) treatments (as defined by not achieving at least a 50% reduction in severity of scores for depression on a standardized rating scale such as the PHQ-9, OR at least a 30% reduction in severity scores for OCD on a standardized rating scale such as the YBOCS by the end of acute phase treatment, **OR**
2. Maintenance treatment of major depression (i.e., "booster treatments") **OR**
3. Novel delivery mechanisms (i.e., multiple TMS sessions/day).

Other Circumstances for Treatment

TMS **is considered experimental, investigational, and/or unproven** in all other circumstances, including but not limited to:

1. The individual is actively psychotic;
2. The individual has dementia or a cognitive disorder;
3. The individual has excessive use of alcohol or illicit substances within the last 30 days;
4. Any other psychiatric or neurologic disorder including, but not limited to:
   a. Schizophrenia,
   b. Migraine headaches,
   c. Epilepsy or other seizure disorder, or any history of seizure disorder (except those induced by ECT or isolated febrile seizures in infancy without subsequent treatment or recurrence),
   d. Cardiovascular disease/stroke,
   e. Dementia,
   f. Alzheimer's disease,
   g. Attention deficit disorder/hyperactivity disorder,
   h. Bulimia nervosa,
   i. Dysphagia,
   j. Fibromyalgia,
   k. Panic disorder,
   l. Parkinson's disease,
   m. Postpartum depression,
   n. Post-traumatic stress disorder.

NOTE 4. The following clinical scenarios may be evaluated on a case-by-case basis, and will not be authorized without viable clinical justification/rationale supported by evidence-based practices and/or accepted guidelines:

1. Incomplete treatment due to extenuating circumstances;
2. Remapping requests.

Policy Guidelines

Procedure code 90867 is reported once per course of treatment. Codes 90868 and 90869 cannot be reported for the same session.

Description

Transcranial magnetic stimulation (TMS) is a noninvasive method of delivering electrical stimulation to the brain. TMS involves 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. Repetitive TMS is being evaluated for the treatment of treatment-resistant depression (TRD) and a variety of other psychiatric or neurologic disorders. A variety of TMS modalities have been developed, which differ on parameters including stimulation intensity, frequency, pattern, and site of the brain stimulation. 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. Deep TMS employs an H-coil helmet designed 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 TMS.

Transcranial Magnetic Stimulation

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. TMS 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.

Regulatory Status

Devices for transcranial stimulation have been cleared for marketing by the U.S. Food and Drug Administration (FDA) for diagnostic uses (FDA Product Code: GWF). A number of devices subsequently received FDA clearance for the treatment of major depressive disorder in adults who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode. Some of these devices use deep TMS or theta burst protocols. For example, the Brainsway Deep TMS system was FDA cleared for treatment resistant depression in 2013 based on substantial equivalence to the Neurostar TMS Therapy System, and the Horizon (Magstim) and MagVita (Tonica Elektronik) have FDA clearance for their theta burst protocols.

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, lithium battery pack, and 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 520(k) classification by the FDA as an adjunct for the treatment of adult patients suffering from 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 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 a 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.

In 2022, the Magnus Neuromodulation System (NMS) with Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) Technology (Magnus Medical, Inc.) received approval to treat major depressive disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.

In 2024, NeuroStar (Neuronetics, Inc) received approval to treat major depressive disorder in adolescents. This is the first and only device approved for adolescents, and it must be used as an augmentation agent in connection with antidepressant medications.

Table 1 lists some devices that are FDA cleared for major depressive disorder (Product Code: OBP), migraine headache pain (Product Code: OKP), and obsessive-compulsive disorder (Product Code: QCI).

Table 1. Repetitive TMS Devices Cleared by the FDA for the Treatment of Major Depression, Migraine, or Obsessive-Compulsive Disorder

Device	Manufacturer	Indication	FDA Clearance Number	FDA Clearance Date
Horizon 3.0 TMS Therapy System	Magstim	Major Depressive Disorder and obsessive-compulsive disorder	K22171	01/13/2023
ALTMS Magnetic Stimulation Therapy System	REMED Co.; Ltd	Major Depressive Disorder	K220625	04/06/2022
NeuroStar	Neuronetics	Major Depressive Disorder	K083538	12/16/2008
		Major Depressive	K231926	03/21/2024

		Disorder in adolescents (15-18 years of age) as an augmentation agent along with antidepressant medications		
		Obsessive Compulsive Disorder	K212289	05/06/2022
Brainsway Deep TMS System	Brainsway	Major Depressive Disorder	K122288	01/07/2013
		Obsessive-Compulsive Disorder	K183303	03/18/2019
Springtms Total Migraine System	Eneura	Migraine headache with aura	K140094	05/21/2014
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	08/14/2018
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
NeurostarAdvanced Therapy System	Neuronetics	Major Depressive Disorder and Obsessive-Compulsive Disorder (OCD)	K230029	04/04/2023
Magnus Neuromodulation System (NMS) with SAINT Technology, Model Number 1001K	Magnus Medical, Inc	Major Depressive Disorder	K220177	09/01/2022

FDA: Food and Drug Administration; TMS: transcranial magnetic stimulation; SAINT: Stanford Accelerated Intelligent Neuromodulation Therapy.

The listing noted above may not be an "all inclusive" list of TMS systems and is subject to change. Refer to the FDA web site at: <https://www.fda.gov> for additional information on devices.

Rationale

This medical document was created in 2010 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through August 18, 2023.

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), 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, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one 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.

Treatment-Resistant Depression

Clinical Context and Therapy Purpose

The purpose of repetitive transcranial magnetic stimulation (rTMS) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with treatment-resistant depression (TRD).

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

Populations

The relevant populations of interest is individuals with TRD.

Interventions
The therapy being considered is rTMS.

Comparators
The following therapies are currently being used to treat TRD: pharmacotherapy, psychological and behavioral therapy, and electroconvulsive therapy (ECT).

Outcomes
The general outcomes of interest are reductions in symptoms and improvements in QOL and functional outcomes.

Table 2. Health Outcome Measures Relevant to Treatment-Resistant Depression, Major Depressive Disorder, Suicidal Ideation, and Suicidal Behavior

Outcome	Description	Scale	Clinically Meaningful Difference
MADRS	• Physician scored. • Rates presence and severity of depression. • Symptom domains include sadness; pessimism; inability to feel; suicidality.	• Contains 10 items (scored from 0 to 6) with higher scores indicating more severe depression. • No validated cut-off score but generally 0 to 6 normal (no depression); 7 to 19 mild depression; 20 to 34 moderate depression; 35 to 59 severe depression; 60 or greater very severe depression. (1)	• No consensus to define remission. Thresholds for remission have ranged from 6 to 12 in trials. • One literature review reported that the mean weighted MADRS score for remission was 4.0 (95% CI, 3.5-4.5) based on 10 studies. (2) The definition of remission was a complete absence of clinically significant symptoms of depression. • As per FDA, for drugs that have been approved to treat MDD as monotherapy or adjunctive

			treatment, treatment differences were typically closer to 3 or 4 points in MADRS scores. The observed treatment differences in esketamine studies were in that range. (3)
HAM-D	• Physician scored. • Rates presence and severity of depression. • Used in a number of registration studies of approved oral antidepressants. • Symptom domains include sadness; pessimism; inability to feel; suicidality.	• There are 2 versions: 17 or 25 items; 17 items is more common. • Each item scored in a range of 0 to 2 or 0 to 4, with higher scores indicating a greater degree of depression. • Scores range from 0 to 48. • Scores as low as 17 are associated with moderate depression and those at or above 24 are associated with severe depression. (2)	• Remission is defined as total score of 7 or less. But 2 or less has been suggested as optimal. • Response to treatment is defined as a 50% reduction from baseline scores.
SIBAT	• Contains both patient- and clinician-reported modules and can be assessed by patient or rated by the physician. • Includes assessments of: o Severity of Suicidality (CGI-SS-r). o Imminent Suicide Risk (CGI-SR-I).	• CGI-SS-r: rated from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal patients) • CGI-SR-I: rates best clinical judgment of participant's imminent risk for suicide within the next 7 days. Scale indicates: 0 (No imminent suicide risk), 1 (Minimal imminent), 2 (Mild imminent), 3 (Moderate imminent), 4 (Marked imminent), 5 (Severely imminent), 6 (Extreme imminent).	• No literature was identified for a consensus definition for a clinically meaningful change in scores.

	○ Frequency of Suicidal Thinking (FoST). (4)	• FoST: describes the clinician determined estimate of the frequency of the participant's suicidal thinking. Scored on a 6-point Likert scale: 0 (Never), 1 (Rarely), 2 (Sometimes), 3 (Often), 4 (Most of the time), 5 (All of the time). (4)	

CGI-SR-I: Clinical Global Impression of Imminent Suicide Risk Scale, CGI-SS-r: Clinical Global Impression of Severity of Suicidality-Revised, CI: confidence interval; FDA: U.S. Food and Drug Administration; FoST: Frequency of Suicidal Thinking, HAM-D: Hamilton Rating Scale for Depression, MADRS: Montgomery-Asberg Depression Rating Scale, MDD: major depressive disorder; SIBAT: Suicide Ideation and Behavior Assessment Tool.

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; and
- Studies with duplicative or overlapping populations were excluded.

Evaluation of rTMS for TRD includes RCTs comparing rTMS with sham as well as evidence when used as a replacement for or adjunct to pharmacotherapy that has not improved depressive symptoms. In addition, evaluation of rTMS in TRD includes the use of rTMS as an alternative to ECT. However, some individuals may not want to use ECT due to its requirement for general anesthesia and induction of seizures.

There has been a trend to use rTMS at increased levels of intensity, trains of pulses, total pulses per session, and number of sessions. (5) Unless otherwise indicated, stimulation was set at 100% to 120% of motor threshold, clinical response was defined as an improvement of 50% or more on the Hamilton Rating Scale for Depression (HAM-D), and remission was considered to be a score of 7 or less on the HAM-D. Refer to the 2009 meta-analysis by Schutter for a summary of study characteristics and stimulation parameters used in trials conducted prior to 2008. (6)

Systematic Reviews

The Health Quality Ontario (2016) published a systematic review of left DLPFC rTMS for TRD. (7) Reviewers included 23 RCTs (n=1156 patients) that compared rTMS with sham and 6 RCTs (n=266 patients) that compared rTMS with ECT. In 16 studies, patients received rTMS in addition to antidepressant medication. Seven studies used intensities of less than 100% motor threshold and the definition of remission in the included studies varied (from ≤7 to ≤10 on the HAM-D). Meta-analysis showed a statistically significant improvement in depression scores compared with sham, with a weighted mean difference (WMD) of 2.31 (see Table 3). However, this was smaller than the prespecified clinically important difference of 3.5 points on the HAM-D, and the effect size was small (0.33; 95% confidence interval [CI], 0.17 to 0.5; p<0.001). Subgroup analysis showed a larger and clinically significant treatment effect in the rTMS studies using 20 Hz with shorter train duration compared with other rTMS techniques (WMD=4.96; 95% CI, 1.15 to 8.76; p=0.011). Secondary analyses showed rTMS demonstrated a statistically greater rate of response among 20 studies (pooled relative risk [RR], 1.72) as well as statistically greater rate of remission among 13 studies (pooled relative risk, 2.20). For the 6 trials that compared rTMS with ECT, the WMD of 5.97 was both statistically and clinically significant in favor of ECT. The relative risk for remission and response rates are shown in Table 1, which while favoring ECT were not statistically significant. Remission and relapse rates at the 6-month follow-up were reported in 2 studies (n=40 and n=46 subjects), comparing rTMS and ECT. While 1 study reported a slightly higher remission rate for ECT (27.3%) than for rTMS (16.7%), the other study did not find a significant difference between ECT and rTMS for mean depression scores at 3 or 6 months but did note relapses were less frequent for ECT. Statistical comparisons were either not significant or not available, limiting the interpretation of these findings.

Table 3. Statistical Comparisons for Depression Scores After rTMS

Comparison	Favors	WMD (95% CI)	p	RR for Remission (95% CI)	p	RR for Response (95% CI)	p
rTMS vs sham	rTMS	2.31 (1.19 to 3.43)	<0.001	2.20 (1.44 to 3.38)	0.001	1.72 (1.13 to 2.62)	0.01
rTMS vs ECT	ECT	5.97 (0.94 to 11.0)	0.02	1.44 (0.64 to 3.23)	0.38	1.72 (0.95 to 3.11)	0.07

CI: confidence interval; ECT: electroconvulsive therapy; rTMS: repetitive transcranial magnetic stimulation; RR: relative risk; WMD: weighted mean difference; vs: versus.

Brunoni et al. (2017) conducted a systematic review to compare different modalities of rTMS for TRD. (8) Bilateral, high frequency rTMS, low-frequency rTMS, and theta burst stimulation were statistically significantly more effective than sham with respect to response (odds ratio [OR], 3.39; 95% CI, 1.91 to 6.02]; OR, 3.28 [95% CI, 2.33 to 4.61]; OR, 2.48 [95% CI, 1.22 to 5.05]; OR, 2.57 [95% CI, 1.17 to 5.62], respectively). In network meta-analysis, deep TMS was not more effective than sham TMS for response (OR 1.49; 95% CI 0.50 to 4.47) or remission (OR 2.45; 95% CI 0.74 to 8.07), but this result was based on only 1 RCT.

A systematic review conducted by Voigt et al. (2021) focused on theta burst stimulation of TRD. (9) The reviewers included 8 RCTs comparing theta burst stimulation to sham treatment and 1 comparing theta burst stimulation to conventional rTMS. As measured by the HAM-D, theta burst stimulation was superior to sham on response (RR 2.4; 95% CI: 1.27 to 4.55; p=.007; I^2 = 40%). There was no statistically significant difference between theta burst stimulation and conventional rTMS (RR 1.02; 95% CI: 0.85 to 1.23; p=.80; I^2 = 0%). There was no difference between theta burst stimulation and rTMS in the incidence of adverse events.

Randomized Controlled Trials

Theta Burst Stimulation Compared to Conventional Transcranial Magnetic Stimulation

Blumberger et al. (2018) published a multicenter, randomized noninferiority trial, Conventional Versus Theta Burst Repetitive Transcranial Magnetic Stimulation in the Treatment of Major Depressive Disorder comparing 10-Hz rTMS with intermittent theta burst stimulation (iTBS). (10) Between 2013 and 2016, 414 patients with TRD were enrolled and randomized to 4 to 6 weeks of rTMS (n=205) or iTBS (n=209). Treatment resistance was defined as the failure to tolerate two or more antidepressant trials of inadequate dose and duration or no clinical response to an adequate dose of an antidepressant. Patients who failed more than three antidepressant trials of adequate dosage were excluded from the trials. Patients could alter their medication during this trial. Treatment with rTMS (37 minutes) and iTBS (3 minutes) was delivered 5 times a week for 4 to 6 weeks. The primary outcome measure was the 17-item HAM-D, for which scores for patients treated with rTMS improved by 10.1 points and scores for patients treated with iTBS improved by 10.2 points (adjusted difference, 0.103; lower 95% CI, -1.16; p=0.001). Treatment with iTBS resulted in a higher self-rated intensity of pain (mean score, 3.8) than treatment with rTMS (mean score, 3.4; p=0.011). Headache was the most common treatment-related adverse event for both groups (rTMS=64% [131/204]; iTBS=65% [136/208]). Serious adverse events were noted in patients treated with rTMS (one case of myocardial infarction) and iTBS (one case each of agitation, worsening suicidal ideation, worsening depression); there was no significant difference in the number of adverse events in the two groups. The trial lacked a treatment group with a placebo.

Deep Transcranial Magnetic Stimulation

The RCT leading to 510(k) clearance of the Brainsway deep TMS system in 2013 was conducted at 20 centers across the United States (n=13), Israel (n=4), Germany (n=2), and Canada (n=1). (11) The trial included 229 patients with major depressive disorder who had not received benefit from 1 to 4 antidepressant trials or were intolerant to at least 2 antidepressant treatments. Using per-protocol analysis, which excluded 31 patients who did not receive adequate TMS treatment and 17 patients who did not meet the inclusion and exclusion criteria, the RCT showed a significant benefit for both response rate (38.4% vs 21.4%) and remission rate (32.6% vs 14.6%). A modified intention-to-treat analysis, which excluded the 17 patients not meeting selection criteria, showed a significant benefit in both response rate (37% vs 22.8%) and remission rate (30.4% vs 15.8%). At the end of the maintenance period (16-week follow-up), the response rate remained significantly improved for deep TMS. Remission rates were not reported. Intention-to-treat analysis found no significant benefit of treatment at 4 or 16 weeks.

Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) for Treatment-Resistant Depression

Cole et al. (2020) conducted a clinical trial that lead to the 510(k) clearance of the Magnus Neuromodulation System (NMS) with SAINT Technology. (69) Recent methodological advances suggest that the current iTBS protocol might be improved through 1) treating patients with multiple sessions per day at optimally spaced intervals, 2) applying a higher overall pulse dose of stimulation, and 3) precision targeting of the left dorsolateral prefrontal cortex (DLPFC) to subgenual anterior cingulate cortex (sgACC) circuit. The authors examined the feasibility, tolerability, and preliminary efficacy SAINT, an accelerated, high-dose resting-state functional connectivity MRI (fcMRI)-guided iTBS protocol for treatment-resistant depression. Twenty-two participants with treatment-resistant depression received open-label SAINT. Fifty iTBS sessions (1,800 pulses per session, 50-minute intersession interval) were delivered as 10 daily sessions over 5 consecutive days at 90% resting motor threshold (adjusted for cortical depth). Neuropsychological testing was conducted before and after SAINT. Nineteen of 21 participants (90.5%) met remission criteria (defined as a score ,11 on the Montgomery-Åsberg Depression Rating Scale). In the intent-to-treat analysis, 19 of 22 participants (86.4%) met remission criteria. Neuropsychological testing demonstrated no negative cognitive side effects. In conclusion, SAINT protocol was well tolerated and safe. Further double-blinded sham-controlled trials are needed to confirm the remission rate observed in this initial study.

Cole et al. (2022) conducted a sham-controlled double-blind trial of Stanford neuromodulation therapy (SNT; previously referred to as Stanford Accelerated Intelligent Neuromodulation Therapy, or SAINT). (70) Intermittent theta-burst stimulation (iTBS) is approved by the U.S. Food and Drug Administration for the treatment of treatment-resistant depression but is limited by suboptimal efficacy and a 6-week duration. The authors addressed these limitations by developing a neuroscience-informed accelerated iTBS protocol, Stanford neuromodulation therapy. Participants (32) with treatment-resistant depression currently experiencing moderate to severe depressive episodes were randomly assigned to receive active or sham SNT. The mean percent reduction from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) score 4 weeks after treatment was 52.5% in the active treatment group and 11.1% in the sham treatment group. However, larger, double-blinded, sham-controlled trials are required to confirm the results from this initial study.

<u>Durability of Conventional Transcranial Magnetic Stimulation</u>

Systematic Reviews

Kedzior et al. (2015) examined the durability of the antidepressant effect of high-frequency rTMS on the left DLPFC in the absence of maintenance treatment. (12) Included were 16 double-blind, sham-controlled randomized trials (total N=495 patients). The range of follow-up was 1 to 16 weeks, but most studies only reported follow-up to 2 weeks. The overall effect size was small with a standardized mean difference (SMD; Cohen's d) of -.48, and the effect sizes were lower in RCTs with 8 to 16 weeks of follow-up (d = -.42) than with 1 to 4 weeks of follow-up (d = -0.54). The effect size was larger when antidepressant medication was initiated

concurrently with rTMS (5 RCTs, d = -.56) than when patients were on a stable dose of medication (9 RCTs, d = -.43) or were unmedicated (2 RCTs, d = -.26).

Observational Studies

Dunner et al. (2014) reported 1-year follow-up with maintenance therapy from a large multicenter observational study (42 sites) of rTMS for patients with TRD. (13) A total of 257 patients agreed to participate in the follow-up study of 307 who were initially treated with rTMS. Of them, 205 completed the 12-month follow-up, and 120 patients had met the Inventory of Depressive Symptoms-Self Report response or remission criteria at the end of treatment. Ninety-three (36.2%) of the 257 patients who enrolled in the follow-up study received additional rTMS (mean, 16.2 sessions). Seventy-five (62.5%) of the 120 patients who met response or remission criteria at the end of the initial treatment phase (including a 2-month taper phase) continued to meet response criteria through 1-year follow-up.

A variety of tapering schedules are being studied. For example, Richieri et al. (2013) used propensity-adjusted analysis of observational data and found that patients who had maintenance rTMS tapered over 20 weeks (from 3 times per week to once a month) had a significantly reduced relapse rate than patients who had no additional treatment (37.8% vs 81.8%). (14) Connolly et al. (2012) reported that in the first 100 cases treated at their institution, the response rate was 50.6% and the remission rate was 24.7%. (15) At 6 months after the initial rTMS treatment, 26 (62%) of 42 patients who received tapered maintenance therapy (from 2 sessions per week for the first 3 weeks to monthly) maintained their response. In another study, Janicak et al. (2010), patients who met criteria for partial response during either a sham-controlled or an open-label phase of a prior study were tapered from rTMS and simultaneously started on maintenance antidepressant monotherapy. (16) During the 24-week follow-up, 10 of 99 patients relapsed, 38 had symptom worsening, and of these 32 (84%) had symptomatic benefit with adjunctive rTMS.

Section Summary: Treatment-Resistant Depression (TRD)

There are a large number of sham-controlled randomized trials and meta-analyses of these RCTs on rTMS for depression. Meta-analyses found a clinical benefit associated with rTMS for TRD, with improved response rates and rates of remission compared with sham TMS. Additionally, a head-to-head trial showed noninferiority of theta burst stimulation to conventional rTMS, with no difference in the incidence of adverse events. There is some evidence that rTMS, when given in conjunction with the initiation of pharmacologic therapy, improves the response rate compared with pharmacologic therapy alone, while the effect of rTMS is less robust when it is given in combination with a stable dose of antidepressant medication. There is limited evidence to compare the effects of these treatments on cognition, although the adverse effects of rTMS appear to be minimal. While the most recent meta-analyses find that the effect of rTMS is smaller than the effect of ECT on TRD, given that rTMS does not require general anesthesia or induction of seizures, some individuals may not want to use ECT, so the balance of incremental benefits and harms associated with rTMS may be a reasonable balance compared with ECT. One RCT and one clinical trial found clinical benefit for

using Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) for Treatment-Resistant Depression.

Migraine Headache

Clinical Context and Therapy Purpose

The purpose of rTMS 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 policy.

Populations

The relevant populations of interest is individuals with migraine headaches.

Interventions

The therapy being considered is rTMS.

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 QOL 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; and
- Studies with duplicative or overlapping populations were excluded.

Systematic Review

Saltychev et al. (2022) conducted a systematic review and meta-analysis of 8 RCTs that compared rTMS to sham stimulation in patients with migraine. (17) 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 Tables 4 and 5.

Table 4. Systematic Review & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N(Range)	Design	Duration
Saltychev et al. (2022) (17)	2004-2021	8	Adults with migraine	339 (11 to 100)	RCTs	3 to 12 rTMS sessions over 3 days to 8 weeks

Table 5. Systematic Review & Meta-Analysis Results

Study	Migraine days per month	Migraine pain (scale 0 to 100)
Saltychev et al. (2022) (17)		
N=339	N=339	N=257
Difference (95% CI)		
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 for the de novo application. (18) Enrolled in the trial were 201 patients with a history of an aura preceding more than 30% of headaches with moderate or severe headache 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 [0-3], 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 end point 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 end point (37.74% pain free after 2 hours for Cerena vs 16.67% for sham, p=0.018) and for the proportion of subjects who were pain free after 24 hours (33.96% for Cerena vs 10% for sham; p=0.002). 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 rTMS reduced migraine pain and intensity compared to sham. The results of the pivotal trial are also limited by the 46% dropout rate and post hoc analysis. According to the Food and Drug Administration (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). (18)

Obsessive-Compulsive Disorder

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 policy.

Populations

The relevant populations 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 TMS.

The use of TMS for patients with OCD is based on the observation that OCD symptoms are associated with excessive activity in certain cortical areas. TMS 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 QOL 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. (19) 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 0-13 correspond to 'mild symptoms' on the Clinical Global Impression of Severity (CGI-Severity=0-2), 14-25 with 'moderate symptoms' (CGI-Severity=3), 26-34 with 'moderate-severe symptoms' (CGI-Severity=4) and 35-40 with 'severe symptoms' (CGI-Severity=5-6). (20) An improvement of ≥ 35% on the YBOCS is most predictive of treatment response. (21)

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; and
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A systematic review by Trevizol et al. (2016) included 15 RCTs (total N=483 patients) that compared active with sham rTMS for OCD (Tables 6 and 7). (22) All studies were sham-controlled and double-blinded. 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 standardized mean difference for the primary outcome (YBOCS score). Response rates were not reported.

The pooled mean difference between groups on the YBOCS was 2.94 (95% Cl, 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. (23) 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 7). 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). (24)

Perera et al. (2021) conducted a systematic review and meta-analysis of rTMS in the treatment of OCD. (25) 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 6. Systematic Review of TMS in Patients with OCD: Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Perera et al. (2021) (25)	Up to October 2020	26	Mean age, 33 years	781	RCT, sham-controlled	1 week to 6 weeks
Liang et al. (2021) (23)	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) (22)	Up to March 2016	15	Mean age, 31.9 (SD=7.6) years; 44.1% women	483 (18-65); mean 16.1 (SD 8.45)	RCT, sham-controlled	1 week to 6 weeks

OCD: obsessive-compulsive disorder; RCT: randomized controlled trial; TMS: transcranial magnetic stimulation; SD: standard deviation; TMS: transcranial magnetic stimulation.

Table 7. Systematic Review & Meta-Analysis: Results

Study	YBOCS Score	Dropouts
Perera et al. (2021) (25)		
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) (23)		
	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 (0.9 to 7.62)	0.98 (0.37 to 2.67)
Low frequency rTMS applied over the orbitofrontal cortex	4.43 (-2.57 to 1131)	0.59 (0.06 to 5.68)
High-frequency rTMS applied over the cingulate cottex/medical prefrontal cortex (deep TMS)	4.25 (-1.16 to 9.59)	1.62 (0.26 to 15.98)
Trevizol et al. (2016) (22)		
Total N	483	483
	Standardized Mean Difference: 0.45 (0.20 to 0.71)	Odd ratio: 1.02 (0.76-1.36)
	I^2 43%, P=0.039	
	Mean Difference: 2.94 (1.26, 4.62)	
	I^2 58% (P=0.002)	

YBOCS: Yale-Brown Obsessive-Compulsive Score; Crl: credible interval; OR: odds ratio; rTMS: repetitive transcranial magnetic stimulation; SMD: standardized mean difference,NR: not reported.

Randomized Controlled Trial

This section discusses in detail the sham-controlled RCT of deep TMS for OCD conducted by Carmi et al. (2019). (24) 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. (26) Study characteristics and results are summarized in Tables 8 and 9, and limitations are shown in Tables 10 and 11. 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 intent-to-treat (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=0.003). 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% Cl, -3.8 to -8.2) in the active group and by -4.1 points (95% Cl, -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=0.0988). Results on the secondary outcomes were mixed. More patients in the active treatment group were considered improved based on the Clinical Global Impression of Improvement and the CGI-S at 6 weeks, but there was no significant difference between groups on the Sheehan Disability Scale (See Table 10).

Table 8. Summary of Key RCT Characteristics – TMS for Patients with OCD

Study; Trial	Countries	Sites	Dates	Participants	Interventions		Duration of Follow-up
Carmi et al. (2019) (24) NCT 02229903	United States; Israel; Canada	11	2014-2017	N=99 Adults ages 22-68 years, diagnosis of OCD as a primary disorder, receiving treatment in an outpatient setting, and	Deep TMS 6-week treatment phase (consisting of 5 weeks of daily treatments 5 days a week and	Sham	6 weeks (primary) 10 weeks (secondary)

				have 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 one 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.	four treatments during the 6th week)		

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

Table 9. Summary of Key RCT Results – RMS for Patients with OCD

Study	YBOCS (Primary Outcome)	YBOCS Response	CGI-1	CGI-s (modified)	Sheehan Disability Scale	Adverse Events (all)	Dropouts
Carmi et al. (2019) (24) NCT02229903	*Mean change from baseline at 6 weeks*	*(≥30% change from baseline to 6 weeks)*	*Moderate to very much improved from baseline*				

			at 6 weeks				
N analyzed	94	94	94	94			
TMS	-6.0 points (95% CI=4.0, 8.1)	38.1% (16/42)	20/41 (49%)	25/41 (61%)	-3.8 points (95% CI -1.5, -6.1)	73%	6/48 (12.5%)
Sham	-3.3 points (95% CI=1.2, 5.3)	11.1% (5/45)	9/43 (21%)	14/43 (32.6%)	-3.0 points (95% CI -0.8, -5.3)	69%	6/51 (12.0%)
Difference; P-value	2.8 points; P=0.01 Effect size: 0.69	P=0.003	P=0.011	P=0.022	NS (p-value not reported)	P=0.639	NS (p-value not reported)

RCT: randomized controlled trial; TMS: transcranial magnetic stimulation; OCD: obsessive-compulsive disorder; YBOCS: Yale-Brown Obsessive- Compulsive Scale; CGI-1: Clinical Global Impression of Improvement; CGI-S: Clinical Global Impression of Severity; CI: confidence interval; NS: non- significant.

Table 10. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Carmi et al. (2019) (24) NCT 02229903					1, 2. 6 weeks (primary)

The study limitations stated in this table are those notable in the current literature 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, 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, 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. No CONSORT 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 11. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]

Carmi et al. (2019) (24) NCT 02229903				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; NCT: national clinical trial.

The study limitations stated in this table are those notable in the current literature 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.

Storch et al. (2020) (27) studied a sample of 94 adults with OCD undergoing daily sessions of deep TMS (dTMS) of the dorsal medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) or sham dTMS over a period of six weeks. Significantly greater reductions in OCD symptoms were observed in the dTMS group relative to the sham group both at post-treatment and at 4-weeks follow up as reported previously (Carmi et al., 2019 [24]). Among the different factors examined, older age, lower baseline OCD severity and lower baseline functional disability significantly predicted greater OCD symptom reduction at post-treatment, regardless of treatment condition. This is one of the first studies to investigate the predictors and moderators of response to dTMS of the mPFC/ACC in adults with OCD. Findings suggest older participants and those with lower OCD severity and disability respond faster to both dTMS and Sham. Importantly, dTMS of the dorsal mPFC/ACC appeared to have larger benefits for individuals with greater OCD severity, whereas the difference between treatment arms was minimal in those with lower severity. This suggests that having a higher minimum YBOCS inclusion criterion may best serve to understand the actual treatment effects since those with lower OCD severity seem to respond similarly to active and sham interventions.

Inspection of the data suggest that there was a substantial effect of dTMS vs. sham for those with more severe symptoms; the half of the sample with higher baseline YBOCS scores (i.e., at least 28, roughly corresponding with at least moderate to severe symptoms) were estimated to experience a 7.1 point YBOCS reduction in dTMS versus a 2.9 point YBOCS reduction in sham. For those with lower baseline symptoms (i.e., 27 or below, roughly corresponding to those with moderate OCD severity), there did not appear to be a substantial difference between active and sham treatment, with those in dTMS estimated to experience a 5.7 point reduction and those in sham experiencing a 4.7 point reduction.

In 2020, Roth et al. (28) studied participants with primary diagnosis of OCD, who did not respond to at least one past trial with serotonin reuptake inhibitors (SRI), were on maintenance therapy of SRI indicated for ICD +/- maintenance cognitive behavior therapy (CBT), and nevertheless had a YBOCS score of >20. There were no significant differences in age or gender between the cohorts. Response at post treatment was significantly higher in the dTMS group compared to the sham in the larger cohorts of 3+ meds (dTMS: 41.4%; sham:8.3%; p=0.0109) and of past CBT (dTMS: 33.3%; sham: 3.3%; p= 0.0041). The analysis demonstrates that dTMS is an effective treatment option for OCD patients, regardless of prior non-response to SRIs, antipsychotics or CBT sessions.

Section Summary: Obsessive-Compulsive Disorder

The evidence on rTMS for OCD includes a number of small-to-moderate size sham-controlled double-blind randomized trials and meta-analyses of these RCTs. The meta-analysis of 15 RCTs (total n=483 patients, range 18-65 patients) 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. A more recent RCT 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=0.003), as measured by a 30% or greater increase in the YBOCS. Recent studies from 2020 looking at dMTS show lower baseline OCD severity and lower baseline functional disability significantly predicted greater OCD symptom reduction at post-treatment, regardless of treatment condition. These studies also suggest that having a higher minimum YBOCS inclusion criterion may best serve to understand the actual treatment effects since those with lower OCD severity seem to respond similarly to active and sham interventions. These analyses demonstrate that dTMS is an effective treatment option for OCD patients, regardless of prior non-response to SRIs, antipsychotics or CBT sessions.

Psychiatric and Neurologic Disorders Other Than Depression, Migraine, or Obsessive-Compulsive Disorder

Clinical Context and Therapy Purpose

The purpose of rTMS is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with psychiatric disorders other than depression, migraine, or OCD.

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

Populations
The relevant populations of interest is individuals with psychiatric disorders other than depression, migraine, or OCD.

Interventions
The therapy being considered is rTMS.

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 QOL and functional outcomes. Follow-up over months is of interest to monitor 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; and
- Studies with duplicative or overlapping populations were excluded.

Bipolar Disorder
Systematic Review
Konstantinou et al. (2022) conducted a systematic review of 31 RCTs of rTMS for the treatment of bipolar disorder; meta-analysis was not performed. (29) 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. (30) Eight trials of rTMS in bipolar depression showed small but statistically significant improvements in depression scores compared to sham control (standardized mean difference = 0.302, $P < 0.05$). 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.

Generalized Anxiety Disorder

Systematic Review

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. (31) Results of the analysis showed that rTMS improved anxiety symptoms as measured by the Hamilton Anxiety Scale, (standardized mean difference = −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.

Panic Disorder

Systematic Review

A Cochrane review by Li et al. (2014) identified 2 RCTs (total N=40 patients) that compared low-frequency rTMS with sham rTMS over the right dorsolateral prefrontal cortex (DLPFC). (32) The larger of the 2 studies was a 2013 randomized, double-blind, sham-controlled trial by Mantovani et al. (2013) who assessed 21 patients with panic disorder with comorbid major depression. (33) The response was defined as a 40% or greater decrease on the Panic Disorder Severity Scale and a 50% or greater decrease in HAM-D scores. After 4 weeks of treatment, the response rate for panic was 50% with active rTMS and 8% with sham. The trial had a high risk of attrition bias. The overall quality of evidence for the 2 trials was considered low, and the sample sizes were small, precluding any conclusions about the efficacy of rTMS for panic disorder.

Posttraumatic Stress Disorder

Systematic Review

Trevizol et al. (2016) published a systematic review on the efficacy of low- and high-frequency rTMS for posttraumatic stress disorder (PTSD). (34) Five sham-controlled randomized trials (total 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 one 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

PTSD 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.

Schizophrenia

Systematic Reviews

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. (35) For 1-Hz rTMS, 13 studies were included. Compared with sham, the rTMS group showed greater improvement in auditory hallucinations (standard mean difference, -0.29; 95% CI, -0.57 to -0.01). However, significant heterogeneity across the studies was found (p=0.06). 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<0.001). 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) included 41 studies with a total of 1473 participants. (36) 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 state 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 robust enough 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 below (Tables 12 and 13). (37-40) These studies were limited by their small sample sizes, very high loss to follow-up, and inadequate duration of follow-up (Tables 14 and 15). 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 12. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions		Duration of follow-up
					Active	**Comparator**	
Zhu et al. (2021) (40)	China	7	2017-2018	Inpatients ages 18 to 50 years with a diagnosis of schizophrenia	Intermittent theta burst stimulation over the cerebellum	Sham intermittent theta burst stimulation (N=32)	24 weeks

				per ICD-10 criteria who were right-handed and clinically stable for the past 3 months (N=32)	(3 pulses at 50 Hz repeated at a rate of 5 Hx for a total of 600 pulses administered 5 times a week (Monday to Friday) for 2 weeks (N=32)		
Guan et al. (2020) (37)	China	1	Not reported	Male patients ages 20-60 with DSM-IV diagnosis of schizophrenia >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) (38)	India	1	Not reported	Patients who were right-handed, clinically diagnoses as having schizophrenia per ICD-10 criteria for at least 1 year; on stable doses of medicines (if receiving) for the last 4 weeks but continued to have significant negative	Active rTMS20 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

				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) (39)	China	1	2013-2014	Adults ages 20-60 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; history of epilepsy or seizure; significant or unstable	Active rTMS20 treatment sessions on consecutive weekdays. 20Hz rTMS applied to the left DLPFC (N=35)	Sham rTMS (N=35)	4 weeks

				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; RCT: randomized controlled trial; rTMS: repetitive transcranial magnetic stimulation.

Table 13. Summary of Key RCT Results

Study	Main Results
Zhu et al. (2021) (40)	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) (37)	At 2 weeks, 4 weeks, and 6 weeks, no significant differences in PANSS total score and sub scores between the sham and treatments 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) (38)	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) (39)	Significant decrease in negative symptoms but no significant improvement in cognition.

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

Table 14. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Zhu et al. (2021) (40)	4. Included inpatients only				
Guan et al. (2020) (37)	4. Included men only				1. 8 weeks not sufficient to show durability of effects.
Kumar et al. (2020) (38)					
Zhuo et al. (2019) (39)					1. 4 weeks not sufficient to show durability of effects.

The evidence limitations stated in this table are those notable in the current literature 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. Clinically 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 15. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Zhu et al. (2021) (40)					1. power calculation not reported	
Guan et al. (2020) (37)				1. 15/56 (26.8%) patients discontinued	1. power calculation not reported	

Kumar et al. (2020) (38)				1. 33% attrition (32% active and 38% sham)		
Zhuo et al. (2019) (39)				1. 10/70 discontinued (14.3%)	1. power calculation not reported	

The evidence limitations stated in this table are those notable in the current literature 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.

<u>Substance Use Disorders and Craving</u>

Systematic Review

Jansen et al. reported a 2013 meta-analysis evaluating the effect of rTMS and transcranial direct current stimulation of the DLPFC on substance dependence (alcohol, nicotine, cocaine, marijuana) or food craving. (41) Seventeen double-blind, sham-controlled trials that used high-frequency stimulation were included in the analysis. Thirteen studies stimulated the left DLPFC and 7 studies stimulated the right DLPFC or both sides. Twelve of the studies gave only 1 or 2 sessions. The standardized effect size was 0.476 (95% CI, 0.316 to 0.636), indicating a medium effect size for active stimulation over sham for a reduction in craving. However, the studies were small (range, 9-48 patients) and there was significant heterogeneity in selected studies. No significant differences were found in the effectiveness of rTMS vs. transcranial direct current stimulation, the different substances, or the side of stimulation, although this analysis might have been biased by the number of studies for each condition.

Chang et al. (2022) conducted a meta-analysis of 7 double-blind RCTs (N=462) that used rTMS to treat methamphetamine use disorder. (42) All studies targeted the left DLPFC and the number of sessions ranged among studies from 5 to 20. Mean craving scores at baseline ranged from 22.63 to 57.68. A random effects model showed that clinical craving scores were significantly lower with rTMS than sham treatment (SMD, 0.983; 95% CI, 0.620 to 1.345; $p \leq .001$; $I^2=67.814\%$). According to a subgroup analysis, intermittent theta burst stimulation had

a greater effect than 10-Hz rTMS. The authors concluded that further trials with larger sample sizes are needed.

Neurologic Disorders Other Than Migraine

Amyotrophic Lateral Sclerosis or Motor Neuron Disease

A Cochrane review by Fang et al. (2013) identified 3 RCTs with a total of 50 participants with amyotrophic lateral sclerosis that compared rTMS with sham TMS. (43) All trials were considered of poor methodologic quality. Heterogeneity prevented pooling of results, and the high rate of attrition further increased the risk of bias. Reviewers concluded that evidence was insufficient to draw conclusions about the efficacy and safety of rTMS in the treatment of amyotrophic lateral sclerosis.

Chronic Pain

A Cochrane review by O'Connell et al. (2018) evaluating noninvasive brain stimulation techniques was first published in 2010 and was updated in 2014 (44) and 2018. (45) The reviewers identified 42 RCTs (range 4 to 70 participants) on TMS for chronic pain. Meta-analysis of 27 rTMS studies vs. sham (N=655 participants) for pain intensity at short-term follow-up (0 to < 1-week postintervention), (27 studies, involving 655 participants), 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 of the motor cortex and transcranial direct current stimulation (tDCS) 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. There was no evidence that low-frequency rTMS, rTMS applied to the dorsolateral prefrontal cortex 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. (46) 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.

Epilepsy

A Cochrane review by Chen et al. (2016) included 7 RCTs on rTMS for epilepsy, 5 of which were completed studies with published data. (47) The total number of participants was 230. All studies had active or placebo controls, and four were double-blinded. However, a meta-analysis could not be conducted due to heterogeneity in designs, interventions, and outcomes of the

studies. Therefore, a qualitative synthesis was performed. For the outcome of seizure rate, 2 studies showed a significant reduction and 5 studies did not. Of the 4 studies evaluating the mean number of epileptic discharges, 3 studies showed a statistically significant reduction in discharges. Adverse events were uncommon and mild, involving headache, dizziness, and tinnitus. There were no significant changes in medication use.

A more recent meta-analysis conducted by Mishra and colleagues (2020) included 7 RCTs that compared rTMS with sham or placebo controls in patients with epilepsy. (48) Two of the included studies showed statistically significant reductions in the seizure rate from baseline, 3 trials failed to show any statistically significant difference in seizure frequency, and 2 had unclear results due to inadequate power. In a meta-regression, when adjusted for other potential variables such as the type of coil used, stimulation frequency, and the total duration of the active intervention, seizure frequency worsened by 2.00 ± 0.98 (p=0.042) for each week of lengthening of the posttreatment follow-up period. These results suggested that rTMS exerted only a short-term effect. The reviewers concluded that although the procedure may be a therapeutic alternative for patients with drug-resistant epilepsy, further RCTs using standardized protocols and with adequate sample sizes and duration are still needed.

Fibromyalgia

Su et al. (2021) conducted a meta-analysis of 18 RCTs (N=643) with rTMS in patients with fibromyalgia. (49) 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. (50) The meta-analysis included 7 sham-controlled double-blinded controlled trials with low risk of bias. The sample sizes of the trials ranged from 18 to 54. Five of the 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.

Parkinson Disease

A meta-analysis by Chou et al. (2015) included 20 sham-controlled randomized trials (total N=470 patients) evaluating Parkinson disease. (51) Sample sizes ranged from 8 to 102 patients. The total effect size of low- and high-frequency rTMS on Unified Parkinson's Disease Rating Scale part III score was 0.46, which is considered a small-to-medium effect size, and the mean

change in the Unified Parkinson's Disease Rating Scale part III score (-6.42) was considered a clinically important difference. The greatest effect on motor symptoms was from high-frequency rTMS over the primary motor cortex (SMD=0.77, p<0.001) and low-frequency rTMS over other frontal regions (SMD=0.50, p=0.008). High-frequency rTMS at other frontal regions and low-frequency rTMS over the primary motor cortex did not have a statistically significant benefit. The largest trial included in the systematic review was an exploratory, multicenter, double-blind trial reported by Shirota et al. (2013) who randomized 106 patients to 8 weeks of 1-Hz rTMS, 10-Hz rTMS, or sham stimulation over the supplementary motor area. (52) At 9 weeks, all groups showed a similar amount of improvement.

Li et al. (2022) conducted a meta-analysis of 32 sham-controlled RCTs of rTMS in patients with Parkinson disease and motor dysfunction (N=1048 patients). (53) Motor dysfunction was assessed using the United Parkinson's Disease Rating Scale part III score. Overall, rTMS had a significant effect on motor symptoms compared to sham (SMD, 0.64; 95% CI, 0.47 to 0.80; p<.0001; I^2=64%). High-frequency rTMS to the primary motor cortex was the most effective intervention. Significant benefit of rTMS was also demonstrated for akinesia, rigidity, and tremor.

Stroke Recovery

A number of RCTs and systematic reviews have evaluated rTMS for recovery from stroke. For example, a Cochrane review by Hao et al. (2013) included 19 RCTs (total N=588 participants) evaluating the effect of low- and high-frequency TMS for improving function after stroke. (54) The 2 largest trials (n=183 patients) showed that rTMS was not associated with a significant improvement in Barthel Index scores. Four trials (n=73) found no significant effect on motor function. Subgroup analyses for different stimulation frequencies or durations of illness also did not show a significant benefit of rTMS compared with sham rTMS or no treatment. Reviewers concluded that current evidence did not support the routine use of rTMS for the treatment of stroke.

A meta-analysis by Le et al. (2014) assessed the effect of rTMS on the recovery of hand function and excitability of the motor cortex after stroke. (55) Eight RCTs (total N=273 participants) were selected. The quality of the trials was rated moderate to high, although the size of the studies was small. There was variability in the time since stroke (5 days to 10 years), in the frequency of rTMS applied (1-25 Hz for 1 second to 25 min/d), and the stimulation sites (primary motor cortex or premotor cortex of the unaffected hemisphere). Meta-analysis found a positive effect on finger motor ability (4 studies; n=79 patients; SMD=0.58) and hand function (3 studies; n=74 patients; SMD = -0.82), but no significant change in motor evoked potentials (n=43) or motor threshold (n=62).

A meta-analysis by Li et al. (2015) included 4 RCTs on low-frequency rTMS over the right parstriangularis for patients (total N=137) with aphasia after stroke. (56) All studies used double-blinding, but therapists were not blinded. Every trial used a different outcome measure, and sample sizes were small (range, 12-40 patients). Meta-analysis showed a medium effect size for naming (p=0.004), a trend for a benefit on repetition (p=0.08), and no significant benefit

for comprehension (p=0.18). Additional study in a larger number of patients would be needed to determine with greater certainty the effect of this treatment on aphasia after stroke.

Qiao et al. (2022) performed a meta-analysis of RCTs that assessed the effect of rTMS in 433 patients with post-stroke dysphagia. (57) Twelve trials that used dysphagia severity rating scales (Dysphagia Grade and Penetration Aspiration Scale) were included. The specific controls used in each study were not specified. Study characteristics included duration of treatment of 1 to 10 days, stimulation frequency of 1 to 10 Hz, and duration of stimulation of 5 to 20 minutes. The analysis favored rTMS (SMD, -0.67; 95% CI, -0.88 to -0.45; p<.001; I^2=42%). Subgroup analyses identified treatment duration >5 days and rTMS during the subacute phase after stroke as potential situations with greater clinical benefit, but there was no difference in efficacy according to stimulation frequency, location, or duration of each stimulation. The authors noted that publication bias was present and there may be limited clinical applicability of the dysphagia rating scales.

Zhang et al. (2017) published a systematic review and meta-analysis evaluating the effects of rTMS on upper-limb motor function after stroke. (58) A search through October 2016 yielded 34 RCTs with a total of 904 participants (range, 6-108 participants). Pooled estimates found improvement with rTMS for both short-term (SMD=0 .43; p<0.001) and long-term (SMD=0 .49; p<0.001) manual dexterity. Of the 28 studies reporting on adverse events, 25 studies noted none. Mild adverse events, such as headache and increased anxiety were reported in three studies. The review was limited by variation in TMS protocols across studies.

Graef et al. (2016) reported a systematic review of rTMS combined with upper-limb training for improving function after stroke. (59) Included were 11 sham-controlled randomized trials with 199 patients that evaluated upper-limb motor and functional status and spasticity; 8 RCTs with sufficient data were included in the meta-analysis. These studies were considered to have a low-to-moderate risk of bias. In the overall analysis, there was no benefit of rTMS on upper-limb function or spasticity (SMD=0.03; 95% CI, -0.25 to 0.32).

Section Summary: Psychiatric or Neurologic Disorders Other Than Depression, Migraine or Obsessive-Compulsive Disorder

For individuals who have psychiatric disorders other than depression or OCD (e.g., panic disorder, posttraumatic stress disorder, schizophrenia, substance use disorder and craving) 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. A number of sham-controlled randomized trials and a meta-analysis of these have found a medium effect size of rTMS for the reduction of substance dependence or food craving. Most studies examined acute craving after 1 or 2 rTMS sessions, and there is limited evidence on the longer-term efficacy of this treatment approach. 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 disorders other than migraine (e.g., amyotrophic lateral sclerosis, chronic pain, epilepsy, fibromyalgia, Parkinson disease, 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.

Summary of Evidence

For individuals who have treatment-resistant depression (TRD) who receive transcranial magnetic stimulation (TMS) or Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) for Treatment-Resistant Depression, the evidence includes a large number of sham-controlled randomized controlled trials (RCTs), a meta-analyses of these trials and a clinical trial. Relevant outcomes are symptoms, functional outcomes, and quality of life (QOL). Meta-analyses found improved response rates and rates of remission for conventional TMS and theta burst stimulation compared with sham TMS. Additionally, a head-to-head trial showed noninferiority of theta burst stimulation to conventional TMS, with no difference in the incidence of adverse events. Meta-analyses have concluded that the effect of TMS on average depression scores is smaller than the effect of electroconvulsive therapy (ECT) on TRD and that the mean improvement in depression scores with TMS did not reach the minimal clinically important difference; however, clinically meaningful improvements were noted in a subgroup of studies using higher frequency pulses. One potential area of benefit for TMS is in accelerating or enhancing the response to antidepressant medications, and there is some evidence that TMS, when given in conjunction with the initiation of pharmacologic therapy, improves the response rate compared with pharmacologic therapy alone. The effect of TMS appears to be less robust when it is given in combination with a stable dose of antidepressant medication. Meta-analyses have also found that the efficacy of TMS decreases with longer follow-up, though some studies have reported a persistent response up to 6 months in some patients. There is limited evidence to compare the effects of these treatments on cognition, although the adverse events of TMS appear to be minimal. While meta-analyses have reported that the effect of TMS is smaller than the effect of ECT on TRD, because TMS does not require general anesthesia or induce seizures, some individuals may decline ECT so the balance of incremental benefits and harms associated with TMS may be reasonable compared with ECT. Based on the short-term benefit observed in RCTs and the lack of alternative treatments aside from ECT in patients with TRD, TMS may be considered a treatment option in patients with TRD who meet specific criteria. Intermittent theta-burst stimulation (iTBS) is limited by suboptimal efficacy and a 6-week duration, therefore using SAINT can be beneficial. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have migraine headaches who receive 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 rTMS 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 outcome.

For individuals who have obsessive-compulsive disorder (OCD) who receive TMS, the evidence includes a number of small-to-moderate sized sham-controlled RCTs and a meta-analysis of these studies. The meta-analysis of 15 RCTs (total n=483 patients, range 18-65 patients) found a benefit of TMS on patient-reported OCD symptom severity at time points ranging from 2 to 6 weeks. A more recent RCT 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 intent-to-treat (ITT) analysis (n=94), there was a larger mean change from baseline on the primary efficacy outcome; Yale-Brown Obsessive-Compulsive Scale (YBOCS) score 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=0.003), as measured by a 30% or greater decrease in the YBOCS. There was a benefit for TMS on clinician-reported measures of improvement regardless of prior non-response to serotonin reuptake inhibitor (SRIs), antipsychotics or cognitive behavioral therapy (CBT) sessions. Studies showed lower baseline OCD severity and lower baseline functional disability significantly predicted greater OCD symptom reduction at post-treatment, regardless of treatment condition. The evidence is sufficient to determine to that the technology results in an improvement in the net health outcome.

For individuals who have psychiatric or neurologic disorders other than depression, migraine, or OCD (including but not limited to: bipolar disorder, generalized anxiety disorder, Alzheimer's disease, attention deficit disorder/hyperactivity disorder, chronic pain, epilepsy, fibromyalgia, panic disorder, Parkinson disease, posttraumatic stress disorder, schizophrenia, stroke, substance use disorder and craving) 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.

Practice Guidelines and Position Statements

American Academy of Child and Adolescent Psychiatry

In 2013, the American Academy of Child and Adolescent Psychiatry published practice parameters on the assessment and treatment of children and adolescents with tic disorders. (61) The Academy did not recommend rTMS, citing the limited evidence on the safety, ethics, and long-term impact on development.

American Psychiatric Association

The American Psychiatric Association (2018) published consensus recommendations on rTMS for the treatment of depression. (60) The guidelines state, "Multiple randomized controlled trials and published literature have supported the safety and efficacy of rTMS antidepressant therapy." The recommendations include information on the following variables: clinical environment, operator requirements, documentation, coils, cortical targets, coil positioning methods, determination of motor threshold, number of treatment sessions for acute treatment, and allowable psychotropic medications during TMS treatment.

The American Psychiatric Association's (2007, reaffirmed in 2012) guidelines on the treatment of patients with OCD have indicated that "findings of the four published trials of repetitive TMS (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." (62)

Veteran's Affairs/Department of Defense

The 2022 Veteran's Affairs/Department of Defense guideline for management of major depressive disorder recommends offering rTMS to patients who have experienced partial response or no response to an adequate trial of 2 or more pharmacologic treatments (strength of recommendation: weak). (68) Recommended options for the second treatment attempt after the initial therapy tried including switching to another antidepressant or adding augmentation therapy with a second-generation antipsychotic. The recommendation for rTMS was graded as weak due to limitations of the available literature including small study effects, high rates of discontinuation, lack of allocation concealment, and the practical limitations of the need for daily treatment and lack of widespread access to facilities that offer this therapy. The guideline also concluded that there is limited evidence to recommend for or against theta-burst stimulation for treatment of depression.

National Institute for Health and Care Excellence

In 2015, the National Institute for Health and Care Excellence provided revised guidance, stating that evidence on the short-term efficacy of rTMS for depression is adequate, although the clinical response is variable, and some patients may not benefit. (63)

In 2014, the Institute provided guidance on the use of rTMS for treating and preventing migraine. (64) The guidance stated that evidence on the efficacy of TMS for the treatment of a migraine is limited in quantity and for the prevention of a migraine is limited in both quality and quantity. Evidence on its safety in the short and medium term is adequate, but there is uncertainty about the safety of long-term or frequent use of TMS.

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. (65, 66)

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. (67) 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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished and ongoing trials that might influence this policy are listed in Table 16.

Table 16. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT02977299	Augmentation Versus Switch: Comparative Effectiveness Research Trial for Antidepressant Incomplete and Non-Responders with Treatment- Resistant Depression (ASCERTAIN-TRD)	278	Apr 2022
NCT02910024	Theta-Burst-Stimulation in Early Rehabilitation of Stroke (TheSiReS)	150	Sep 2022
NCT03556722	Effectiveness and Tolerability of Repetitive Transcranial Magnetic Stimulation For Preventive Treatment Of Episodic Migraine: A Single Centre, Randomised, Double-Blind, Sham-Controlled Phase 2 Trial	76	Apr 2022
Ongoing			
NCT02927236	Neuroplasticity Following Theta-Burst Stimulation in Cocaine Use Disorder	170	Dec 2023
NCT05389670	Theta-burst Repetitive Transcranial Magnetic Stimulation (TBS) of the Right Inferior Frontal Gyrus for Treatment of Nicotine Dependence	60	Apr 2025
NCT05331937	Transcranial Magnetic Stimulation (TMS) for Patients With Exposure Therapy-resistant	250	Sep 2027

	Obsessive-compulsive Disorder (OCD): TETRO - a Multicenter Randomized Controlled Trial		
NCT05100888	Theta-burst rTMS in Schizophrenia to Ameliorate Negative and Cognitive Symptoms: a Double-blind, Randomized Clinical Trial	90	Dec 2025

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	90867, 90868, 90869, 0858T, 0889T, 0890T, 0891T, 0892T
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change

10/01/2024	Document updated with literature review. The following change was made to coverage: added conditional coverage under major depressive disorder for adolescents 15-18 (as an augmentation agent along with antidepressant medications). Reference 68-70 added; others updated.
07/15/2023	Document updated with literature review. Coverage unchanged. References 1-4, 17, 25, 29, 40, 42, 46, 49, 53, 57 and 65-67 added; others removed.
08/15/2022	Document updated with literature review. The following change was made to the Coverage: Theta burst stimulation added to conditional coverage. Novel delivery mechanisms (i.e., multiple TMS sessions/day) added to experimental, investigational, and/or unproven list. Note 4 added stating "The following clinical scenarios may be evaluated on a case-by-case basis and will not be authorized without viable clinical justification/rationale supported by evidence-based practices and/or accepted guidelines: 1) Incomplete treatment due to extenuating circumstances and 2) Remapping requests." Note 2: clarified session limits for MDD and OCD. References 4, 5 and 18 added; others deleted.
07/01/2021	Document updated with literature review. The following changes were made to the Coverage: 1) Added Obsessive Compulsive Disorder as a conditionally covered when criteria are met; 2) Added criteria for Transcranial Magnetic Stimulation treatment. References 25-26, 33-35, 41 and 56-57 added; 1 reference removed.
07/01/2020	Document updated with literature review. Coverage has changed. 1) The following statement was changed from "Patient has had 4 failed trials of FDA cleared antidepressant medications from at least 2 different classes of antidepressants in the current episode; AND" TO: "Patient has tried and had an inadequate response to 2 antidepressant agents from 2 different antidepressant classes (i.e., selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, bupropion, or mirtazapine). An adequate trial of an antidepressant is defined by the following: The trial length was at least 6 weeks at generally accepted doses or of sufficient duration as determined by the treating physician at the generally accepted doses without significant improvement/response in depressive symptoms; AND" 2) Added the following statement: "The rTMS treatment is delivered by a device that is FDA-approved or FDA-cleared for the treatment of MDD in a safe and effective manner. rTMS treatment should generally follow the protocol and parameters specified in the manufacturer's user manual, with modifications only as supported by the published clinical evidence base; AND". References revised and renumbered; some removed; added references 10, 19-21, 23-24, 28, 34, 43, 45.
05/15/2018	Document updated with literature review. Coverage unchanged. References 9, 19, 21, 24, 29, 35, 38, 45, 46 added, some references were removed.
07/01/2017	Document updated with literature review. Coverage has changed: 1) The following statement changed from: "Diagnosis of major depression, either

	single episode or recurrent (non-psychotic); AND" TO: "Diagnosis of severe major depressive disorder, either single episode or recurrent (non-psychotic) documented by standardized rating scales that reliably measure depressive symptoms; AND". 2) The following words "U.S. Food and Drug Administration (FDA) cleared" were added to the statement: "Patient has had 4 failed trials of U. S. Food and Drug Administration (FDA) approved antidepressant medications from at least 2 different classes of antidepressants in the current episode; AND". 3) The following statement was changed from: "Patient is currently, or has been, in formal cognitive behavioral therapy; AND" TO: "Patient has failed a trial of a psychotherapy known to be effective in the treatment of major depressive disorder (i.e., cognitive behavioral therapy) of an adequate frequency and duration, without significant improvement in depressive symptoms, as documented by standardized rating scales that reliably measure depressive symptoms; AND". The following phrase was added to both the Initial rTMS Treatment statement and Subsequent rTMS Treatment statement: "using a U.S. Food and Drug Administration (FDA) cleared device in accordance with the FDA labeled indications."
02/15/2016	Reviewed. No changes.
07/01/2014	Document updated with literature review. The following changed: 1) rTMS may be considered medically necessary for treatment of major depressive disorder that is resistant to other treatment, when the specific criteria are met; 2) Navigated TMS has been moved to MED205.037 Navigated Transcranial Magnetic Stimulation (nTMS). Title changed from Transcranial Magnetic Stimulation (TMS).
01/01/2013	The following was added: Navigated transcranial magnetic stimulation (nTMS) is considered experimental, investigational and unproven. CPT/HCPCS code(s) updated.
06/01/2012	Document updated with literature review. Rationale completely revised. Coverage unchanged.
05/01/2010	New medical document. Transcranial magnetic stimulation (TMS) is considered experimental, investigational and unproven as a treatment of depression and other psychiatric or neurologic disorders including, but not limited to, schizophrenia or migraine headaches. (Coverage is unchanged. This topic was previously addressed on PSY301.000.)