Medical Policy

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Title: Transcranial Magnetic Stimulation (TMS) as a Treatment of Depression and Other Psychiatric/Neurologic Disorders

Related Policies:	▪ *Vagus Nerve Stimulation* ▪ *Treatment of Tinnitus*

Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: • With treatment-resistant depression	Interventions of interest are: ▪ Repetitive transcranial magnetic stimulation	Comparators of interest are: ▪ Pharmacotherapy ▪ Psychological and behavioral therapy ▪ Electroconvulsive therapy	Relevant outcomes include: ▪ Symptoms ▪ Functional outcomes ▪ Quality of life
Individuals: • With psychiatric or neurologic disorders other than depression, migraine or obsessive-compulsive disorder	Interventions of interest are: ▪ Repetitive transcranial magnetic stimulation	Comparators of interest are: ▪ Pharmacotherapy ▪ Therapy as appropriate including either physical and occupational therapy or psychological and behavioral therapy	Relevant outcomes include: ▪ Symptoms ▪ Functional outcomes ▪ Quality of life
Individuals: • With obsessive-compulsive disorder	Interventions of interest are: ▪ Repetitive transcranial magnetic stimulation	Comparators of interest are: ▪ Pharmacotherapy ▪ Psychological and behavioral therapy	Relevant outcomes include: ▪ Symptoms ▪ Functional outcomes ▪ Quality of life
Individuals: • With migraine	Interventions of interest are: ▪ Repetitive transcranial magnetic stimulation	Comparators of interest are: • Pharmacotherapy	Relevant outcomes include: ▪ Symptoms ▪ Functional outcomes ▪ Quality of life

DESCRIPTION

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

OBJECTIVE

The objective of this evidence review is to evaluate whether the use of repetitive transcranial magnetic stimulation of the brain improves the net health outcome for individuals with various psychiatric or neurologic conditions.

BACKGROUND

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. Transcranial magnetic stimulation was initially used to investigate nerve conduction (e.g., TMS over the motor cortex will produce a contralateral muscular-evoked potential). The motor threshold, which is the minimum intensity of stimulation required to induce a motor response, is empirically determined for each person by localizing the site on the scalp for optimal stimulation of a hand muscle, then gradually increasing the intensity of stimulation. Interest in the use of TMS as a treatment for depression was augmented by the development of a device that could deliver rapid, repetitive stimulation. Imaging studies had shown a decrease in the activity of the left dorsolateral prefrontal cortex in depressed patients, and early studies suggested that high-frequency (e.g., 5 to 10 Hz) TMS of the left dorsolateral prefrontal cortex had antidepressant effects. In contrast to electroconvulsive therapy (ECT), TMS does not require general anesthesia and does not generally induce a convulsion. Repetitive TMS (TMS) 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, a lithium battery pack, and a smaller size. The stimulation parameters are unchanged. The rTMS Mini (eNeura Therapeutics) received marketing clearance by the FDA in 2016. FDA product code: OKP.

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

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

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

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

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 FDA for Major Depression, Migraine, or Obsessive-Compulsive Disorder

Device	Manufacturer	Indication	FDA Clearance No.	FDA Clearance Date
Neurostar	Neuronetics	Major Depressive Disorder	K083538	12/16/2008
Brainsway Deep TMS System	Brainsway	Major Depressive Disorder	K122288	01/07/2013
		Obsessive-Compulsive Disorder	K183303	03/08/2019
Springtms Total Migraine System	Eneura	Migraine headache with aura	K140094	05/21/2014

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

FDA: U.S. Food and Drug Administration; TMS: transcranial magnetic stimulation

POLICY

A. Repetitive transcranial magnetic stimulation (rTMS) of the brain using an FDA-cleared device and modality, which can include but is not limited to, conventional TMS, deep TMS, and theta burst stimulation (see Policy Guidelines) may be considered **medically necessary** as a treatment of major depressive disorder when all of the following conditions (1-3) have been met:

1. Confirmed diagnosis of severe major depressive disorder (single or recurrent) documented by standardized rating scales that reliably measure depressive symptoms;

   AND

2. Any one of the following (a, b, c, or d):

   a. Failure of 4 trials of psychopharmacologic agents including 2 different agent classes and 2 augmentation trials; **OR**

   b. Inability to tolerate a therapeutic dose of medications as evidenced by 4 trials of psychopharmacologic agents with distinct side effects; **OR**

   c. History of response to rTMS in a previous depressive episode (at least 3 months since the prior episode); **OR**

   d. Is a candidate for electroconvulsive therapy (ECT) and ECT would not be clinically superior to rTMS (e.g., in cases with psychosis, acute suicidal risk, catatonia or life-threatening inanition rTMS should NOT be utilized);

   AND

3. Failure of a trial of a psychotherapy known to be effective in the treatment of major depressive disorder of an adequate frequency and duration, without significant improvement in depressive symptoms, as documented by standardized rating scales that reliably measure depressive symptoms.

B. Repetitive TMS for major depressive disorder that does not meet the criteria listed above is considered **experimental / investigational**.

C. Continued treatment with rTMS of the brain as maintenance therapy is considered **experimental / investigational**.

D. Transcranial magnetic stimulation of the brain is considered **experimental / investigational** as a treatment of all other psychiatric/neurologic disorders including, but not limited to, bipolar disorder, schizophrenia, obsessive-compulsive disorder, or migraine headaches.

POLICY GUIDELINES

1. Repetitive Transcranial magnetic stimulation (TMS) should be performed using a U.S. Food and Drug Administration cleared device in appropriately selected patients over age 18 years, by physicians who are adequately trained and experienced in the specific techniques used.

2. The physician is responsible for the initial mapping (once per course or delivery) and the management of the treatment. The physician is also responsible for the re-determinations.

3. A trained technician may perform the subsequent delivery of treatment.

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

5. 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.

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

7. Deep TMS employs an H-coil helmet designed to encompass a broader surface area and stimulate deeper brain structures than conventional TMS.

8. A treatment course should not exceed 5 days a week for 6 weeks (total of 30 sessions), followed by a 3-week taper of 3 TMS treatments in week one, 2 TMS treatments the next week, and 1 TMS treatment in the last week.

9. Theta burst stimulation may be administered using an accelerated protocol. One example of an accelerated theta burst protocol is the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol, consisting of 10 daily sessions over 5 consecutive days.

10. Contraindications to repetitive TMS include:
    a. Seizure disorder or any history of seizure with increased risk of future seizure; or
    b. Presence of acute or chronic psychotic symptoms or disorders (e.g., schizophrenia, schizophreniform or schizoaffective disorder) in the current depressive episode; or
    c. Neurologic conditions that include epilepsy, cerebrovascular disease, dementia, increased intracranial pressure, having a history of repetitive or severe head trauma, or with primary or secondary tumors in the central nervous system; or
    d. Presence of an implanted magnetic-sensitive medical device located 30 centimeters or less from the TMS magnetic coil or other implanted metal items, including but not limited to a cochlear implant, implanted cardioverter defibrillator, pacemaker, vagus nerve stimulator, or metal aneurysm clips or coils, staples, or stents.

11. The following should be present for the administration of repetitive TMS:
    a. An attendant trained in basic cardiac life support and the management of complications such as seizures, as well as the use of the equipment must be present at all times; and

b. Adequate resuscitation equipment including, e.g., suction and oxygen; and
c. The facility must maintain awareness of response times of emergency services (either fire/ambulance or "code team"), which should be available within 5 minutes. These relationships are reviewed on at least a 1-year basis and include mock drills.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through September 3, 2021.

This review was informed by 3 TEC Assessments (2009, 2011, 2013).[1,2,3,]

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials 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.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR 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 patients with treatment-resistant depression (TRD).

The question addressed in this evidence review is: Does the use of rTMS of the brain for patients with TRD improve the net health outcome?

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

Populations
The relevant population 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 quality of life and functional outcomes.

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Review of Evidence
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 elect 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 the number of sessions.[4,] 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 meta-analysis by Schutter (2009) for a summary of study characteristics and stimulation parameters used in trials conducted prior to 2008.[5,]

Systematic Reviews
The Health Quality Ontario (2016) published a systematic review of left dorsolateral prefrontal cortex (DLPFC) rTMS for TRD.[6,] 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 (Table 2). 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<.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=.011). Secondary analyses showed rTMS demonstrated statistically greater response rates among 20 studies (pooled relative risk [RR}, 1.72) as well as statistically greater remission rates among 13 studies (pooled RR, 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 RR for remission and response rates are shown in Table 2, 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 with 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 2. Statistical Comparisons for Depression Scores after Repetitive Transcranial Magnetic Stimulation

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)	<.001	2.20 (1.44 to 3.38)	.001	1.72 (1.13 to 2.62)	.01
rTMS vs. ECT	ECT	5.97 (0.94 to 11.0)	.02	1.44 (0.64 to 3.23)	.38	1.72 (0.95 to 3.11)	.07

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

Brunoni et al (2017) conducted a systematic review to compare different modalities of rTMS for TRD.[7,] 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.[8,] 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).[9,] 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 2 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 3 antidepressant trials of adequate dosage were excluded from the trials. Patients could alter their medications during this trial. Treatment with conventional 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=.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=.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 (1 case of myocardial infarction) and iTBS (1 case each of agitation, worsening suicidal ideation, worsening depression); there was no significant difference in the number of adverse events in the 2 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 U.S. (n=13), Israel (n=4), Germany (n=2), and Canada (n=1).[10,] The trial included 229 patients with major depressive disorder who had not received benefits from 1 to 4 antidepressant trials or were intolerant of at least 2 antidepressant treatments. Using a 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 (ITT), 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. The ITT analysis found no significant benefit of treatment at 4 or 16 weeks.

DURABILITY OF CONVENTIONAL TRANSCRANIAL MAGNETIC STIMULATION

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.[11,] Included were 16 double-blind, sham-controlled, randomized trials (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 -0.48, and the effect sizes were lower in RCTs with 8 to 16 weeks of follow-up (*d*=-0.42) than with 1 to 4 weeks of follow-up (*d*=-0.54). The effect size was larger when an antidepressant medication was initiated concurrently with rTMS (5 RCTs, *d*=-.56) than when patients were on a stable dose of medication (9 RCTs, *d*=-0.43) or were unmedicated (2 RCTs, *d*=-0.26).

Observational Studies

Dunner et al (2014) reported a 1-year follow-up with maintenance therapy from a large multicenter observational study (42 sites) of rTMS for patients with TRD.[12,] 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 a 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 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%).[13,] 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%.[14,] 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) evaluated patients who met criteria for a 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.[15,] 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: Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression

There are a large number of sham-controlled randomized trials and meta-analyses of these RCTs evaluating the use of rTMS for depression. Meta-analyses found improved response rates and rates of remission for conventional rTMS and theta burst stimulation 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 events of rTMS appear to be minimal. While the most recent meta-analyses have found that the effect of rTMS is smaller than the effect of ECT on TRD, given that rTMS does not require general anesthesia or induce seizures and some individuals may not elect ECT, the balance of incremental benefits and harms associated with rTMS may be reasonable compared with ECT.

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 patients with migraine headache pain.

The question addressed in this evidence review is: Does the use of rTMS of the brain for patients with migraine headaches improve the net health outcome?

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

Populations
The relevant population of interest is individuals with migraine headaches.

Interventions
The therapy being considered is 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 quality of life and functional outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

REVIEW OF EVIDENCE

Randomized Controlled Trial
A pivotal randomized, double-blind, multicenter, sham-controlled trial was performed with the Cerena TMS device to demonstrate the safety and effectiveness of a de novo application.[16,] Enrolled in the trial were 201 patients with a history of an aura preceding more than 30% of headaches of moderate or severe severity for approximately 90% of migraine attacks. Following a month-long baseline phase to establish the frequency and severity of the migraine, patients were randomized to a treatment phase consisting of 3 treatments or 3 months, whichever occurred first. Patients were instructed to treat their migraine headache during the aura phase and to record their pain severity (0-3), severity of associated migraine symptoms (photophobia, phonophobia, nausea), presence of vomiting, and use of rescue medications at the time of treatment and at 1, 2, 24, and 48 hours after treatment. The primary endpoint was the proportion of patients who were pain-free 2 hours after treatment. Of the 201 patients enrolled, 164 recorded at least 1 treatment and 113 recorded at least 1 treatment when there was pain. Post hoc analysis of these 113 patients showed a benefit of the device for the primary endpoint (37.74% pain free after 2 hours for Cerena vs. 16.67% for sham, p=.018) and for the proportion of subjects who were pain free after 24 hours (33.96% for Cerena vs. 10% for sham; p=.002). Active treatment was not inferior to sham for the proportion of subjects free of photophobia, suggesting that the device does not worsen photophobia. However, the device was not inferior to sham for the proportion of subjects free of nausea and phonophobia.

Section Summary: Migraine Headache
There is little evidence on the use of TMS devices to treat a migraine headache. The results of the pivotal trial were limited by the 46% dropout rate and post hoc analysis. According to the FDA labeling, the device has not been demonstrated as safe or effective when treating cluster headache, chronic migraine headache, or migraine headache during the aura phase. The device has not been demonstrated to be as effective in relieving the associated symptoms of migraine (photophobia, phonophobia, nausea).[16,] No recent studies have been identified with these devices.

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 patients with obsessive-compulsive disorder (OCD).

The question addressed in this evidence review is: Does the use of rTMS in patients with OCD improve the net health outcome?

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

Populations
The relevant population of interest is individuals with OCD.

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

Interventions
The therapy being considered is rTMS.

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. Transcranial magnetic stimulation is proposed as a treatment to modulate these brain areas.

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

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

The Yale-Brown Obsessive Compulsive Scale (YBOCS) is a clinician-rated, 10-item scale commonly used to assess the severity of symptoms in OCD.[17,] 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).[18,] An improvement of ≥35% on the YBOCS is most predictive of treatment response.[19,]

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

REVIEW OF EVIDENCE

Systematic Reviews

A systematic review by Trevizol et al (2016) included 15 RCTs (N=483) that compared active with sham rTMS for OCD (Tables 3 and 4).[20,] All studies were sham-controlled and double-blind. The sample sizes in the trials ranged from 18 to 65 patients. Seven studies used low-frequency stimulation and 8 studies used high-frequency stimulation. The cortical regions varied among the studies, targeting the supplementary motor area, orbitofrontal cortex, or left, right, or bilateral DLPFC. The researchers calculated the SMD for the primary outcome (YBOCS score). Response rates were not reported.

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

More recently, Liang et al (2021) conducted a systematic review and meta-analysis of different TMS modalities for the treatment of OCD.[21,]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 3). 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).[22,] The overall quality of the evidence was rated very low for efficacy and low for tolerability, and the reviewers concluded that high quality RCTs with low selection and performance bias are needed to further verify the efficacy of specific rTMS strategies for OCD treatment.

Table 3. Systematic Review of TMS in Patients with OCD: Characteristics

Study	Dates	Trials Included	Participants	N (Range)	Design	Duration

Liang et al (2021)[21,]	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)[20,]	Up to March 2016	15	Mean age 31.9 (SD 7.6) years, 44.1% women	483 (18 to 65); mean 16.1 (SD 8.45)	RCT, sham-controlled	1 week to 6 weeks

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

Table 4. Systematic Review and Meta-Analysis: Results

Study	YBOCS Score	Dropouts
Liang et al (2021)[21,]		
	Mean Difference (95% CrI)	OR (95% CrI)
Low frequency rTMS applied over the dorsolateral prefrontal cortex	6.34 (2.12 to 10.42)	0.81 (0.08 to 8.17)
High-frequency rTMS applied over the dorsolateral prefrontal cortex	3.75 (1.04 to 6.81)	1.08 (0.37 to 3.19)
Low-frequency rTMS applied over the supplementary motor area	4.18 (0.83 to 7.62)	0.98 (0.37 to 2.67)
Low-frequency rTMS applied over the orbitofrontal cortex	4.43 (-2.57 to 11.31)	0.59 (0.06 to 5.68)
High-frequency rTMS applied over the anterior cingulate cortex/medial prefrontal cortex (deep TMS)	4.25 (-1.16 to 9.59)	1.62 (0.26 to 15.98)
Trevizol et al (2016)[20,]		
Total N	483	483
	SMD: 0.45 (0.20 to 0.71)	OR: 1.02 (0.76 to 1.36)
	I^2 43%, p=.039	
	Mean Difference: 2.94 (1.26 to 4.62)	
	I^2 58%, p=.002	

CrI: credible interval; OR: odds ratio; rTMS: repetitive transcranial magnetic stimulation; SMD: standardized mean difference; YBOCS: Yale-Brown Obsessive-Compulsive Scale.

Randomized Controlled Trial of Deep Transcranial Magnetic Stimulation for Obsessive Compulsive Disorder

This section discusses in detail the sham-controlled RCT of deep TMS for OCD conducted by Carmi et al (2019).[22,]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.[23,] Study characteristics and results are summarized in Tables 5 and 6, and limitations are shown in Tables

7 and 8. 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 CGI-S and the Sheehan Disability Scale, a patient-reported measure of disability and impairment. Results at 10 weeks were also reported as secondary outcomes.

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

Table 5. 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)[22],NCT02229903	U.S., 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 having a YBOCS score >20; in maintenance treatment with a therapeutic dosage of a SRI for at least 2 months before randomization or, if they were not on	Deep TMS 6-week treatment phase (consisting of 5 weeks of daily treatments 5 days a week and 4 treatments during the 6th week)	Sham	6 weeks (primary) 10 weeks (secondary)

Study; Trial	Countries	Sites	Dates	Participants	Interventions		Duration of follow-up
				an SRI, in maintenance treatment on CBT and have failed to respond adequately to at least 1 past trial of an SRI. Exclusions: primary axis I diagnosis other than OCD, severe neurological impairment, any condition associated with an increased risk of seizures.			

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

Table 6. Summary of Key RCT Results - TMS for Patients with OCD

Study	YBOCS (Primary Outcome)	YBOCS Response	CGI-I	CGI-S (modified)	Sheehan Disability Scale	Adverse events (all)	Dropouts
Carmi et al (2019)[22], 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 to 8.1)	38.1% (16/42)	20/41 (49%)	25/41 (61%)	-3.8 points (95% CI -1.5 to -6.1)	73%	6/48 (12.5%)
Sham	-3.3 points (95% CI, 1.2 to 5.3)	11.1% (5/45)	9/43 (21%)	14/43 (32.6%)	-3.0 points	69%	6/51 (12.0%)

Study	YBOCS (Primary Outcome)	YBOCS Response	CGI-I	CGI-S (modified)	Sheehan Disability Scale	Adverse events (all)	Dropouts
					(95% CI -0.8 to -5.3)		
Difference; P-value	2.8 points; p=.01 Effect size: 0.69	p=.003	p=.011	p=.022	NS (p value not reported)	p=.639	NS (p value not reported)

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

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Carmi et al (2019)[22],NCT02229903					1,2. 6 weeks (primary)

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinically significant difference not supported.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Carmi et al (2019)[22],NCT02229903				6. Modified ITT analysis of 94/100 patients who were enrolled. The difference in the primary outcome was not statistically significant in the ITT data set (n=99)		

ITT: intention-to-treat.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Obsessive-Compulsive Disorder

The evidence on rTMS for OCD includes a number of small-to-moderate sized, sham-controlled, double-blind randomized trials and meta-analyses of these RCTs. A meta-analysis of 15 RCTs (N=483 patients, range 18-65 patients) conducted in 2016 found a benefit of rTMS on patient-reported OCD symptom severity at time points ranging from 2 to 6 weeks, but there was substantial variability in the stimulation parameters, including the cortical region that was stimulated and the frequency of stimulation. A second meta-analysis conducted in 2021 included 22 RCTs. Three of 5 TMS protocols assessed were significantly more efficacious than sham TMS, and all treatment strategies were similar to sham TMS regarding tolerability. Deep TMS was not more effective than sham TMS, but there was direct evidence from only 1 RCT for this comparison. The overall quality of the evidence was rated very low for efficacy and low for tolerability, and the reviewers concluded that high quality RCTs with low selection and performance bias are needed to further verify the efficacy of specific rTMS strategies for OCD treatment. In a network meta-analysis that included both direct and indirect evidence, the authors did not find that deep TMS was more effective than sham rTMS. The RCT that was the basis of FDA clearance of deep TMS for treatment of OCD compared deep rTMS to sham in 99 patients for 6 weeks, with an additional 4 weeks of follow-up as a secondary outcome. Using a modified ITT analysis (n=94), there was a larger mean decrease from baseline (improvement) on the YBOCS score (the primary efficacy outcome) in the active treatment group (-6.0 points) than the sham group (-2.8 points), translating to a moderate effect size of 0.69. At 6 weeks, the response rate was 38.1% in the active treatment group compared to 11.1% in the sham group (p=.003), as measured by a 30% or greater increase in the YBOCS. The difference in the primary outcome measure between active and sham groups was not statistically significant in the ITT analysis. There was a benefit for rTMS on clinician-reported measures of improvement, but no significant difference between groups on patient-reported disability and impairment. Additional trials with sufficient sample size and follow-up duration are needed to confirm these results.

PSYCHIATRIC DISORDERS OTHER THAN DEPRESSION 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 patients with psychiatric disorders other than depression or OCD.

The question addressed in this evidence review is: Does the use of rTMS of the brain for various psychiatric conditions improve the net health outcome?

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

Populations
The relevant population of interest is individuals with psychiatric disorders other than depression 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.

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

REVIEW OF EVIDENCE

BIPOLAR DISORDER

Systematic Review
Tee et al (2020) conducted a systematic review and meta-analysis of sham-controlled RCTs of rTMS for the treatment of bipolar disorder.[24,] Eight trials of rTMS in bipolar depression showed small but statistically significant improvements in depression scores compared to sham control (SMD, 0.302, $p<.05$). However, most studies had a high risk of bias, which could have exaggerated the treatment effects. The effect of rTMS was inconclusive in bipolar mania due to the high heterogeneity and limited number of controlled trials.

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.[25,] Results of the analysis showed that rTMS improved anxiety symptoms as measured by the Hamilton Anxiety Scale, (SMD, −0.68, 95% CI −0.89 to −0.46). The conclusions that could be drawn from the body of evidence were limited by significant heterogeneity across

studies, and the authors concluded that additional high-quality studies are needed to confirm the results.

PANIC DISORDER

Systematic Review

A Cochrane review by Li et al (2014) identified 2 RCTs (N=40 patients) that compared low-frequency rTMS with sham rTMS over the right DLPFC.[26,] The larger of the 2 studies was a randomized, double-blind, sham-controlled trial by Mantovani et al (2013) who assessed 21 patients with panic disorder and comorbid major depression.[27,] 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 certainty in the 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.[28,] Five sham-controlled randomized trials (N=118 patients) were included. Most trials used stimulation of the right DLPFC, though some delivered rTMS to the left DLPFC or bilaterally. Three trials used high-frequency stimulation while 1 used low-frequency stimulation and another compared high- with low-frequency stimulation; the percent motor threshold ranged from 80% to 120%. Some trials provided rTMS in combination with a scripted narrative of the traumatic event, and different posttraumatic stress disorder scales were used. In a meta-analysis, active rTMS was found to be superior to sham (SMD, 0.74; 95% CI, 0.06 to 1.42), although heterogeneity across the trials was high.

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

A Cochrane review by Dougall et al (2015) selected 41 studies (N=1473 participants).[30,] Based on very low-quality evidence, there was a significant benefit of low- and high-frequency temporoparietal TMS compared with sham for the global state (7 RCTs) and positive symptoms (5 RCTs). For prefrontal rTMS compared with sham, the evidence on global and cognitive state was of very low-quality and equivocal. Reviewers concluded that the evidence was insufficient to support or refute the use of TMS to treat symptoms of schizophrenia and, although some

evidence suggested that temporoparietal TMS might improve certain symptoms (e.g., auditory hallucinations, positive symptoms of schizophrenia), the results were not sufficiently robust to provide certainty.

A TEC Assessment (2011) evaluated TMS as an adjunct treatment for schizophrenia.[31,] Five meta-analyses were reviewed, along with RCTs in which measurements were carried out beyond the treatment period. The Assessment concluded that the evidence available was insufficient to demonstrate that TMS is effective in the treatment of schizophrenia.

Randomized Controlled Trials

Several additional small, single center RCTs of rTMS for the treatment of schizophrenia have been published since the systematic reviews described above (Tables 9 and 10).[32,33,34,] These studies were limited by their small sample sizes, very high loss to follow-up, and inadequate duration of follow-up (Tables 11 and 12). 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 9. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions[1]		Duration of follow-up
					Active	Comparator	
Guan et al (2020)[32,]	China	1	Not reported	Male patients ages 20–60 with a 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)[33,]	India	1	Not reported	Patients who were right-handed, clinically diagnosed as having schizophrenia as per ICD-10 criteria for at least 1 year; on stable doses of medicines (if receiving) for the last 4 weeks, but continued to have significant negative symptoms.	Active rTMS: 20 sessions of high frequency rTMS per day (5 consecutive sessions per week for 4 weeks) at 20 Hz frequency (N=50)	Sham rTMS (N=50)	4 months

Study; Trial	Countries	Sites	Dates	Participants	Interventions[1]		Duration of follow-up
				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[34,])	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 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.	Active rTMS: 20 treatment sessions on consecutive weekdays. 20 Hz rTMS applied to the left DLPFC (N=35)	Sham rTMS (N=35)	4 weeks

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 10. Summary of Key RCT Results

Study	Main Results
Guan et al (2020)[32,]	At 2 weeks, 4 weeks, and 6 weeks, no significant differences in PANSS total score and sub scores between the sham and treatment groups. Immediate memory performance was higher in the rTMS group compared with the sham group at week 8 after covarying for education, age, and dose of drug. The improvement in immediate memory score was correlated with a decrease in the excitement factor score.
Kumar et al (2020)[33,]	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[34,])	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 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Guan et al (2020)[32,]	4. Included men only				1. 8 weeks not sufficient to show durability of effects
Kumar et al (2020)[33,]					
Zhuo et al (2019[34,])					1. 4 weeks not sufficient to show durability of effects

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 12. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Guan et al (2020)[32,]				1. 15/56 (26.8%) patients discontinued	1. power calculation not reported	
Kumar et al (2020)[33,]				1. 33% attrition (32% active and 38% sham)		
Zhuo et al (2019[34,])				1. 10/70 discontinued (14.3%)	1. power calculation not reported	

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

SUBSTANCE USE DISORDER AND CRAVING

Systematic Review

Jansen et al (2013) reported on results from a 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.[35,] Seventeen double-blind, sham-controlled trials that used high-frequency stimulation were analyzed. 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 to 48 patients) and there was significant heterogeneity in selected studies. No significant differences were found in the effectiveness of rTMS versus 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.

Section Summary: Psychiatric Disorders Other than Depression or Obsessive-Compulsive Disorder

For individuals who have psychiatric disorders other than depression or OCD (e.g., panic disorder, generalized anxiety 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.

NEUROLOGIC DISORDERS OTHER THAN MIGRAINE

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 patients with neurologic disorders other than migraine.

The question addressed in this evidence review is: Does the use of rTMS of the brain for various psychiatric or neurologic conditions improve the net health outcome?

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

Populations

The relevant population of interest is individuals with neurologic disorders other than migraine.

Interventions

The therapy being considered is rTMS.

Comparators

The following therapies are currently being used to treat neurologic disorders other than migraine: pharmacotherapy and therapy as appropriate including either physical and occupational therapy

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

REVIEW OF EVIDENCE

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.[36,] 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[37,] and 2018.[38,] The reviewers identified 42 RCTs (range 4 to 70 participants) on TMS for chronic pain. Meta-analysis of rTMS studies versus sham 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 rTMS of the motor cortex may have short-term effects on chronic pain and quality of life, but multiple sources of bias exist that may have influenced the observed effects. We did not find evidence that low-frequency rTMS, rTMS applied to the DLPFC, and cranial electrotherapy stimulation are effective for reducing pain intensity in chronic pain.

Epilepsy

A Cochrane review by Chen et al (2016) included 7 RCTs on low-frequency rTMS for epilepsy, 5 of which were completed studies with published data.[39,] The total number of participants was 230. All studies had active or placebo controls and 4 were double-blind. However, a meta-analysis could not be conducted due to heterogeneity in designs, interventions, and outcomes of the trials. 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 headaches, 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.[40,] 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=.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

Saltychev and Laimi (2017) published a meta-analysis of rTMS for the treatment of patients with fibromyalgia.[41,] The meta-analysis included 7 sham-controlled, double-blind trials with a low risk

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

Parkinson Disease

A meta-analysis by Chou et al (2015) included 20 sham-controlled randomized trials (N=470 patients) evaluating Parkinson disease.[42,] 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<.001) and low-frequency rTMS over other frontal regions (SMD=0.50, p=.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.[43,] At 9 weeks, all groups showed a similar amount of improvement.

Stroke

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 (N=588 participants) evaluating the effect of low- and high-frequency TMS for improving function after stroke.[44,] 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.

Hand Function

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.[45,] Eight RCTs (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 to 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).

Aphasia

A meta-analysis by Li et al (2015) included 4 RCTs on low-frequency rTMS over the right parstriangularis for patients (N=137) with aphasia after stroke.[46,] All studies used double-blinding, but therapists were not blinded. Every trial used a different outcome measure, and sample sizes were small (range, 12 to 40 patients). Meta-analysis showed a medium effect size for naming (p=.004), a trend for a benefit on repetition (p=.08), and no significant benefit for comprehension (p=.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.

Upper-Limb Motor Function

Zhang et al (2017) published a systematic review and meta-analysis evaluating the effects of rTMS on upper-limb motor function after stroke.[47,] A search through October 2016 yielded 34 RCTs with a total of 904 participants (range, 6 to 108 participants). Pooled estimates found improvement with rTMS for both short-term (SMD, 0.43; p<.001) and long-term (SMD, 0.49; p<.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 3 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.[48,] 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: Neurologic Disorders Other Than Migraine

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 TRD who receive TMS, the evidence includes a large number of sham-controlled randomized controlled trials (RCTs) and meta-analyses of these trials. Relevant outcomes are symptoms, functional outcomes, and quality of life. 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. 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 sham-controlled RCT of 201 patients conducted for submission to the U.S. Food and Drug Administration for clearance in 2013. Relevant outcomes are symptoms, functional outcomes, and quality of life. 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, double-blind RCTs and meta-analyses of these studies. Relevant outcomes are symptoms, functional outcomes, and quality of life. A meta-analysis of 15 RCTs (N=483 patients, range 18-65 patients) conducted in 2016 found a benefit of TMS on patient-reported OCD symptom severity at time points ranging from 2 to 6 weeks, but there was substantial variability in the stimulation parameters, including the cortical region that was stimulated and the frequency of stimulation. A meta-analysis conducted in 2021 included 22 RCTs. Three of 5 TMS protocols assessed were significantly more efficacious than sham TMS, and all treatment strategies were similar to sham TMS regarding tolerability. Deep TMS was not more effective than sham TMS, but there was direct evidence from only 1 RCT for this comparison. The overall quality of the evidence was rated very low for efficacy and low for tolerability, and the reviewers concluded that high quality RCTs with low selection and performance bias are needed to further verify the efficacy of specific TMS strategies for OCD treatment. The RCT that was the basis of FDA clearance of deep TMS for treatment of OCD compared deep TMS to sham in 99 patients for 6 weeks, with an additional 4 weeks of follow-up as a secondary outcome. Using a modified intention-to-treat (ITT) analysis (n=94), there was a larger mean decrease from baseline (improvement) on the Yale-Brown Obsessive Compulsive Scale (YBOCS) score (the primary efficacy outcome) in the active treatment group (-6.0 points) than the sham group (-2.8 points), translating to a moderate effect size of 0.69. At 6 weeks, the response rate was 38.1% in the active treatment group compared to 11.1% in the sham group (p=.003), as measured by a 30% or greater increase in the YBOCS. The difference in the primary outcome measure between active and sham groups was not statistically significant in the ITT analysis. There was a benefit for TMS on clinician-reported measures of improvement, but no significant difference between groups on patient-reported disability and impairment. Additional trials with sufficient sample size and follow-up duration are needed to confirm these results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have psychiatric or neurological disorders other than depression, migraine, or OCD (e.g., amyotrophic lateral sclerosis, 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.

SUPPLEMENTAL INFORMATION

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

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2014 Input

In response to requests, input was received from 1 physician specialty society and 3 academic medical centers while this policy was under review in 2014. Reviewers considered repetitive transcranial magnetic stimulation (rTMS) to be medically necessary for treatment-resistant depression. Input agreed with the proposed criteria for treatment of treatment-resistant depression with repetitive transcranial magnetic stimulation, as included in the policy statement.

Practice Guidelines and Position Statements

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

American 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.[49,] 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.[50,] 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 obsessive-compulsive disorder have indicated that "findings of the 4 published trials of rTMS are inconsistent, perhaps because the studies differed in design, stimulation sites, duration, and stimulation parameters. The available results and the technique's non-invasiveness and good tolerability should encourage future research, but the need for daily treatment may limit the use of TMS in practice."

National Institute for Health and Care Excellence

In 2015, the National Institute for Health and Care Excellence (NICE) 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.[51,]

In 2014, the NICE provided guidance on the use of rTMS for treating and preventing migraine.[52,] The guidance stated that evidence on the efficacy of TMS for the treatment of migraine was limited in quantity and for the prevention of migraine was limited in both quality and quantity. Evidence on its safety in the short- and medium-term was adequate, but there was uncertainty about the safety of long-term or frequent use of TMS.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 13.

Table 13. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02977299	Augmentation Versus Switch: Comparative Effectiveness Research Trial for Antidepressant Incomplete and Non-responders With Treatment-Resistant Depression (ASCERTAIN-TRD)	639	Jan 2022
NCT02910024	Theta-Burst-Stimulation in Early Rehabilitation of Stroke (TheSiReS)	150	Feb 2024
NCT02927236	Neuroplasticity Following Theta-Burst Stimulation in Cocaine Use Disorder	170	Dec 2022
NCT03556722	Effectiveness and Tolerability of Repetitive Transcranial Magnetic Stimulation For Preventive Treatment Of Episodic Migraine: A Single Centre, Randomized, Double-Blind, Sham-Controlled Phase 2 Trial	76	Dec 2021

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS

90867	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management
90868	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent deliver and management, per session
90869	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold re-determination with delivery and management

ICD-10 DIAGNOSES

F32.2	Major depressive disorder, single episode, severe without psychotic features
F32.3	Major depressive disorder, single episode, severe with psychotic features
F32.4	Major depressive disorder, single episode, in partial remission
F32.5	Major depressive disorder, single episode, in full remission
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms
F33.8	Other recurrent depressive disorders

REVISIONS

12-07-2012	Policy added to the bcbsks.com web site.
05-07-2013	Updated Description section.
	Updated Rationale section.
	Updated Reference section.
10-15-2014	Updated Description section.
	In Policy section: Removed the following, "Transcranial magnetic stimulation of the brain is considered investigational as a treatment of all other psychiatric/neurologic disorders, including but not limited to bipolar disorder, schizophrenia, obsessive-compulsive disorder, or migraine headaches." And added: A. Repetitive transcranial magnetic stimulation (rTMS) of the brain may be considered medically necessary as a treatment of major depressive disorder when all of the following conditions (1-3) have been met: 1. Confirmed diagnosis of severe major depressive disorder (single or recurrent) documented by standardized rating scales that reliably measure depressive symptoms; AND

	2. Any one of the following (a, b, c, or d): a. Failure of 4 trials of psychopharmacologic agents including 2 different agent classes and 2 augmentation trials; OR b. Inability to tolerate a therapeutic dose of medications as evidenced by 4 trials of psychopharmacologic agents with distinct side effects; OR c. History of response to rTMS in a previous depressive episode (at least 3 months since the prior episode); OR d. Is a candidate for electroconvulsive therapy (ECT) and ECT would not be clinically superior to rTMS (e.g., in cases with psychosis, acute suicidal risk, catatonia or life-threatening inanition rTMS should NOT be utilized); AND 3. Failure of a trial of a psychotherapy known to be effective in the treatment of major depressive disorder of an adequate frequency and duration, without significant improvement in depressive symptoms, as documented by standardized rating scales that reliably measure depressive symptoms. B. rTMS for major depressive disorder that does not meet the criteria listed above is considered experimental / investigational. C. Continued treatment with rTMS of the brain as maintenance therapy is considered experimental / investigational.
	Added Policy Guideline section.
	In Coding section: • Added ICD-9 diagnoses: 296.23, 296.33 • Added ICD-10 diagnoses: F32.2, F33.2
	Updated Rationale section.
	Updated References section.
03-18-2015	Updated Description section.
	In Policy section: ▪ Added Item D: " Transcranial magnetic stimulation of the brain is considered experimental / investigational as a treatment of all other psychiatric/neurologic disorders, including but not limited to bipolar disorder, schizophrenia, obsessive-compulsive disorder, or migraine headaches."
	Updated Rationale section.
	Updated References section.
02-17-2016	Updated Description section.
	Updated Rationale section.
	Updated References section.
08-15-2017	
	Updated Description section.
	Updated Rationale section.
	Updated References section.
11-07-2018	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes.
	Updated References section.
05-22-2020	Updated Description section
	In Policy section: Update Policy Guidelines ▪ Added Items 2 and 3 to read "2. The physician is responsible for the initial mapping (once per course or delivery) and the management of the treatment. The physician is also responsible for the re-determinations. 3. A trained technician may perform the subsequent delivery of treatment."

	▪ In Item 5 a removed "An attendant trained" and "as well as the use of the equipment" to read "A trained technician in administration of the treatments, and in basic cardiac life support, the management of complications such as seizures, must be present at all times;"
	Updated Rationale section
	Updated References
04-16-2021	Updated Description section.
	Updated Rationale section.
	Updated References section.
12-18-2021	Updated Title to:
	Updated Description Section Transcranial Magnetic Stimulation (TMS) as a Treatment of Depression and Other Psychiatric/Neurologic Disorders
	Updated Policy Section: ▪ Section A to read: Repetitive transcranial magnetic stimulation (rTMS) of the brain using an FDA-cleared device and modality, which can include but is not limited to, conventional TMS, deep TMS, and theta burst stimulation (see Policy Guidelines) may be considered medically necessary as a treatment of major depressive disorder when all of the following conditions (1-3) have been met:
	Updated Policy Guidelines ▪ Added lines 4, 5, 7, 9
	Updated Rationale Section
	Updated Coding section: ▪ Added ICD-10 Codes: F32.2, F32.3, F32.4, F32.5, F33.3, F33.8.
	Updated References Section

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