

# Medical Policy



## Title: Transcranial Magnetic Stimulation (TMS)

See also: *Vagus Nerve Stimulation*  
*Treatment of Tinnitus*

### Professional

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Revision Date(s): December 7, 2012;  
May 7, 2013; October 15, 2014;  
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### Institutional

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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	Interventions of interest are: • Repetitive transcranial magnetic stimulation	Comparators of interest are: • Pharmacotherapy • Therapy as appropriate including either physical and occupational therapy	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. TMS involves placement of a small coil over the scalp and passing a rapidly alternating current through the coil wire. The electrical current produces a magnetic field that passes unimpeded through the scalp and bone that stimulate neuronal function. Repetitive transcranial magnetic stimulation (rTMS) is being evaluated for the treatment of treatment-resistant depression (TRD) and other psychiatric and neurologic disorders.

**OBJECTIVE**

The objective of this policy 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) was first introduced in 1985 as a new method of noninvasive stimulation of the brain. The technique involves placement of a small coil over the scalp; passing a rapidly alternating current through the coil wire, which produces a magnetic field that passes unimpeded through the scalp and bone, resulting in electrical stimulation of the cortex. TMS was initially used to investigate nerve conduction; for example, 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 individual by localizing the site on the scalp for optimal stimulation of a hand muscle, then gradually increasing the intensity of stimulation. The stimulation site for treatment is usually 5 cm anterior to the motor stimulation site.

In contrast to electroconvulsive therapy, TMS does not require general anesthesia and does not generally induce a convulsion. 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 activity of the left dorsolateral prefrontal cortex (DLPFC) in depressed patients, and early studies suggested that high-frequency (eg, 5-10 Hz) TMS of the left DLPFC had antidepressant effects. Low-frequency (1-2 Hz) stimulation of the right DLPFC has also been investigated. The rationale for low-frequency TMS is inhibition of right frontal cortical activity to correct the interhemispheric imbalance. A combination approach (bilateral stimulation), or deep stimulation with an H1 coil, is also being explored, as is theta burst stimulation.

Repetitive TMS (rTMS) is also being tested as a treatment for a variety of other disorders including alcohol dependence, Alzheimer's disease, neuropathic pain, obsessive-compulsive disorder (OCD), post-partum depression, depression associated with Parkinson's disease, stroke, posttraumatic stress disorder, panic disorder, epilepsy, dysphagia, Tourette's syndrome, schizophrenia, migraine, spinal cord injury,

fibromyalgia, and tinnitus. In addition to the potential for altering interhemispheric imbalance, it has been proposed that high frequency rTMS may facilitate neuroplasticity.

### REGULATORY STATUS

Devices for transcranial stimulation have received clearance by the U.S. Food and Drug Administration (FDA) for diagnostic uses. The NeoPulse, now known as NeuroStar® TMS, was granted a de novo 510(k) classification by FDA in 2008. A number of devices subsequently received FDA clearance for the treatment of major depressive disorders in adults who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode. Some devices are listed in Table 1. FDA product code: OBP.

**Table 1.** rTMS Devices Cleared by FDA for the Treatment of Major Depressive Disorder

Device	Manufacturer	FDA Clearance No.	FDA Clearance Date
NeuroStar® TMS	Neuronetics	DEN070003	2008
Brainsway™ H-Coil Deep TMS	Brainsway	K122288	2013
Rapid <sup>2</sup> Therapy System	Magstim	K162935	2015
MagVita TMS Therapy System	Tonica Elektronik	K150641	2015
Neurosoft TMS	TeleEMG	K160309	2016
Mag Vita TMS Therapy System with Theta Burst Stimulation	Tonica Elektronik	K173620	2018

FDA: Food and Drug Administration; rTMS: repetitive transcranial magnetic stimulation.

In 2013, the Cerena™ TMS device (Eneura Therapeutics) received de novo marketing clearance 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 use by 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 or effective:
  - when treating cluster headache or chronic migraine headache.
  - when treating during the aura phase.
  - in relieving the associated symptoms of migraine (photophobia, phonophobia, and nausea).
  - in pregnant women, children under the age of 18, and adults over the age of 65.

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, eNeura Therapeutics received 510(k) marketing clearance for the SpringTMS® for the treatment of migraine headache. The device differs from the predicate Cerena™

TMS device with the addition of an LCD screen, a use authorization feature, lithium battery pack, and smaller size. The stimulation parameters are unchanged. The sTMS Mini (eNeura Therapeutics) received marketing clearance by the FDA in 2016. FDA product code: OKP.

In August 2018, the Deep TMS System (Brainsway) was granted a de novo 510(k) classification by FDA (DEN170078). The new classification applies to this device and substantially equivalent devices of this generic type. The Brainsway Deep TMS System is cleared for treatment of adults with obsessive-compulsive disorder. FDA product code: QCI.

### **POLICY**

- 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 (eg, 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**.
- 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 should be performed using an FDA-cleared device in appropriately selected patients, by physicians who are adequately trained and experienced in the specific techniques used. 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.
2. Contraindications to rTMS 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 (such as 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 (CNS); 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 (ICD), pacemaker, vagus nerve stimulator, or metal aneurysm clips or coils, staples, or stents.
3. The following should be present for the administration of rTMS:
  - 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, for example, 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 five minutes. These relationships are reviewed on at least a one year basis and include mock drills.

## **RATIONALE**

This policy is updated periodically with searches of the MEDLINE database, with the most recent literature update performed through August 23, 2018.

This review was informed by 3 TEC Assessments (2009, 2011, 2013).<sup>1-3</sup>

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

### **Treatment-Resistant Depression**

#### **Clinical Context and Test 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 use of rTMS of the brain for patients with TRD improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

#### **Patients**

The relevant population of interest is individuals with TRD.

#### **Interventions**

The therapies being considered is rTMS.

#### **Comparators**

The following therapies are currently being used to treat rTMS: 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.

### Timing

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

### Setting

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

### 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 longer 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.

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 number of sessions.<sup>4</sup> 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.<sup>5</sup>

### Repetitive TMS for TRD

#### Systematic Reviews

The Health Quality Ontario (2016) published a systematic review of left dorsolateral prefrontal cortex (DLPFC) rTMS for TRD.<sup>6</sup> 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  $\leq 7$  to  $\leq 10$  on the HAM-D). Meta-analysis showed a statistically significant improvement in depression scores compared with sham, with a weighted mean difference (WMD) of 2.31 (see Table 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;  $p < 0.001$ ). Subgroup analysis showed a larger and clinically significant treatment effect in the rTMS studies using 20 Hz with shorter train duration compared with other rTMS techniques (WMD=4.96; 95% CI, 1.15 to 8.76;  $p = 0.011$ ). Secondary analyses showed rTMS demonstrated a

statistically greater response rates among 20 studies (pooled relative risk, 1.72) as well as statistically greater remission rates among 13 studies (pooled relative risk, 2.20). For the 6 trials that compared rTMS with ECT, the WMD of 5.97 was both statistically and clinically significant in favor of ECT. The relative risk for remission and response rates are shown in Table 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 w 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 rTMS

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

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

Berlim et al (2013) reported on a meta-analysis assessing the effect of rTMS for accelerating and enhancing the clinical response to antidepressants.<sup>7</sup> Data were obtained from 6 double-blind RCTs (total N=392 patients). The response was defined as a 50% or greater reduction in the HAM-D or the Montgomery-Asberg Depression Rating Scale scores. At an average of 2.7 weeks after the start of the combined treatments, response rates were significantly higher with rTMS plus antidepressant treatment (43.3%) compared with sham rTMS (26.8%; odds ratio [OR], 2.50); remission rates did not differ significantly. At the end of the studies (average, 6.8 weeks), response and remission rates were significantly higher with combined high-frequency rTMS plus antidepressant treatment than with sham rTMS (response, 62% vs 46%; OR = 1.9; remission, 53.8% vs 38.6%; OR=2.42).

Another systematic review by Berlin et al (2013) identified 7 RCTs (total N=294 patients) that directly compared rTMS with ECT treatment for patients who had depression.<sup>8</sup> After an average of 15.2 sessions of high-frequency rTMS over the left DLPFC, 33.6% of patients were classified as remitters. Fifty-two percent of patients were classified as remitters following an average of 8.2 ECT sessions. The pooled odds was 0.46, indicating a significant difference in outcome favoring ECT.

The Agency for Healthcare Research and Quality published a comparative effectiveness review, conducted by Gaynes et al (2011), on nonpharmacologic interventions for TRD in adults.<sup>9</sup> Reviewers concluded that comparative clinical research on nonpharmacologic interventions in a TRD population was early in its infancy, and many clinical questions about efficacy and effectiveness remained unanswered. The finding of low strength of evidence was most notable in 2 cases: rTMS compared with ECT resulted in similar clinical outcomes in patients who had failed at least 1 course of antidepressant treatment (based on 2 trials with small sample size), and ECT produced better outcomes than pharmacotherapy. In 2 trials that enrolled patients with probable TRD, ECT produced better outcomes than rTMS. No trials directly compared the likelihood of maintaining remission with nonpharmacologic interventions. The few trials addressing adverse

events, subpopulations, subtypes, and health-related outcomes provided low or insufficient evidence of differences between nonpharmacologic interventions.

### *Randomized Controlled Trials*

More recently, Blumberger et al (2018) published a multicenter, randomized noninferiority trial (THREE-D) comparing 10-Hz rTMS with intermittent theta burst stimulation (iTBS).<sup>10</sup> Between 2013 and 2016, 414 patients with treatment-resistant major depressive disorder were enrolled and randomized to 4 to 6 weeks of rTMS (n=205) or iTBS (n=209). Treatment resistance was defined as 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 medication during this trial. Treatment with rTMS (37 minutes) and iTBS (3 minutes) was delivered 5 times a week for 4 to 6 weeks. The primary outcome measure was the 17-item HAM-D, for which scores for patients treated with rTMS improved by 10.1 points and scores for patients treated with iTBS improved by 10.2 points (adjusted difference, 0.103; lower 95% CI, -1.16; p=0.001). Treatment with iTBS resulted in a higher self-rated intensity of pain (mean score, 3.8) than treatment with rTMS (mean score, 3.4; p=0.011). Headache was the most common treatment-related adverse event for both groups (rTMS=64% [131/204]; iTBS=65% [136/208]). Serious adverse events were noted in patients treated with rTMS (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 placebo.

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

The largest trial included in the systematic reviews is a double-blind multicenter (23 study sites) trial by O'Reardon et al (2007), which randomized 325 TRD patients to daily sessions (Monday to Friday for 6 weeks) of high-frequency active or sham rTMS of the DLPFC.<sup>12</sup> TRD was defined as failure of at least 1 adequate course of antidepressant treatment. Patients had failed an average of 1.6 treatments in the current episode, with approximately half of the trial population failing to benefit from at least 2 treatments. Intention-to-treat analysis showed a trend favoring the active rTMS group in the primary outcome measure (2 points on the Montgomery-Asberg Depression Rating Scale; p=0.057) and a modest (2-point) but significant improvement over sham treatment on the HAM-D scores. Reviewers reported that, after 6 weeks of treatment, subjects in the active rTMS group were more likely to have achieved remission than the sham controls (14% vs 5%, respectively), although this finding was limited by a loss to follow-up.

## Durability of rTMS

### 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.<sup>13</sup> Included were 16 double-blind, sham-controlled randomized trials (total N=495 patients). The range of follow-up was 1 to 16 weeks, but most studies only reported follow-up to 2 weeks. The overall effect size was small with a standardized mean difference (SMD; Cohen's  $d$ ) of -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 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 1-year follow-up with maintenance therapy from a large multicenter observational study (42 sites) of rTMS for patients with TRD.<sup>14</sup> A total of 257 patients agreed to participate in the follow-up study of 307 who were initially treated with rTMS. Of them, 205 completed the 12-month follow-up, and 120 patients had met the Inventory of Depressive Symptoms–Self Report response or remission criteria at the end of treatment. Ninety-three (36.2%) of the 257 patients who enrolled in the follow-up study received additional rTMS (mean, 16.2 sessions). Seventy-five (62.5%) of the 120 patients who met response or remission criteria at the end of the initial treatment phase (including a 2-month taper phase) continued to meet response criteria through 1-year follow-up.

A variety of tapering schedules are being studied. For example, Richieri et al (2013) used propensity-adjusted analysis of observational data and found that patients who had 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%).<sup>15</sup> 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%.<sup>16</sup> 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 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.<sup>17</sup> During the 24-week follow-up, 10 of 99 patients relapsed, 38 had symptom worsening, and of these 32 (84%) had symptomatic benefit with adjunctive rTMS.

### *Section Summary: Treatment-Resistant Depression*

There are a large number of sham-controlled randomized trials and meta-analyses of these RCTs evaluating use of rTMS for depression. The meta-analyses found a clinical benefit associated with rTMS for TRD, with improved response rates and remission rates compared with sham. 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. Meta-analyses also found that the efficacy of rTMS decreases with longer follow-up, though some studies have reported 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 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.

## **Psychiatric and Neurologic Disorders Other Than Depression**

### Clinical Context and Test 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 or neurologic disorders other than depression.

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

The following PICOTS were used to select literature to inform this review.

### Patients

The relevant population of interest is individuals with psychiatric or neurologic disorders other than depression

### Interventions

The therapy being considered is rTMS.

### Comparators

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

### Outcomes

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

### Timing

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

### Setting

Patients with psychiatric or neurologic disorders other than depression are actively managed by psychiatrists and other mental health professionals in an outpatient clinical setting.

### 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 longer 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.

### 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.<sup>18</sup> 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 (2014), evaluating noninvasive brain stimulation techniques, identified 30 RCTs (total N=528 patients) on TMS for chronic pain.<sup>19</sup> There was low to very low quality evidence that low-frequency rTMS or rTMS to the DLPFC is ineffective. Studies on high-frequency rTMS to the motor cortex were heterogeneous, of low quality, and did not demonstrate a significant effect.

### 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.<sup>20</sup> The total number of participants was 230. All studies had active or placebo controls, and 4 were double-blinded. 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 headache, dizziness, and tinnitus. There were no significant changes in medication use.

#### *Section Summary: Epilepsy*

A number of RCTs have been conducted on the effect of rTMS on epilepsy. All but one were conducted between 2002 and 2008, with the most recent study conducted in 2012.<sup>21</sup> Some trials reported a significant reduction in epileptic discharges, but most did not find a reduction in seizures. The lack of recent primary studies may suggest a loss of interest and support for this intervention following the initial negative results.

### Fibromyalgia

Saltychev and Laimi (2017) published a meta-analysis of rTMS for the treatment of patients with fibromyalgia.<sup>22</sup> The meta-analysis included 7 sham-controlled double-blinded controlled trials with 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.

#### *Section Summary: Fibromyalgia*

A 2017 meta-analysis of 7 sham-controlled randomized trials found that the reduction in pain with rTMS, while statistically significant, was not clinically significant. These results do not

support the use of rTMS for the treatment of pain in fibromyalgia. A limitation of the meta-analysis was the relatively small size of the studies and differences in stimulation parameters. In addition, the effect of rTMS on depression, anxiety, sleep, and quality of life was not assessed.

### Migraine Headache

A pivotal randomized, double-blind, multicenter, sham-controlled trial was performed with the Cerena TMS device to demonstrate the safety and effectiveness for a de novo application.<sup>23</sup> 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 end point was the proportion of patients who were pain-free 2 hours after treatment. Of the 201 patients enrolled, 164 recorded at least 1 treatment and 113 recorded at least 1 treatment when there was pain. Post hoc analysis of these 113 patients showed a benefit of the device for the primary end point (37.74% pain free after 2 hours for Cerena vs 16.67% for sham,  $p=0.018$ ) and for the proportion of subjects who were pain free after 24 hours (33.96% for Cerena vs 10% for sham;  $p=0.002$ ). Active treatment was not inferior to sham for the proportion of subjects free of photophobia, suggesting that the device does not worsen photophobia. However, the device was not inferior to sham for the proportion of subjects free of nausea and phonophobia.

### *Section Summary: Migraine Headache*

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 Food and Drug Administration 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).<sup>23</sup> No recent studies have been identified with these devices.

### Obsessive-Compulsive Disorder

A systematic review by Trevizol et al (2016) included 15 RCTs (total N=483 patients) that compared active with sham rTMS for obsessive-compulsive disorder (OCD).<sup>24</sup> All studies were sham-controlled and double-blinded. Sample sizes in the trials were small-to-moderate, ranging from 18 to 65 patients (mean size, 16.1 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 effect size for active stimulation was modest at 0.45 (95% CI, 0.2 to 0.71). The SMD was 2.94 (95% CI, 1.26 to 4.62). Regression did not identify any significant factors. There was no evidence of publication bias from funnel plots.

A meta-analysis by Berlim et al (2013) included 10 small RCTs (total N=282 patients) assessing OCD.<sup>25</sup> Response rates of rTMS augmentation therapy were 35% for active and 13% for sham rTMS. The pooled odds was 3.39, and the number needed to treat was 5. There was no evidence of publication bias. Exploratory subgroup analysis suggested that the most promising stimulation

parameters were low-frequency rTMS and non-DLPFC regions (ie, orbitofrontal cortex or supplementary motor area).

#### *Section Summary: Obsessive-Compulsive Disorder*

The evidence on rTMS for OCD includes a number of small-to-moderate size sham-controlled double-blind randomized trials and meta-analyses of these RCTs. Both meta-analyses found a benefit of rTMS for OCD, but there was substantial variability in the stimulation parameters, including the cortical region that was stimulated and the frequency of stimulation.

#### Panic Disorder

A Cochrane review by Li et al (2014) identified 2 RCTs (total N=40 patients) that compared low-frequency rTMS with sham rTMS over the right DLPFC.<sup>26</sup> 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.<sup>27</sup> 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.

#### Parkinson's Disease

A meta-analysis by Chou et al (2015) included 20 sham-controlled randomized trials (total N=470 patients) evaluating Parkinson's disease.<sup>28</sup> Sample sizes ranged from 8 to 102 patients. The total effect size of low- and high-frequency rTMS on Unified Parkinson's Disease Rating Scale part III score was 0.46, which is considered a small-to-medium effect size, and the mean change in the Unified Parkinson's Disease Rating Scale part III score (-6.42) was considered a clinically important difference. The greatest effect on motor symptoms was from high-frequency rTMS over the primary motor cortex (SMD=0.77,  $p<0.001$ ) and low-frequency rTMS over other frontal regions (SMD=0.50,  $p=0.008$ ). High-frequency rTMS at other frontal regions and low-frequency rTMS over the primary motor cortex did not have a statistically significant benefit. The largest trial included in the systematic review was an exploratory, multicenter, double-blind trial reported by Shirota et al (2013) who randomized 106 patients to 8 weeks of 1-Hz rTMS, 10-Hz rTMS, or sham stimulation over the supplementary motor area.<sup>29</sup> At 9 weeks, all groups showed a similar amount of improvement.

#### *Section Summary: Parkinson's Disease*

A meta-analysis of 20 trials found a medium effect size on motor symptoms in patients with Parkinson's disease. However, trials were heterogeneous for the site and frequency of stimulation, and the largest trial found no significant differences between active and sham treatment. It cannot be determined from these results whether the negative results of this trial were due to a lack of effect of rTMS on motor symptoms in general or to stimulation location. Additional study with a larger number of subjects and longer follow-up is needed to determine whether high-frequency rTMS over the primary motor cortex improves motor symptoms in patients with Parkinson's disease.

#### Posttraumatic Stress Disorder

Trevizol et al (2016) published a systematic review on the efficacy of low- and high-frequency rTMS for posttraumatic stress disorder (PTSD).<sup>30</sup> Five sham-controlled randomized trials (total

N=118 patients) were included. Most trials used stimulation of the right DLPFC, though some delivered rTMS to the left DLPFC or bilaterally. Three trials used high-frequency stimulation while one used low-frequency stimulation and another compared high- with low-frequency stimulation; the percent motor threshold ranged from 80% to 120%. Some trials provided rTMS in combination with a scripted narrative of the traumatic event, and different PTSD scales were used. In a meta-analysis, active rTMS was found to be superior to sham (SMD=0.74; 95% CI, 0.06 to 1.42), although heterogeneity across the trials was high.

#### *Section Summary: Posttraumatic Stress Disorder*

A meta-analysis of 5 small RCTs (total N=118 patients) found improvement of PTSD with rTMS over the right or left DLPFC. The trials varied by interventions, control conditions, and outcome measures. Additional study in a larger number of patients is needed to confirm an effect of rTMS on PTSD. In addition, the most effective stimulation parameters and the durability of any effect are unknown.

#### Schizophrenia

One of the largest areas of TMS research outside of depressive disorders is the treatment of auditory hallucinations in schizophrenia resistant to pharmacotherapy. 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.<sup>31</sup> For 1-Hz rTMS, 13 studies were included. Compared with sham, the rTMS group showed greater improvement in auditory hallucinations (standard mean difference, -0.29; 95% CI, -0.57 to -0.01). However, significant heterogeneity across the studies was found ( $p=0.06$ ). In the 7 studies using 10-Hz rTMS, the overall effect size for improvement in negative symptoms was -0.41 (95% CI, -1.16 to -0.35); again, there was significant heterogeneity across studies ( $p<0.001$ ). The review was further limited by the small number of articles included and by the lack of original data for some studies.

A Cochrane review by Dougall et al (2015) selected 41 studies (total N=1473 participants).<sup>32</sup> Based on very low quality evidence, there was a significant benefit of low- and high-frequency temporoparietal TMS compared with sham for global state (7 RCTs) and positive symptoms (5 RCTs). For prefrontal rTMS compared with sham, the evidence on global state and cognitive state was of very low quality and equivocal. Reviewers concluded that the evidence was insufficient to support or refute the use of TMS to treat symptoms of schizophrenia and, although some evidence suggested that temporoparietal TMS might improve certain symptoms (eg, 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.<sup>33</sup> 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.

#### *Section Summary: Schizophrenia*

The evidence on rTMS for the treatment of auditory hallucinations in schizophrenia consists of small RCTs. Evidence to date has shown small-to-moderate effects on hallucinations when measured at the end of treatment, but suggested the effect is not durable.

### 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 (total N=588 participants) evaluating the effect of low- and high-frequency TMS for improving function after stroke.<sup>34</sup> 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.<sup>35</sup> Eight RCTs (total N=273 participants) were selected. The quality of the trials was rated moderate to high, although the size of the studies was small. There was variability in the time since stroke (5 days to 10 years), in the frequency of rTMS applied (1-25 Hz for 1 second to 25 min/d), and the stimulation sites (primary motor cortex or premotor cortex of the unaffected hemisphere). Meta-analysis found a positive effect on finger motor ability (4 studies; n=79 patients; SMD=0.58) and hand function (3 studies; n=74 patients; SMD = -0.82), but no significant change in motor evoked potentials (n=43) or motor threshold (n=62).

### Aphasia

A meta-analysis by Li et al (2015) included 4 RCTs on low-frequency rTMS over the right pars triangularis for patients (total N=137) with aphasia after stroke.<sup>36</sup> All studies used double-blinding, but therapists were not blinded. Every trial used a different outcome measure, and sample sizes were small (range, 12-40 patients). Meta-analysis showed a medium effect size for naming (p=0.004), a trend for a benefit on repetition (p=0.08), and no significant benefit for comprehension (p=0.18). Additional study in a larger number of patients would be needed to determine with greater certainty the effect of this treatment on aphasia after stroke.

### 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.<sup>37</sup> A search through October 2016 yielded 34 RCTs with a total of 904 participants (range, 6-108 participants). Pooled estimates found improvement with rTMS for both short-term (SMD=0.43; p<0.001) and long-term (SMD=0.49; p<0.001) manual dexterity. Of the 28 studies reporting on adverse events, 25 studies noted none. Mild adverse events, such as headache and increased anxiety were reported in 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.<sup>38</sup> 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: Stroke*

Evidence consists of a number of RCTs and meta-analyses assessing the effect of rTMS on recovery from stroke. Results are conflicting, and efficacy may depend on the location of the stroke and frequency of the rTMS. Additional study would be needed to determine whether rTMS facilitates standard speech or physical therapy in patients with stroke.

Substance Abuse and Craving

Jansen et al (2013) reported 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.<sup>39</sup> Seventeen double-blind, sham-controlled 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, 9-48 patients) and there was significant heterogeneity in selected studies. No significant differences were found in the effectiveness of rTMS vs transcranial direct current stimulation, the different substances, or the side of stimulation, although this analysis might have been biased by the number of studies for each condition.

*Section Summary: Substance Abuse and Craving*

A number of sham-controlled randomized trials and a meta-analysis of these have that found a medium effect size of rTMS for reduction of substance dependence or food craving. Most studies examined acute craving after 1 or 2 rTMS sessions, and there is limited evidence on longer term efficacy of this treatment approach.

**SUMMARY OF EVIDENCE**

For individuals who have TRD who receive rTMS, the evidence includes a large number of sham-controlled randomized trials and meta-analyses of these trials. Relevant outcomes are symptoms, functional outcomes, and quality of life. The meta-analyses found a clinical benefit associated with rTMS for TRD with improved response rates and rates of remission compared with sham. The most recent meta-analyses have concluded that the effect of rTMS, on average depression scores, is smaller than the effect of ECT on TRD and that the mean improvement in depression scores with rTMS 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 rTMS is in accelerating or enhancing the response to antidepressant medications, and 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. The effect of rTMS 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 rTMS decreases with longer follow-up, though some studies have reported 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 rTMS appear to be minimal. While the most recent meta-analyses have reported that the effect of rTMS is smaller than the effect of ECT on TRD, because rTMS does not require general anesthesia or induce seizures, some individuals may decline ECT so the balance of incremental benefits and harms associated with rTMS may be a 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, rTMS may be considered a treatment option in patients with TRD who meet specific criteria. The

evidence for theta burst stimulation includes a large randomized trial showing noninferiority with another method of rTMS; no significant differences were noted in the number of adverse events. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have psychiatric or neurologic disorders other than depression (eg, amyotrophic lateral sclerosis, chronic pain, epilepsy, fibromyalgia, migraine headache, obsessive-compulsive disorder, panic disorder, Parkinson's disease, posttraumatic stress disorder, schizophrenia, stroke, substance abuse and craving) who receive rTMS, 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 the effects of the technology on health outcomes.

### **CLINICAL INPUT RECEIVED 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.

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. The reviewers considered rTMS to be medically necessary for TRD. Input agreed with the proposed criteria for treatment of TRD with rTMS, as included in the policy statement.

### **PRACTICE GUIDELINES AND POSITION STATEMENTS**

#### American Psychiatric Association

The American Psychiatric Association (APA) 2010 (reaffirmed in 2015) practice guidelines for the treatment of patients with major depressive disorder states that treatment in the acute phase should be aimed at inducing remission of the major depressive episode and achieving a full return to the patient's baseline level of functioning [recommended with substantial clinical confidence].<sup>40</sup> Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as ECT, TMS, or light therapy. APA states that a number of strategies are available when a change in the treatment plan seems necessary, such as transdermal selegiline, a relatively selective MAO B inhibitor with fewer dietary and medication restrictions, or transcranial magnetic stimulation could also be considered [recommended with moderate clinical confidence].

The Association's guidelines on the treatment of patients with obsessive-compulsive disorder (2007, reaffirmed in 2012) have indicated that "findings of the four published trials of repetitive TMS (rTMS) are inconsistent, perhaps because the studies differed in design, stimulation sites, duration, and stimulation parameters. The available results and the technique's non-invasiveness and good tolerability should encourage future research, but the need for daily treatment may limit the use of TMS in practice."<sup>41</sup>

American Academy of Child and Adolescent Psychiatry

In 2013, the American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues published practice parameters on the assessment and treatment of children and adolescents with tic disorders.<sup>42</sup> AACAP does not recommend rTMS, citing the limited evidence regarding safety, ethics, and long-term impact on development.

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.<sup>43</sup>

In 2014, NICE provided guidance on the use of rTMS for treating and preventing migraine.<sup>44</sup> The guidance states that evidence on the efficacy of TMS for the treatment of migraine is limited in quantity and for the prevention of migraine is limited in both quality and quantity. Evidence on its safety in the short and medium term is adequate, but there is uncertainty about the safety of long-term or frequent use of TMS.

American Academy of Neurology

The American Academy of Neurology issued practice guidelines in 2006 on the evaluation and treatment of depression, psychosis, and dementia in Parkinson's disease.<sup>45</sup> The guidelines found the evidence insufficient to support or refute the efficacy of TMS or ECT in the treatment of depression associated with Parkinson's disease (level U; data inadequate or conflicting given current knowledge, treatment is unproven).

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**

Not applicable.

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**

Some currently unpublished trials that might influence this review are listed in Table 3.

**Table 3.** Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02376491	Efficacy of Intermittent ThetaBurst Stimulation Compared to 10 Hz Stimulation on Dorsolateral Prefrontal Cortex in Treatment Resistant Major Depressive Disorder: a Double-blind Randomized Study	60	Aug 2019
NCT02977299	Augmentation Versus Switch: Comparative Effectiveness Research Trial for Antidepressant Incomplete and Non-responders With Treatment Resistant Depression (ASCERTAIN-TRD)	639	Jan 2022

NCT: national clinical trial.

**CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. 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.**

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

- Code 90867 is reported once per course of treatment, and codes 90868 and 90869 cannot be reported for the same session.

ICD-10 Diagnoses

- F32.2 Major depressive disorder, single episode, severe without psychotic features
- F33.2 Major depressive disorder, recurrent severe without psychotic features

**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	<p>Updated Description section.</p> <p>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:</p> <ol style="list-style-type: none"> <li>1. Confirmed diagnosis of severe major depressive disorder (single or recurrent) documented by standardized rating scales that reliably measure depressive symptoms; AND</li> <li>2. Any one of the following (a, b, c, or d):                             <ol style="list-style-type: none"> <li>a. Failure of 4 trials of psychopharmacologic agents including 2 different agent classes and 2 augmentation trials; OR</li> <li>b. Inability to tolerate a therapeutic dose of medications as evidenced by 4 trials of psychopharmacologic agents with distinct side effects; OR</li> <li>c. History of response to rTMS in a previous depressive episode (at least 3 months since the prior episode); OR</li> <li>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</li> </ol> </li> <li>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.</li> </ol>

	<p>B. rTMS for major depressive disorder that does not meet the criteria listed above is considered experimental / investigational.</p> <p>C. Continued treatment with rTMS of the brain as maintenance therapy is considered experimental / investigational.</p>
	Added Policy Guideline section.
	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>• Added ICD-9 diagnoses: 296.23, 296.33</li> <li>• Added ICD-10 diagnoses: F32.2, F33.2</li> </ul>
	Updated Rationale section.
	Updated References section.
03-18-2015	<p>Updated Description section.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ 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."</li> </ul>
	Updated Rationale section.
	Updated References section.
02-17-2016	<p>Updated Description section.</p> <p>Updated Rationale section.</p> <p>Updated References section.</p>
08-15-2017	<p>Title changed from "Transcranial Magnetic Stimulation (TMS) as a Treatment of Depression and Other Psychiatric Disorders."</p> <p>Updated Description section.</p> <p>Updated Rationale section.</p> <p>Updated References section.</p>
11-07-2018	<p>Updated Description section.</p> <p>Updated Rationale section.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Removed ICD-9 codes.</li> </ul> <p>Updated References section.</p>

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