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

Description/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. TMS was initially used to investigate nerve conduction; eg, 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 of depression 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
Repetitive TMS (rTMS) is also being tested as a treatment for a variety of other disorders. In addition to the potential for altering interhemispheric imbalance, it has been proposed that high-frequency repetitive TMS may facilitate neuroplasticity.

Regulatory Status

Devices for transcranial stimulation have received clearance by the U.S. Food & Drug Administration (FDA) for diagnostic uses (FDA Product Code: GWF). A number of devices subsequently received the 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. Indications were expanded to include treating pain associated with certain migraine headaches in 2013, and obsessive-compulsive disorder in 2018.

In 2008, the NeoPulse, now known as NeuroStar® TMS, was granted a de novo 510(k) classification by the FDA. 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 2013, the Cerena™ TMS device (eNeura Therapeutics) was granted a de novo 510(k) classification by the FDA for the acute treatment of pain associated with a migraine headache with aura. Warnings, precautions, and contraindications include the following:
- The device is only intended for patients experiencing the onset of pain associated with a migraine headache with aura.
- The device should not be used:
  - on headaches due to underlying pathology or trauma.
  - for medication overuse headaches.
- The device has not been demonstrated as safe and/or effective:
  - when treating cluster headache or a chronic migraine headache.
  - when treating during the aura phase.
  - in relieving the associated symptoms of a migraine (photophobia, phonophobia, and nausea).
  - in pregnant women, children under the age of 18, and adults over the age of 65.

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

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

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>FDA Clearance No.</th>
<th>FDA Clearance Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurostar</td>
<td>Neuronetics</td>
<td>Major Depressive Disorder</td>
<td>K083538</td>
<td>12/16/2008</td>
</tr>
<tr>
<td>Brainsway Deep TMS System</td>
<td>Brainsway</td>
<td>Major Depressive Disorder</td>
<td>K122288</td>
<td>01/07/2013</td>
</tr>
<tr>
<td>Springtms Total Migraine System</td>
<td>Eneura</td>
<td>Migraine headache with aura</td>
<td>K140094</td>
<td>05/21/2014</td>
</tr>
<tr>
<td>Rapid Therapy System</td>
<td>Magstim</td>
<td>Major Depressive Disorder</td>
<td>K143531</td>
<td>05/08/2015</td>
</tr>
<tr>
<td>Magvita</td>
<td>Tonica Elektronik</td>
<td>Major Depressive Disorder</td>
<td>K150641</td>
<td>07/31/2015</td>
</tr>
<tr>
<td>Neurosoft</td>
<td>TeleEMG</td>
<td>Major Depressive Disorder</td>
<td>K160309</td>
<td>12/22/2016</td>
</tr>
<tr>
<td>Horizon</td>
<td>Magstim</td>
<td>Major Depressive Disorder</td>
<td>K171051</td>
<td>09/13/2017</td>
</tr>
<tr>
<td>Nexstim</td>
<td>Nexstim</td>
<td>Major Depressive Disorder</td>
<td>K171902</td>
<td>11/10/2017</td>
</tr>
<tr>
<td>Apollo</td>
<td>Mag &amp; More</td>
<td>Major Depressive Disorder</td>
<td>K180313</td>
<td>05/04/2018</td>
</tr>
<tr>
<td>Brainsway Deep TMS System</td>
<td>Brainsway</td>
<td>Obsessive-Compulsive Disorder</td>
<td>K183303</td>
<td>03/08/2019</td>
</tr>
</tbody>
</table>

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

**Medical Policy Statement**

Transcranial magnetic stimulation of the brain has been established. It may be a useful treatment option in specified situations.

**Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)**

**Inclusions:**
Transcranial magnetic stimulation must be administered by an approved U.S. Food & Drug Administration (FDA) cleared device for the treatment of major depressive disorder (MDD) according to specified stimulation parameters, 5 days a week for 6 weeks (total of 30
sessions), followed by a 3 week taper of 3 TMS treatments in 1 week, 2 TMS treatments the next week, and 1 TMS treatment in the last week.

Must meet all:
1. The member is 18 to 70 years of age (includes ages 18 and 70).
2. A drug screen is obtained if indicated by history, current clinical evaluation, or a high degree of clinical suspicion.
3. A confirmed diagnosis of severe major depressive disorder (single or recurrent episode) measured by evidence-based scales such as Beck Depression Inventory (score 30-63), Zung Self-Rating Depression Scale (>70), PHQ-9 (>20), Hamilton Depression Rating Scale (>20), or Montgomery-Asberg Depression Rating Scale (MADRS) (score >34).
4. At least one of the following:
   ▪ Current depressive episode treatment:
     Medication treatment resistance, evidenced by:
     o Lack of a clinically significant response to 4 trials of psychopharmacologic agents:
       ➢ Two single agent trials of antidepressants from at least two different agent classes
       ➢ Two augmentation trials with different classes of augmenting agents utilizing either (or both) of the agents used in the single agent trials
       NOTE: Each agent in the treatment trial must have been administered at an adequate course of mono- or poly-drug therapy.
       NOTE: Trial criteria is 6 weeks of maximal FDA recommended dosing or maximal tolerated dose of medication with objectively measured evaluation at initiation and during the trial showing no evidence of response (ie, < 50% reduction of symptoms or scale improvement).
   ▪ The patient is unable to tolerate a therapeutic dose of medications. Intolerance is defined as severe somatic or psychological symptoms that cannot be modulated by any means including but not limited to additional medications to ameliorate side effects. Examples of somatic side effects: persistent electrolyte imbalance, pancytopenia, severe weight loss, poorly controlled metabolic syndrome or diabetes.
   Examples of psychological side effects: suicidal-homicidal thinking/attempts, impulse dyscontrol.
   Note: A trial of less than one week of a medication is not be considered a qualifying trial to establish intolerance.
   ▪ The patient has a history of response to rTMS in a previous depressive episode (and it has been at least 3 months since the prior episode)
   ▪ The patient is a candidate for electroconvulsive therapy; further, electroconvulsive therapy would not be clinically superior to transcranial magnetic stimulation (eg, in cases with psychosis, acute suicidal risk, catatonia or life-threatening inanition rTMS should NOT be utilized).
5. The patient failed a trial of an evidence-based psychotherapy known to be effective in the treatment of MDD of an adequate frequency and duration without significant improvement in depressive symptoms as documented by standardized rating scales that reliably measure depressive symptoms (eg, Becks Depression Inventory, Zung Self-Rating Depression Scale, PHQ-9, Hamilton Depression Rating Scale or MADRS).
6. Conditions that must be met during the entire rTMS treatment:
   ▪ A board-certified psychiatrist, trained in this therapy, must deliver the treatment
An attendant trained in BCLS, the management of complications (such as seizures), and the use of the equipment must be present.

Adequate resuscitation equipment must be available (e.g., suction and oxygen).

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.

Exclusions:

- All other behavioral health, neuropsychiatric or medical conditions (e.g., anxiety disorders, mood disorders, schizophrenia, Alzheimer’s, dysphagia, seizures)
- Pregnancy
- Maintenance treatment
- Presence of psychosis in the current episode
- Seizure disorder or any history of seizure, except those induced by ECT or isolated febrile seizures in infancy without subsequent treatment or recurrence
- Presence of an implanted magnetic-sensitive medical device located less than or equal to 30 centimeters 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

**Note:** Dental amalgam fillings are not affected by the magnetic field and are acceptable for use with TMS.

- If the patient (or, when indicated, the legal guardian) is unable to understand the risk and benefits of rTMS and provide informed consent
- Presence of a medical or co-morbid psychiatric contraindication to rTMS
- Patient lacks a suitable environmental, or social and/or professional support system for post-treatment recovery
- There is not a reasonable expectation that the patient will be able to adhere to post-procedure recommendations

**Note:** Caution should be exercised in any situation where the patient’s seizure threshold may be decreased. Examples include:

- Presence in the bloodstream of a variety of agents, including but not limited to tricyclic antidepressants, clozapine, antivirals, theophylline, amphetamines, PCP, MDMA, alcohol, cocaine as these present a significant risk
- Presence of the following agents, including but not limited to SSRIs, SNRIs, bupropion, some antipsychotics, chloroquine, some antibiotics, some chemotherapeutic agents as they present a RELATIVE risk and should be considered when making risk-benefit assessments
- Withdrawal from alcohol, benzodiazepines, barbiturates and chloral hydrate also present a strong relative hazard

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**CPT/HCPCS Level II Codes** *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

**Established codes:**

- 90867
- 90868
- 90869
Other codes (investigational, not medically necessary, etc.):
N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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, two 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 PICOs were used to select literature to inform this review.

Patients
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 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 want to use ECT due to its requirement for general anesthesia and induction of seizures.

There has been a trend to use rTMS at increased levels of intensity, trains of pulses, total pulses per session, and 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)

Repetitive TMS for Treatment-Resistant Depression

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 (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 six 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 two studies (n=40 and n=46 subjects) comparing rTMS w ECT. While one 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.

Berlim et al (2013) reported on a meta-analysis assessing the effect of rTMS for accelerating and enhancing the clinical response to antidepressants. (7) Data were obtained from six 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 compared with sham rTMS (response, 62% vs 46%; OR = -1.9; remission, 53.8% vs 38.6%; OR=2.42).

Another systematic review by Berlim et al (2013) identified 7 RCTs (total n=294 patients) that directly compared rTMS and ECT treatment for patients who had depression. (8) After an average of 15.2 sessions of high-frequency rTMS over the 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 ratio 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. (9,) 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 two cases: rTMS compared with ECT resulted in similar clinical outcomes in
patients who had failed at least 1 course of antidepressant treatment (based on two trials with small sample size), and ECT produced better outcomes than pharmacotherapy. In two 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 Conventional Versus Theta Burst Repetitive Transcranial Magnetic Stimulation in the Treatment of Major Depressive Disorder, comparing 10-Hz rTMS with intermittent theta burst stimulation (iTBS). (10) Between 2013 and 2016, 414 patients with TRD were enrolled and randomized to 4 to 6 weeks of rTMS (n=205) or iTBS (n=209). Treatment resistance was defined as failure to tolerate two or more antidepressant trials of inadequate dose and duration or no clinical response to an adequate dose of an antidepressant. Patients who failed more than three antidepressant trials of adequate dosage were excluded from the trials. Patients could alter their medication during this trial. Treatment with rTMS (37 minutes) and iTBS (3 minutes) was delivered 5 times a week for 4 to 6 weeks. The primary outcome measure was the 17-item HAM-D, for which scores for patients treated with rTMS improved by 10.1 points and scores for patients treated with iTBS improved by 10.2 points (adjusted difference, 0.103; lower 95% CI, -1.16; p=0.001). Treatment with iTBS resulted in a higher self-rated intensity of pain (mean score, 3.8) than treatment with rTMS (mean score, 3.4; p=0.011). Headache was the most common treatment-related adverse event for both groups (rTMS=64% [131/204]; iTBS=65% [136/208]). Serious adverse events were noted in patients treated with rTMS (one case of myocardial infarction) and iTBS (one case each of agitation, worsening suicidal ideation, worsening depression); there was no significant difference in the number of adverse events in the two groups. The trial lacked a treatment group with 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). (11) 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 (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.

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 randomized to daily sessions (Monday to Friday for 6 weeks) of high-frequency active or sham rTMS of the DLPFC. (12) TRD was defined as the failure of at least one adequate course of antidepressant treatment. Patients had failed an average of 1.6 treatments in the current episode, with
approximately half of the study population failing to benefit from at least two treatments. The ITT 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 is 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 of the left DLPFC in the absence of maintenance treatment. (13) 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 higher when an antidepressant medication was initiated concurrently with rTMS (5 RCTs, $d = -0.56$) 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. (14) A total of 257 patients agreed to participate in the follow-up study of 307 who were initially treated with rTMS. Of these, 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. Richieri et al (2013) used propensity-adjusted analysis of observational data and found that the group of patients who had maintenance rTMS tapered over 20 weeks (from 3 times per week to once a month) had a significantly reduced relapse rate compared with patients who had no additional treatment (37.8% vs 81.8%). (15) 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%. (16) 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, Janiack et al (2010) evaluated patients who met criteria for partial response during either a sham-controlled or open-label phase of a prior study and were tapered from rTMS and simultaneously started on maintenance antidepressant monotherapy. (17) 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 on rTMS for depression. The meta-analyses found a clinical benefit associated with rTMS for TRD, with improved response rates and rates of remission 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. There is limited evidence to compare the effects of these treatments on cognition, although the adverse effects of rTMS appear to be minimal. While the most recent meta-analyses find that the effect of rTMS is smaller than the effect of ECT on TRD, given that rTMS does not require general anesthesia or 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 PICOs were used to select literature to inform this review.

Patients
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 QOL and functional outcomes.

Study Selection Criteria
Previously stated under the first indication.

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. (18) 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 three treatments or three 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 two 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=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 & Drug Administration (FDA) labeling, the device has not been demonstrated as safe or effective when treating cluster headache, chronic migraine headache, or migraine headache during the aura phase. The device has not been demonstrated to be as effective in relieving the associated symptoms of migraine (photophobia, phonophobia, nausea). (18) 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 OCD.

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

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

**Patients**

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.

Patients with OCD are actively managed by psychiatrists and other mental health professionals in an outpatient clinical setting.
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. TMS is proposed as a treatment to modulate these brain areas.

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

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

The Yale-Brown Obsessive Compulsive Scale (YBOCS) is a clinician-rated, 10-item scale commonly used to assess the severity of symptoms in OCD. (19) Each item is rated from 0 (no symptoms) to 4 (extreme symptoms) (total range, 0 to 40), with separate subtotals for the severity of obsessions and compulsions.

YBOCS scores of 0-13 correspond to 'mild symptoms' on the Clinical Global Impression of Severity (CGI-Severity=0-2), 14-25 with 'moderate symptoms' (CGI-Severity=3), 26-34 with 'moderate-severe symptoms' (CGI-Severity=4) and 35-40 with 'severe symptoms' (CGI-Severity=5-6). (20) An improvement of ≥ 35% on the YBOCS is most predictive of treatment response. (21)

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

Study Selection Criteria
Previously stated under the first indication.

Systematic Reviews
A systematic review by Trevizol et al (2016) included 15 RCTs (total n=483) that compared active with sham rTMS for OCD (Tables 3 and 4). (22) All studies were sham-controlled and double-blinded. The sample sizes in the trials ranged from 18 to 65 patients. Seven studies used low-frequency stimulation and eight studies used high-frequency stimulation. The cortical regions varied among the studies, targeting the supplementary motor area, orbitofrontal cortex, or left, right, or bilateral DLPFC. The researchers calculated the standardized mean difference for the primary outcome (YBOCS score). Response rates were not reported.

The pooled mean difference between groups on the YBOCS was 2.94 (95% 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.
Table 3. Systematic Review of TMS in Patients with OCD—Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trevizol et al (2016)</td>
<td>Up to March 2016</td>
<td>15</td>
<td>Mean age 31.9 (SD = 7.6) years, 44.1% women</td>
<td>483 (18-65); mean 16.1 (SD 8.45)</td>
<td>RCT, sham-controlled</td>
<td>1 week-6 weeks</td>
</tr>
</tbody>
</table>

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

Table 4. SR & M-A Results

<table>
<thead>
<tr>
<th>Study</th>
<th>YBOCS Score</th>
<th>Dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trevizol et al (2016)</td>
<td>22</td>
<td>483</td>
</tr>
<tr>
<td>Total N</td>
<td>483</td>
<td>483</td>
</tr>
</tbody>
</table>

Standardized Mean Difference: 0.45 (0.20 to 0.71).
Odds ratio: 1.02 (0.76–1.36)

\[ \chi^2 43\%, P=0.039 \]

Mean Difference: 2.94 (1.26, 4.62)

\[ \chi^2 58\% (P=0.002) \]


Randomized Controlled Trial

A more recent RCT was not included in the systematic review conducted by Trevizol et al (2019). The trial was submitted to the FDA as part of the de novo classification request, to establish a reasonable assurance of safety and effectiveness of the device. Study characteristics 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 six 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, the CGI-S and the Sheehan Disability Scale, a patient-reported measure of disability and impairment. Results at ten 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=0.003). The FDA review provides data from the ITT analysis of the mean change in the YBOCS score (n=99). In the ITT data set, the YBOCS score decreased by -6.0 points (95% 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=0.0988). Results on the secondary outcomes were mixed. More patients in the active treatment group were considered improved based on the Clinical Global Impression of Improvement and the CGI-S at six weeks, but there was no significant difference between groups on the Sheehan Disability Scale (See Table 6).
Table 5. Summary of Key RCT Characteristics- TMS for Patients with OCD

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmi et al (2019)(^{23}) NCT02229903</td>
<td>U.S., Israel, Canada</td>
<td>11</td>
<td>2014-2017</td>
<td>N=99</td>
<td>Deep TMS 6-week treatment phase (consisting of 5 weeks of daily treatments 5 days a week and four treatments during the 6th week)</td>
<td>Sham 6 weeks (primary) 10 weeks (secondary)</td>
</tr>
</tbody>
</table>

- Adults ages 22-68 years, diagnosis of OCD as a primary disorder, receiving treatment in an outpatient setting, and have a YBOCS score >20; in maintenance treatment with a therapeutic dosage of a serotonin reuptake inhibitor (SRI) for at least 2 months before randomization or, if they were not on an SRI, in maintenance treatment on cognitive behavioral therapy (CBT) and have failed to respond adequately to at least one past trial of an SRI.

- Exclusions: primary axis I diagnosis other than OCD, severe neurological impairment, any condition associated with an increased risk of seizures.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>YBOCS (Primary Outcome)</th>
<th>YBOCS Response</th>
<th>CGI-I</th>
<th>CGI-S (modifed)</th>
<th>Sheehan Disability Scale</th>
<th>Adverse events (all)</th>
<th>Dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmi et al (2019)(^{23}) NCT02229903</td>
<td>Mean change from baseline at 6 weeks (≥30% change from baseline to 6 weeks)</td>
<td>Moderate to very much improved from baseline at 6 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N analyzed</td>
<td>94</td>
<td>94</td>
<td>94</td>
<td>94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMS</td>
<td>-6.0 points (95% CI=4.0, 8.1)</td>
<td>38.1% (16/42), 20/41 (49%)</td>
<td>25/41 (61%)</td>
<td>-3.8 points (95% CI -1.5, -6.1)</td>
<td>73%</td>
<td>6/48 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>-3.3 points (95% CI=1.2, 5.3)</td>
<td>11.1% (5/45)</td>
<td>9/43 (21%)</td>
<td>14/43 (32.6%)</td>
<td>-3.0 points (95% CI -0.8, -5.3)</td>
<td>69%</td>
<td>6/51 (12.0%)</td>
</tr>
<tr>
<td>Difference; P- value</td>
<td>2.8 points; P=0.01</td>
<td>0.69</td>
<td>p=0.003</td>
<td>p=0.011</td>
<td>p=0.022</td>
<td>NS (p-value not reported)</td>
<td>P=0.639</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; TMS: transcranial magnetic stimulation; OCD: obsessive-compulsive disorder; YBOCS: Yale-Brown Obsessive-Compulsive Scale; CGI-I: Clinical Global Impression of Improvement; CGI-S: Clinical Global Impression of Severity; CI: confidence interval; NS: non-significant.
Table 7. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population a</th>
<th>Intervention b</th>
<th>Comparator c</th>
<th>Outcomes d</th>
<th>Follow-Up e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmi et al (2019)23</td>
<td>NCT02229903</td>
<td></td>
<td></td>
<td></td>
<td>1,2, 6 weeks (primary)</td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation a</th>
<th>Blinding b</th>
<th>Selective Reporting c</th>
<th>Data Completeness d</th>
<th>Power e</th>
<th>Statistical f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmi et al (2019)23</td>
<td></td>
<td></td>
<td></td>
<td>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)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ITT: intention-to-treat; NCT: national clinical trial.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
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: OCD
The evidence on rTMS for OCD includes a number of small-to-moderate sized sham-controlled double-blind randomized trials and a meta-analysis of these RCTs. The meta-analysis of 15 RCTs (total n=483 patients, range 18-65 patients) found a benefit of rTMS on patient-reported OCD symptom severity at time points ranging from 2 to 6 weeks, but there was substantial variability in the stimulation parameters, including the cortical region that was stimulated and the frequency of stimulation. A more recent RCT compared deep rTMS to sham in 99 patients for 6 weeks, with an additional 4 weeks of follow-up as a secondary outcome. Using a modified ITT analysis (n=94), there was a larger mean decrease from baseline (improvement) on the
YBOCS score (the primary efficacy outcome) in the active treatment group (-6.0 points) than the sham group (-2.8 points), translating to a moderate effect size of 0.69. At 6 weeks, the response rate was 38.1% in the active treatment group compared to 11.1% in the sham group (P=0.003), as measured by a 30% or greater increase in the YBOCS. 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 PICOs were used to select literature to inform this review.

Patients
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 QOL and functional outcomes.

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

Study Selection Criteria
Previously stated under the first indication.

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. (25) 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. (26) The response was defined as a 40% or greater decrease on the Panic Disorder Severity Scale and a 50% or greater decrease in HAMD 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 two 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
Trevizol et al (2016) published a systematic review on the efficacy of low and high frequency rTMS for posttraumatic stress disorder. (27) 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 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
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. (28) 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). (29) 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 (seven RCTs) and positive symptoms (five 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 Blue Cross Blue Shield Association TEC Assessment (2011) evaluated TMS as an adjunct treatment for schizophrenia. (30) 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.

Substance Use Disorders 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. (31) Seventeen double-blind, sham-controlled controlled trials that used high-frequency stimulation were analyzed. Thirteen studies stimulated the left DLPFC and seven studies stimulated the right DLPFC or both sides. Twelve of the studies gave only one or two 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: Psychiatric Disorders Other than Depression or OCD
For individuals who have psychiatric disorders other than depression or OCD (eg, panic disorder, posttraumatic stress disorder, schizophrenia, substance use disorder and craving) who receive rTMS, the evidence includes numerous small RCTs and meta-analyses of these randomized trials. The relevant outcomes are symptoms, functional outcomes, and QOL. 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.

NEUROLOGICAL 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 PICOs were used to select literature to inform this review.

Patients
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 QOL and functional outcomes.
Follow-up over months is of interest to monitor outcomes.

Study Selection Criteria
Previously stated under the first indication.

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. (32) 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 (33) and 2018. (34) The reviewers identified 42 RCTs (range 4 to 70 participants) on TMS for chronic pain. Meta-analysis of rTMS studies vs 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 and tDCS may have short-term effects on chronic pain and QOL 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 dorsolateral prefrontal cortex 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. (35) The total number of participants was 230. All studies had active or placebo controls and four were double-blinded. However, a meta-analysis could not be conducted due to heterogeneity in designs, interventions, and outcomes of the trials. Therefore, a qualitative synthesis was performed. For the outcome of seizure rate, two studies showed a significant reduction and five studies did not. Of the four studies evaluating the mean number of epileptic discharges, three 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 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. (36) 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. (37) The meta-analysis included seven sham-controlled double-blinded controlled 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 (total n=470 patients) evaluating Parkinson disease. (38) 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. (39) 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 (total n=588 participants) evaluating the effect of low and high frequency TMS for improving function after stroke. (40) 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. (41) 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 parstriangularis for patients (total n=137) with aphasia after stroke. (42) 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.43, A search through October 2016 yielded 34 RCTs with a total of 904 participants (range, 6-108 participants). Pooled estimates found improvement with rTMS for both short-term (SMD=0.43; p<0.001) and long-term (SMD=0.49; p<0.001) manual dexterity. Of the 28 studies reporting on adverse events, 25 studies noted none. Mild adverse events, such as headache and increased anxiety were reported in three studies. The review was limited by variation in TMS protocols across studies.

Graef et al (2016) reported a systematic review of rTMS combined with upper-limb training for improving function after stroke. (44) 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 (eg, amyotrophic lateral sclerosis, chronic pain, epilepsy, fibromyalgia, Parkinson disease, stroke, substance use disorder, and craving) who receive rTMS, the evidence includes numerous small RCTs and meta-analyses of these randomized trials. The relevant outcomes are symptoms, functional outcomes, and QOL. 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 rTMS, the evidence includes a large number of sham-controlled randomized trials and meta-analyses of these trials. The relevant outcomes are symptoms, functional outcomes, and QOL. 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 six 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 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 migraine headaches who receive rTMS, the evidence includes a sham-controlled RCT of 201 patients conducted for submission to the FDA for clearance in 2013. 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 the effects of the technology on health outcomes.

For individuals who have OCD who receive rTMS, the evidence includes a number of small-to-moderate sized sham-controlled RCTs and a meta-analysis of these studies. The meta-analysis of 15 RCTs (total n=483 patients, range 18-65 patients) found a benefit of rTMS on patient-reported OCD symptom severity at time points ranging from 2 to 6 weeks, but there was substantial variability in the stimulation parameters, including the cortical region that was stimulated and the frequency of stimulation. A more recent RCT compared deep rTMS to sham in 99 patients for 6 weeks, with an additional 4 weeks of follow-up as a secondary outcome. Using a modified ITT analysis (n=94), there was a larger mean change from baseline on the primary efficacy outcome; YBOCS score in the active treatment group (-6.0 points) than the sham group (-2.8 points), translating to a moderate effect size of 0.69. At 6 weeks, the response rate was 38.1% in the active treatment group compared to 11.1% in the sham group (P=0.003), as measured by a 30% or greater decrease in the YBOCS. 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. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have psychiatric or neurological disorders other than depression, migraine, or OCD (eg, amyotrophic lateral sclerosis, chronic pain, epilepsy, fibromyalgia, panic disorder, Parkinson disease, posttraumatic stress disorder, schizophrenia, stroke, substance use disorder and craving) who receive rTMS, the evidence includes numerous small RCTs and meta-analyses of these randomized trials. The 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.

SUPPLEMENTAL INFORMATION

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, Blue Cross Blue Shield Association received input from 1 physician specialty society and 3 academic medical centers while their 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 (2018) published consensus recommendations on repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression. (45) 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 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.” (46)

American Academy of Child and Adolescent Psychiatry
National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (2015) 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. (48)

The Institute (2014) provided guidance on the use of rTMS for treating and preventing migraine. (49) The guidance stated that evidence on the efficacy of TMS for the treatment of a migraine was limited in quantity and for the prevention of a migraine was limited in both quality and quantity. Evidence on its safety in the short- and medium-term is adequate, but there was uncertainty about the safety of long-term or frequent use of TMS.

American Academy of Neurology
The American Academy of Neurology (2006) issued practice guidelines on the evaluation and treatment of depression, psychosis, and dementia in Parkinson disease. (50) The guidelines found the evidence insufficient to support or refute the efficacy of TMS or electroconvulsive therapy in the treatment of depression associated with Parkinson 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 9.

Table 9. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT02376491</td>
<td>Efficacy of Intermittent Theta Burst Stimulation Compared to 10 Hz Stimulation on Dorsolateral Prefrontal Cortex in Treatment-Resistant Major Depressive Disorder: a Double-blind Randomized Study</td>
<td>60</td>
<td>Mar 2019</td>
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<tr>
<td>NCT03762746</td>
<td>TMS for Treatment-Resistant Auditory Verbal Hallucination in Schizophrenia</td>
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<table>
<thead>
<tr>
<th>NCT No.</th>
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<td>NCT02977299</td>
<td>Augmentation Versus Switch: Comparative Effectiveness Research Trial for Antidepressant Incomplete and Non-responders With Treatment-Resistant Depression (ASCertain-TRD)</td>
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<td>NCT03289923</td>
<td>Concurrent fMRI-guided rTMS and Cognitive Therapy for the Treatment of Major Depressive Episodes</td>
<td>50</td>
<td>Jan 2020</td>
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<tr>
<td>NCT02910024</td>
<td>Theta-Burst-Stimulation in Early Rehabilitation of Stroke (TheSiReS)</td>
<td>150</td>
<td>Feb 2021</td>
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NCT: national clinical trial
**Government Regulations**

**National:**
There is no national coverage determination for this topic.

**Local:**
Wisconsin Physicians Service Insurance Corporation, Local Coverage Determination (LCD): Transcranial Magnetic Stimulation (TMS) (L34641)
Original effective date: 10/01/2015
Revision effective date: 11/01/2019

**Coverage Indications, Limitations, and/or Medical Necessity**
Transcranial magnetic stimulation (TMS) is a noninvasive method of brain stimulation. The technique involves placement of a small coil over the scalp and passing a rapidly alternating current through the coil wire which produces a magnetic field that passes unimpeded through the brain. Depending on stimulation parameters (frequency, intensity, pulse duration, stimulation site), repetitive TMS (rTMS) to specific cortical regions can either increase or decrease the excitability of the affected brain structures. The procedure is usually carried out in an outpatient setting and does not require anesthesia or analgesia.

When used as an antidepressant therapy, TMS produces a clinical benefit without the systemic side effects attendant with standard oral medications. TMS does not have adverse effects on cognition. Unlike electroconvulsive therapy (ECT), rTMS does not induce amnesia or seizures.

**Indications for Coverage**
TMS may be covered if prescribed and administered by a licensed physician who is knowledgeable in the use of repetitive transcranial magnetic stimulation. Outpatient rTMS may be indicated for patients with DSM-IV defined Major Depressive Disorder who have failed to benefit from initial treatment of their depression.

**Initial Treatment**
Left Prefrontal rTMS of the brain is considered medically necessary for use in an adult who has a confirmed diagnosis of severe major depressive disorder (MDD) single or recurrent episode; and

**One or more of the following:**
- Resistance to treatment with psychopharmacologic agents as evidenced by a lack of a clinically significant response to one trial of psychopharmacologic agents in the current depressive episode from at least two different agent classes. Each agent in the treatment trial must have been administered at an adequate course of mono- or poly-drug therapy; or
- Inability to tolerate psychopharmacologic agents as evidenced by two trials of psychopharmacologic agents from at least two different agent classes, with distinct side effects; or
- History of response to rTMS in a previous depressive episode; or
- If patient is currently receiving electro-convulsive therapy, rTMS may be considered reasonable and necessary as a less invasive treatment option.
AND
A trial of an evidence-based psychotherapy known to be effective in the treatment of MDD of an adequate frequency and duration without significant improvement in depressive symptoms as documented by standardized rating scales that reliably measure depressive symptoms.

AND
The order for treatment (or retreatment) is written by a psychiatrist (MD or DO) who has examined the patient, and reviewed the record. The physician will have experience in administering TMS therapy. The treatment shall be given under direct supervision of this physician (physician present in the area, but does not necessarily personally provide the treatment).

Coverage Limitations
The benefits of TMS use must be carefully considered against the risk of potential side effects in patients with any of the following:
- Seizure disorder or any history of seizures (except those induced by ECT or isolated febrile seizures in infancy without subsequent treatment or recurrence); or
- Presence of acute or chronic psychotic symptoms or disorders (such as schizophrenia, schizophreniform or schizoaffective disorder) in the current depressive episode; or
- Neurological conditions that include epilepsy, cerebrovascular disease, dementia, increased intracranial pressure, history of repetitive or severe head trauma, or primary or secondary tumors in the central nervous system, or
- Presence of an implanted magnetic-sensitive medical device located less than or equal to 30 cm from the TMS magnetic coil or other implanted metal items including, but not limited to a cochlear implant, implanted cardiac defibrillator (ICD), pacemaker, Vagus nerve stimulator (VNS), or metal aneurysm clips or coils, staples or stents. (Dental amalgam fillings are not affected by the magnetic field and are acceptable for use with TMS).

All other uses of Transcranial Magnetic are experimental and are not covered.

Retreatment
Retreatment may be considered for patients who met the guidelines for initial treatment and subsequently developed relapse of depressive symptoms if the patient responded to prior treatments as evidenced by a greater than 50% improvement in standard rating scale measurements for depressive symptoms.

Wisconsin Physicians Service Insurance Corporation, Local Coverage Article: Billing and Coding: Transcranial Magnetic Stimulation (TMS) (A57598)
Original effective date: 11/01/2019

Utilization Guidelines
The treatment must be provided by use of a device approved by the FDA for the purpose of supplying TRANSCRANIAL MAGNETIC STIMULATION.

It is expected that the services would be performed as indicated by current medical literature and standards of practice. Services performed in excess of established parameters may be subject to review for medical necessity.
TMS is reasonable and necessary for up to 20 visits over a 4-week period followed by five visits for tapering for those in remission; for those who show at least a 25% improvement by means of the standard tests for depression, the therapy may be continued for an additional 2 weeks (an addition 10 visits) with an additional 6 visits for tapering.

Retreatment may be considered for patients who met the guidelines for initial treatment and subsequently developed relapse of depressive symptoms if the patient responded to prior treatments as evidenced by a greater than 50% improvement in standard rating scale measurements for depressive symptoms or if there were a relapse after remission (e.g., GDS, PHQ-9, BDI, HAM-D, MADRS, QIDS or IDS-SR score.) A repeat treatment program is allowed as above.

Maintenance therapy is considered experimental/investigational and therefore not medically necessary.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Vagus Nerve Stimulation
- Electroconvulsive Therapy

References

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcranial magnetic stimulation for depression. TEC Assessments 2009; Volume 24, Tab 5.
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcranial magnetic stimulation for depression. TEC Assessments 2011; Volume 26, Tab 3.
7. Berlim MT, Van den Eynde F, Daskalakis ZJ. High-frequency repetitive transcranial magnetic stimulation accelerates and enhances the clinical response to antidepressants in
major depression: a meta-analysis of randomized, double-blind, and sham-controlled trials. 


The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 7/10/20, the date the research was completed.
## Joint BCBSM/BCN Medical Policy History

<table>
<thead>
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<th>Policy Effective Date</th>
<th>BCBSM Signature Date</th>
<th>BCN Signature Date</th>
<th>Comments</th>
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**Next Review Date:** 3rd Qtr, 2021
BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: TRANSCRANIAL MAGNETIC STIMULATION AS A TREATMENT OF DEPRESSION AND OTHER PSYCHIATRIC/NEUROLOGIC DISORDERS

I. Coverage Determination:

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<th>Coverage Status</th>
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<td>BCNA (Medicare Advantage)</td>
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<td>BCN65 (Medicare Complementary)</td>
<td>Coinsurance covered if primary Medicare covers the service.</td>
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II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member’s certificate and is not guaranteed. Please consult the individual member’s certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.