### Transcranial Magnetic Stimulation as a Treatment of Depression and other Psychiatric/Neurologic Disorders

<table>
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<tr>
<th>Policy Number:</th>
<th>Current Effective Date:</th>
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<tr>
<td>MM.12.015</td>
<td>December 1, 2019</td>
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<th>Lines of Business:</th>
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<tr>
<td>PPO; HMO; QUEST Integration</td>
<td>August 1, 2014</td>
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<th>Place of Service:</th>
<th>Precertification:</th>
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<tr>
<td>Outpatient</td>
<td>Required, see Section IV</td>
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### I. 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 TMS (rTMS) is being evaluated for the treatment of treatment-resistant depression (TRD) and other psychiatric and neurologic disorders.

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 electroconvulsive therapy (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 randomized controlled trials 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 (e.g., amyotrophic lateral sclerosis, chronic pain, epilepsy, fibromyalgia, migraine headache, obsessive-compulsive disorder, panic disorder, Parkinson disease, posttraumatic stress disorder, schizophrenia, stroke, substance abuse and craving) who receive rTMS, the evidence includes numerous small randomized controlled trials 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.

II. Policy Criteria

Initial treatment with rTMS consisting of up to 20 sessions (five days a week for four weeks) is covered (subject to Limitations and Administrative Guidelines) when all of the following criteria are met:

A. The patient has a confirmed diagnosis of severe major depressive disorder (MDD) evidenced by both of the following:

1. A completed psychiatric evaluation that has established a diagnosis of major depressive disorder and has ruled out psychotic disorders, schizoaffective disorder, schizophrenia, bipolar disorder, substance dependence, bipolar spectrum disorder and common medical disorders that present with depressive symptoms.

   a. Antidepressant medications from at least two different agent classes, used at the maximum dose as approved by the FDA or documentation supports that higher doses were not tolerated when the dose is less than the FDA-approved maximum.

   b. Evidence-based augmentation therapies in at least two of the four trials.

   Augmentation therapy is defined as the addition of one or more medications, which are not antidepressants that are added to increase the efficacy of the antidepressant, or a combination of two antidepressants with different mechanisms of action. At least one of the augmentation therapies should be the addition of a medication that is not an antidepressant.

   ii. Antidepressant medications from at least two different agent classes, used at the maximum dose as approved by the FDA or documentation supports that higher doses were not tolerated when the dose is less than the FDA-approved maximum.

   Each trial should include at least one antidepressant.

   Evidence-based augmentation therapies in at least two of the four trials.

   Augmentation therapy is defined as the addition of one or more medications, which are not antidepressants that are added to increase the efficacy of the antidepressant, or a combination of two antidepressants with different mechanisms of action. At least one of the augmentation therapies should be the addition of a medication that is not an antidepressant.
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Inability to tolerate antidepressant medications as evidenced by four trials of such medications from at least two different classes, with distinct side effects. History of refractoriness or intolerance to treatment as noted above and response to TMS in a previous depressive episode.

The patient has had ECT in the past, but cannot tolerate further treatment due to adverse effects.

b. The patient has had a trial of evidence-based psychotherapy such as CBT or Interpersonal psychotherapy known to be effective in the treatment of MDD (e.g., cognitive behavioral therapy or interpersonal psychotherapy) of an adequate frequency and duration without significant improvement in depressive symptoms. The lack of response to general counseling or psychotherapy does not constitute documentation of treatment resistant features is not sufficient.

Additional requirements include: The patient has declined ECT.

TMS is administered by a U.S. Food and Drug Administration (FDA) cleared device for the treatment of MDD under the supervision of a licensed psychiatrist according to specified stimulation parameters.

Coverage of an additional 16 rTMS sessions (given in a tapering sequence) beyond 20 requires documentation using validated depression monitoring scale of at least a 50% reduction in depressive symptoms from baseline and a follow up treatment plan for medication or psychotherapy after the rTMS is completed.

III. Limitations

A. TMS is not covered for all other psychiatric indications including but not limited to bipolar disorder, anxiety disorders, mood disorders, schizophrenia, schizoaffective disorder; and, neurologic disorders as it is not known to be effective in improving health outcomes.

TMS is contraindicated in patients with the following:

1. Seizure disorder or any history of seizure (except those induced by ECT or isolated febrile seizures in infancy without subsequent treatment or recurrence).

2. Presence of a acute or chronic psychotic symptoms or disorders (such as schizophrenia, schizophreniform or schizoaffective disorder) in the current depressive episode.

3. A depressive episode in the context of schizoaffective disorder.

4. 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.

A. TMS is not covered when used as maintenance therapy for MDD as it is not known to be effective in improving health outcomes.

Treatments are limited to 36 treatments in total within the first six weeks, followed by three treatments in the seventh week, two treatments in the eighth week and one treatment in the ninth week.
IV. Administrative Guidelines

Precertification is required for the initial four weeks of treatment with TMS. Behavioral Health precertification review is performed by Beacon Health Options. Please complete the Behavioral Health Precertification Request and fax or mail the form as indicated. The following documentation from the patient’s medical record must be submitted:

1. Psychiatric evaluation confirming a diagnosis of Major Depressive Disorder.
2. A current validated depressive symptom scale within 2 weeks of application that will serve as a baseline for response.
3. Documentation of treatment resistant features; including names, doses and dates of use of at least four antidepressant medications from at least two different classes and at least two augmentation therapies that were tried and found to be ineffective. If applicable, names, doses and dates of use of at least four antidepressant medications from at least two different classes that were tried and not tolerated.
4. Documentation supporting trial and ineffectiveness of evidence-based psychotherapy.
5. If applicable, documentation supporting that the patient was refractory to treatment and has had a response to rTMS during a previous depressive episode.
6. Documentation supporting that the patient has declined ECT.
7. Aftercare plan for maintenance (durable response) of treatment response including pharmacologic and psychotherapeutic or both modalities (if applicable).
8. Precertification is required for continuation of treatment beyond four weeks (20 sessions). Documentation includes from the medical record a validated depressive symptom severity scale supporting that the patient is responding to treatment and must be submitted an update of the aftercare plan.

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
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<tr>
<td>90867</td>
<td>Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management</td>
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<tr>
<td>90868</td>
<td>Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent delivery and management, per session</td>
</tr>
<tr>
<td>90869</td>
<td>Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold re-determination with delivery and management</td>
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V. Scientific Background

For individuals who have TRD who receive rTMS, the evidence includes a large number of sham controlled randomized controlled trials (RCTs) and meta-analyses of these trials. Relevant outcomes are symptoms, functional outcomes, and quality of life. The meta-analyses find 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 electroconvulsive therapy (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. Metaanalyses 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 found 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 balance 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 (e.g., amyotrophic lateral sclerosis, chronic pain, epilepsy, fibromyalgia, migraine headache, obsessive-compulsive disorder, panic disorder, Parkinson disease, posttraumatic stress disorder, schizophrenia, stroke, substance abuse and craving) who receive TMS, the evidence includes numerous small RCTs and meta-analyses of these RCTs. 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. A demonstration of the durability of any treatment effects would also be needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Transcranial Magnetic Stimulation**

Transcranial magnetic stimulation (TMS), introduced in 1985 as a new method of noninvasive stimulation of the brain, involves placement of a small coil over the scalp, passing a rapidly alternating current through the coil wire, which produces a magnetic field that passes unimpeded through the scalp and bone, resulting in electrical stimulation of the cortex. TMS was initially used to investigate nerve conduction; e.g., TMS over the motor cortex will produce a contralateral muscular-evoked potential. The motor threshold, which is the minimum intensity of stimulation required to induce a motor response, is empirically determined for each person by localizing the site on the scalp for optimal stimulation of a hand muscle, then gradually increasing the intensity of stimulation. 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 convolution. 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)
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in depressed patients, and early studies suggested that high frequency (e.g., 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 frontal stimulation), or deep stimulation with an H1 coil, are 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 disease, neuropathic pain, obsessive-compulsive disorder, postpartum depression, Parkinson disease, stroke, posttraumatic stress disorder, panic disorder, epilepsy, dysphagia, Tourette syndrome, schizophrenia, migraine, spinal cord injury, fibromyalgia, and tinnitus. (See evidence review 8.01.39 on rTMS for 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 been cleared for marketing 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

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>FDA Clearance No.</th>
<th>FDA Clearance Date</th>
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<td>Neuronetics</td>
<td>DEN070003</td>
<td>2008</td>
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<td>Brainsway H-Coil Deep TMS</td>
<td>Brainsway</td>
<td>K122288</td>
<td>2013</td>
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<td>Rapid Therapy System</td>
<td>Magstim</td>
<td>K162935</td>
<td>2015</td>
</tr>
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<td>MagVita TMS Therapy System</td>
<td>Tonica Elektronik</td>
<td>K150641</td>
<td>2015</td>
</tr>
<tr>
<td>Neurosoft TMS</td>
<td>TeleEMG</td>
<td>K160309</td>
<td>2016</td>
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<tr>
<td>MagVita TMS Therapy System with Theta Burst Stimulation</td>
<td>Tonica Elektronik</td>
<td>K173620</td>
<td>2018</td>
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FDA: Food and Drug Administration; rTMS: repetitive transcranial magnetic stimulation.

In 2013, the Cerena TMS device (eNeura Therapeutics) was granted a de novo 510(k) classification by 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.
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 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 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 adult patients with Obsessive-Compulsive Disorder. FDA product code: QCI.

In July 2018, the Mag Vita TMS Therapy System with Theta Burst Stimulation device (Tonica Elektronik) was cleared for marketing by FDA through the 510(k) process (K173620). The FDA determined that this device was substantially equivalent to existing devices for use in major depressive disorder. FDA product code: OBP.

RATIONALE

This evidence review was created in November 2001 and has been updated regularly with searches of the MEDLINE database. This review was informed by a 2009, 2011, and 2013 TEC Assessment. The most recent literature review was performed through August 23, 2018.

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
The purpose of repetitive transcranial magnetic stimulation (rTMS) is to provide a treatment option as an alternative to or an improvement to 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 are rTMS.

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

**Outcomes**
The general outcomes of interest are symptoms, quality of life, and functional outcomes.

**Timing**
Follow-up over months is of interest for symptoms, quality of life, and functional outcomes.

**Setting**
Patients with treatment-resistant 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.

Evaluation of rTMS for treatment-resistant depression (TRD) includes RCTs comparing rTMS with sham as well as evidence when used as a replacement for or an 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 electroconvulsive therapy (ECT). However, some individuals may not want to use ECT due to its requirement for general anesthesia and induction of seizures.

Note that there has been a trend to use rTMS at increased levels of intensity, trains of pulses, total pulses per session, and number of sessions. 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. Repetitive TMS for TRD

Systematic Reviews
In 2016, the Health Quality Ontario published a systematic review of left DLPFC rTMS for TRD. 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 rate of response among 20 studies (pooled relative risk, 1.72; 95% CI, 1.13 to 2.62; p=0.11) as well as statistically greater rate of remission among 13 studies (pooled relative risk, 2.20; 95% CI, 1.44 to 3.38, p<0.001). 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 including 40 and 46 subjects, comparing rTMS and ECT. While 1 study reported a slightly higher remission rate for ECT (27.3%) than for rTMS (16.7%), the other study did not find a significant difference between ECT and rTMS for mean depression scores at 3 or 6 months, but did note relapses were less frequent for ECT. Statistical comparisons were either not significant or not available, limiting the interpretation of these findings.

Berlim et al (2013) reported on a meta-analysis assessing the effect of rTMS for accelerating and enhancing the clinical response to antidepressants. 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 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 (2013) et al identified 7 RCTs (total N=294 patients) that directly compared rTMS with ECT treatment for patients with depression. After an average of 15.2 sessions of high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC), 33.6% of patients were classified as remitters. Fifty-two percent 52% of patients were classified as remitters following an average of 8.2 ECT sessions. The pooled OR was 0.46, indicating a significant difference in outcome favoring ECT.

The Agency for Healthcare Research and Quality published a comparative effectiveness review on nonpharmacologic interventions for TRD in adults in 2011. Reviewers concluded at that time 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
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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).10 Between 2013 and 2016, 414 patients with treatment-resistant major depressive disorder were enrolled and randomized to 4 to 6 weeks of MRI-guided 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 a dequate dosage were excluded from the study. Patients could alter their medication through the 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 (HAM-17), 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; SD=2.0) than treatment with rTMS (mean score, 3.4; SD=2.0; p=0.011). Headache was the most common treatment-related adverse event for both groups (rTMS 131/204 [64%]; iTBS 136/208 [65%]). Serious adverse events were noted in patients treated with rTMS (n=1; myocardial infarction) and iTBS (n=3; agitation, worsening suicidal ideation, worsening depression); there was no significant difference in the number of adverse events in the 2 groups. The study was limited by absence of a treatment group with placebo.

The largest trial included in the systematic reviews is a 2007 double-blind multicenter (23 study sites) trial with 325 TRD patients randomized to daily sessions (Monday to Friday for 6 weeks) of high-frequency active or sham rTMS of the DLPFC. 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.

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). The trial included 229 patients with major depressive disorder who had not received benefit from 1 to 4 antidepressant trials or were intolerant to at least 2 antidepressant treatments. Using per-protocol analysis, which excluded 31 patients who did not receive a 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%). By 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.

### Durability of rTMS and Maintenance Therapy

**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. 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 = -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 1-year follow-up with maintenance therapy from a large multicenter observational study (42 sites) of rTMS for patients with TRD. 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 maintenance schedules are being studied. For example, Richieri et al (2013) used propensity-adjusted analysis of observational data and found that patients who had maintenance rTMS tapered over 20 weeks (from 3 times per week to once a month) had a significantly reduced relapse rate than patients who had no additional treatment (37.8% vs 81.8%). 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%. 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 (2010), patients who met criteria for partial response during either a sham-controlled or an open-label phase of a prior study were tapered from rTMS and simultaneously started on maintenance antidepressant monotherapy. 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. 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 effects of
rTMS appear to be minimal. While the most recent meta-analyses find that the effect of rTMS is
smaller than the effect of ECT on TRD, given that rTMS does not require general anesthesia or
induction of seizures, some individuals may not want to use ECT, so the balance of incremental
benefits and harms associated with rTMS may be a reasonable balance compared with ECT.

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 net health outcomes?

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 symptoms, quality of life, and functional outcomes.

Timing
Follow-up over months is of interest for symptoms, quality of life, and functional 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 2013 Cochrane review identified 3 RCTs with a total of 50 participants with amyotrophic lateral
sclerosis that compared rTMS with sham TMS. 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 at that time was insufficient to draw
conclusions about the efficacy and safety of rTMS in the treatment of amyotrophic lateral sclerosis.

Chronic Pain
A 2014 Cochrane review on noninvasive brain stimulation techniques identified 30 RCTs (total N=528 patients) on TMS for chronic pain. 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. Due to the low quality of the identified studies, future studies could have a substantial impact on the conclusions.

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

Section Summary: Epilepsy
A number of RCTs have been conducted on the effect of rTMS on epilepsy. All but one was conducted between 2002 and 2008, with the most recent study conducted in 2016. 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
In Saltychev and Laimi (2017) published a meta-analysis of rTMS for the treatment of patients with fibromyalgia. The meta-analysis included 7 sham-controlled double-blinded controlled trials with low risk of bias. The sample sizes of the trials ranged from 18 to 54. Five of the studies provided high-frequency stimulation to the left primary motor cortex, and the others were to the right or left DLPFC. The number of sessions ranged from 10 to 24, and follow-up ranged from immediately after treatment to 3 months posttreatment. In the pooled analysis, pain severity decreased after the last simulation by 1.2 points (95% CI, -1.7 to -0.8 points) on a 10-point numeric rating scale, while pain severity measured at 1 week to 1 month after the last simulation decreased by 0.7 points (95% CI, -1.0 to -0.3 points). Both were statistically significant but not considered clinically significant, based on a minimal clinically important difference of 1.5 points.

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 the de novo application. Enrolled in the trial were 201 patients with a history of an aura preceding more than 30% of headaches with moderate or severe headache severity for approximately 90% of migraine attacks. Following a month-long baseline phase to establish the frequency and severity of the migraine; patients were randomized to a treatment phase consisting of 3 treatments or 3 months, whichever occurred first. Patients were instructed to treat their migraine headache during the aura phase and to record their pain severity (0-3), severity of associated migraine symptoms (photophobia, phonophobia, nausea), presence of vomiting, and use of rescue medications at the time of treatment and at 1, 2, 24, and 48 hours after treatment. The primary end point was the proportion of patients who were pain-free 2 hours after treatment. Of the 201 patients enrolled, 164 recorded at least 1 treatment and 113 recorded at least 1 treatment when there was pain. Post hoc analysis of these 113 patients showed a benefit of the device for the primary end point (37.74% pain free after 2 hours for Cerena vs 16.67% for sham, p=0.018) and for the proportion of subjects who were pain free after 24 hours (33.96% for Cerena vs 10% for sham; p=0.002). Active treatment was not inferior to sham for the proportion of subjects free of photophobia, suggesting that the device does not worsen photophobia. However, the device was not inferior to sham for the proportion of subjects free of nausea and phonophobia.

Section Summary: Migraine Headache
There is little evidence on the TMS devices for the treatment of a migraine headache. The results of the pivotal trial are also limited by the 46% dropout rate and post hoc analysis. According to the Food and Drug Administration 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). No recent studies have been identified with these devices.

Obsessive-Compulsive Disorder
A 2013 meta-analysis included 10 small RCTs (total N=282 patients) assessing obsessive-compulsive disorder (OCD). Response rates of rTMS augmentation therapy were 35% for active and 13% for sham rTMS. The pooled OR 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 (i.e., orbitofrontal cortex or supplementary motor area).

A 2016 systematic review by Trevizol et al included 15 RCTs (total N=483 patients) that compared active with sham rTMS for OCD. All studies were sham-controlled and double-blinded. Sample sizes in the trials were small-to-moderate, ranging from 18 to 65 patients (mean sample 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.

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. Additional study in larger numbers of patients is
needed to evaluate these parameters.

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

Parkinson Disease
A meta-analysis by Chou et al (2015) included 20 sham-controlled randomized trials (total N=470 patients) evaluating Parkinson disease. 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 (2013) included in the systematic review was an exploratory, multicenter, double-blind trial that randomized 106 patients to 8 weeks of 1-Hz rTMS, 10-Hz rTMS, or sham stimulation over the supplementary motor area. At 9 weeks, all groups showed a similar amount of improvement.

Section Summary: Parkinson Disease
A meta-analysis of 20 trials found a medium effect size on motor symptoms in patients with Parkinson 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 if high-frequency rTMS over the primary motor cortex improves motor symptoms in patients with Parkinson 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). 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 of 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, the effect of adding a scripted narrative of a traumatic event, 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 rTMS (high frequency) for auditory hallucinations and negative symptoms of schizophrenia, respectively.31 For 1-Hz rTMS, 13 studies were included. Compared with sham, the rTMS group showed greater improvement in auditory hallucinations (standard mean difference [SMD], -0.29; 95%CI, -0.57 to -0.01). However, significant heterogeneity between the studies was found (p=0.06). In the 7 studies included for 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 between studies (p<0.001). The study was further limited by the small number of articles included and by the unavailability of original data for some studies.

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

A TEC Assessment (2011) evaluated TMS as an adjunct treatment for schizophrenia.33 Five metaanalyses 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 2013 Cochrane review included 19 RCTs (total N=588 participants) evaluating the effect of low- and high-frequency TMS for improving function after stroke. 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 Lee et al (2014) assessed the effect of rTMS on the recovery of hand function and excitability of the motor cortex after stroke. 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 2015 meta-analysis by Li et al (2015) included four RCTs on low-frequency included 4 RCTs on rTMS over the right pars triangularis for patients (total N=137) with aphasia after stroke. 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 Limbs
Zhang et al (2017) published a systematic review and meta-analysis evaluating the effects of rTMS on upper-limb motor function after stroke. A search for studies published before October 2016 was performed, yielding 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 between studies. Graef et al (2016) reported a systematic review of rTMS combined with upper-limb training for improving function after stroke. Included were 11 sham-controlled randomized trials with 199 patients that evaluated upper-limb motor and functional status and spasticity; Eight 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 craving for high palatable food. Seventeen double-blind, sham-controlled controlled trials that
used high-frequency stimulation were included in the analysis. Thirteen studies stimulated the left DLPFC and 7 studies stimulated the right DLPFC or both sides. Twelve of the studies gave only 1 or 2 sessions. The standardized effect size was 0.476 (95% CI, 0.316 to 0.636), indicating a medium effect size for active stimulation over sham for a reduction in craving. However, the studies were small (range, 9-48 patients) and there was significant heterogeneity in selected studies. No significant differences were found in the effectiveness of rTMS vs transcranial direct current stimulation, the different substances, or the side of stimulation, although this analysis might have been biased by the number of studies for each condition.

Section Summary: Substance Abuse and Craving
A number of sham-controlled randomized trials and a meta-analysis of these have found a medium effect size of rTMS for reduction of substance 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 repetitive transcranial magnetic stimulation (rTMS), the evidence includes a large number of sham-controlled randomized controlled trials (RCTs) and meta-analyses of these trials. Relevant outcomes are symptoms, functional outcomes, and quality of life. The meta-analyses find 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 electroconvulsive therapy (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 found 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 the use of ECT so the balance of incremental benefits and harms associated with rTMS may be a reasonable balance 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 TBS includes 2 randomized trials and 2 nonrandomized studies. Using various methods of assessment, all studies showed improvement with TBS; no serious adverse events were reported. 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 (e.g., amyotrophic lateral sclerosis, chronic pain, epilepsy, fibromyalgia, migraine headache, obsessive-compulsive disorder, panic disorder, Parkinson disease, posttraumatic stress disorder, schizophrenia, stroke, substance abuse and craving) who receive rTMS, the evidence includes numerous small RCTs and meta-analyses of these RCTs. 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. A demonstration of the durability of any treatment effects would also be needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

VI. Supplemental Information

Clinical Input From Physician Specialty Societies And Academic Medical Centers

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

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

Practice Guidelines And Position Statements

American Psychiatric Association

The American Psychiatric Association’s 2010 practice guidelines (reaffirmed in 2015) for the treatment of patients with major depressive disorder have indicated 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). Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or light therapy. The Association stated that a number of strategies are available when a change in the treatment plan seems necessary, such as transdermal selegiline, a relatively selective monoamine oxidase 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.”

American Academy of Child and Adolescent Psychiatry

In 2013, the American Academy of Child and Adolescent Psychiatry published practice parameters on the assessment and treatment of children and adolescents with tic disorders. The Academy did not recommend rTMS, citing the limited evidence on the 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 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.

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

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 disease. The guidelines found the evidence insufficient to support or refute the efficacy of TMS or ECT 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

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing And Unpublished Clinical Trials
A search of ClinicalTrials.gov in May 2017 identified over 300 ongoing trials on rTMS.

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VII. Important Reminder
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4),
generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References

8. Berlim MT, Van den Eynde F, Daskalakis ZJ. Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. Depress Anxiety. Jul 2013;30(7):614-623. PMID 23349112
13. Kedzior KK, Reitz SK, Azorina V, et al. Durability of the antidepressant effect of the high-frequency repetitive transcranial magnetic stimulation (rTMS) in the absence of maintenance treatment in major depression: a systematic review and meta-analysis of 16 double-blind,
randomized, sham-controlled trials. Depress Anxiety. Mar 2015;32(3):193-203. PMID 25683231


Transcranial Magnetic Stimulation as a Treatment of Depression and other Psychiatric/Neurologic Disorders


46. Blue Cross Blue Shield. Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders. Policy # 2.01.50. OctoberJuly 2018.