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

Policy # 00121
Original Effective Date: 06/05/2002
Current Effective Date: 11/15/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider repetitive transcranial magnetic stimulation (rTMS) of the brain as a treatment of major depressive disorder to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility will be considered for repetitive transcranial magnetic stimulation (rTMS) of the brain as a treatment of major depressive disorder when ALL of the following criteria have been met:
- Confirmed diagnosis of severe major depressive disorder (single or recurrent) documented by standardized rating scales that reliably measure depressive symptoms; AND
- Any one of the following:
  - Failure of 4 trials of psychopharmacologic agents including 2 different agent classes and 2 augmentation trials; OR
  - Inability to tolerate a therapeutic dose of medications as evidenced by 4 trials of psychopharmacologic agents with distinct side effects; OR
  - History of response to rTMS in a previous depressive episode (at least 3 months since the prior episode); OR
  - Is a candidate for electroconvulsive therapy (ECT) and electroconvulsive therapy (ECT) would not be clinically superior to repetitive transcranial magnetic stimulation (rTMS) (e.g., in cases with psychosis, acute suicidal risk, catatonia or life-threatening inanition repetitive transcranial magnetic stimulation (rTMS) should NOT be utilized); AND

- Failure of a trial of a psychotherapy known to be effective in the treatment of major depressive disorder of an adequate frequency and duration, without significant improvement in depressive symptoms, as documented by standardized rating scales that reliably measure depressive symptoms.
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When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder when patient selection criteria are not met is considered to be investigational.*

Based on review of available data, the Company considers continued treatment with repetitive transcranial magnetic stimulation (rTMS) of the brain as maintenance therapy to be investigational.*

Based on review of available data, the Company considers transcranial magnetic stimulation (TMS) of the brain as a treatment of all other psychiatric/neurologic disorders, including but not limited to bipolar disorder, schizophrenia, obsessive-compulsive disorder (OCD), or migraine headaches to be investigational.*

Policy Guidelines
rTMS should be performed using a U.S. Food and Drug Administration (FDA)‒cleared device in appropriately selected patients, by physicians who are adequately trained and experienced in the specific techniques used. A treatment course should not exceed 5 days a week for 6 weeks (total of 30 sessions), followed by a 3-week taper of 3 TMS treatments in week 1, 2 TMS treatments the next week, and 1 TMS treatment in the last week.

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

The following should be present for the administration of repetitive TMS:
   a. An attendant trained in basic cardiac life support and the management of complications such as seizures, as well as the use of the equipment must be present at all times; and
   b. Adequate resuscitation equipment including, for example, suction and oxygen; and
   c. The facility must maintain awareness of response times of emergency services (either fire/ambulance or "code team"), which should be available within 5 minutes. These relationships are reviewed on at least a 1-year basis and include mock drills.

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Background/Overview

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.

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 (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 stimulation), or deep stimulation with an H1 coil, are also being explored. In contrast to ECT, TMS does not require general anesthesia and does not generally induce a convulsion.

Repetitive TMS

rTMS is also being tested as a treatment for a variety of other disorders including alcohol dependence, Alzheimer disease, neuropathic pain, OCD, postpartum depression, Parkinson disease, stroke, posttraumatic stress disorder (PTSD), panic disorder, epilepsy, dysphagia, Tourette syndrome, schizophrenia, migraine, spinal cord injury, fibromyalgia, and tinnitus. In addition to the potential for altering interhemispheric imbalance, it has been proposed that high-frequency rTMS may facilitate neuroplasticity.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration

Devices for transcranial stimulation have been cleared for marketing by the U.S. 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>
</tr>
</thead>
<tbody>
<tr>
<td>NeuroStar TMS</td>
<td>Neuronetics</td>
<td>DEN070003</td>
<td>2008</td>
</tr>
<tr>
<td>Brainsway H-Coil Deep TMS</td>
<td>Brainsway</td>
<td>K122288</td>
<td>2013</td>
</tr>
<tr>
<td>Rapid Therapy System</td>
<td>Magstim</td>
<td>K162935</td>
<td>2015</td>
</tr>
</tbody>
</table>

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MagVita TMS Therapy System  Tonica Elektronik  K150641  2015
Neurosoft TMS  TeleEMG  K160309  2016

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 a liquid-crystal display (LCD) screen, a use authorization feature, lithium battery pack, and smaller size. The stimulation parameters are unchanged. The sTMS Mini (eNeura Therapeutics) received marketing clearance by the FDA in 2016. FDA product code: OKP.

Centers for Medicare and Medicaid Services (CMS)
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.

Rationale/Source
The following summary of the key literature to date focuses on systematic reviews of randomized controlled trials (RCTs). The evidence review on rTMS is divided by indication and by key differences in treatment protocols.

TREATMENT-RESISTANT DEPRESSION
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 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.

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 2009 meta-analysis by Schutter for a summary of study characteristics and stimulation parameters used in trials conducted prior to 2008.

Repetitive TMS for TRD

Systematic Reviews

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 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.

Berlim et al reported on a 2013 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 2013 systematic review by Berlim 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 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.
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 1). 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 that 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 1, 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.

### Table 1. Statistical Comparisons for Depression Scores After rTMS

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Favors</th>
<th>WMD (95% CI)</th>
<th>p</th>
<th>RR for Remission (95% CI)</th>
<th>p</th>
<th>RR for Response (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTMS vs sham</td>
<td>rTMS</td>
<td>2.31 (1.19 to 3.43)</td>
<td>&lt;0.001</td>
<td>2.20 (1.44 to 3.38)</td>
<td>0.001</td>
<td>1.72 (1.13 to 2.62)</td>
<td>0.01</td>
</tr>
<tr>
<td>rTMS vs ECT</td>
<td>ECT</td>
<td>5.97 (0.94 to 11.0)</td>
<td>0.02</td>
<td>1.44 (0.64 to 3.23)</td>
<td>0.38</td>
<td>1.72 (0.95 to 3.11)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

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

### Randomized Controlled Trials

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 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**

A 2015 meta-analysis 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 -.48, and the effect sizes were lower in RCTs with 8 to 16 weeks of follow-up (d = -.42) than with 1 to 4 weeks of follow-up (d = -0.54). The effect size was larger when antidepressant medication was initiated concurrently with rTMS (5 RCTs, d = -.56) than when patients were on a stable dose of medication (9 RCTs, d = -.43) or were unmedicated (2 RCTs, d = -.26).

**Observational Studies**

In 2014, Dunner et al 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 (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
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 2016 Cochrane review by Chen et al included 7 RCTs on 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
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performed. For the outcome of seizure rate, 2 studies showed a significant reduction and 5 studies did not. Of the 4 studies evaluating the mean number of epileptic discharges, 3 studies showed a statistically significant reduction in discharges. Adverse events were uncommon and mild, involving headache, dizziness, and tinnitus. There were no significant changes in medication use.

Section Summary: Epilepsy
A number of RCTs have been conducted on the effect of rTMS on epilepsy. All but one were conducted between 2002 and 2008, with the most recent study conducted in 2012. 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 2017, Saltychev and Laimi 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 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). 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 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 from 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 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
In 2016, Trevizol et al published a systematic review on the efficacy of rTMS for 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.
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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. In 2011, TEC Assessment evaluated TMS as an adjunct treatment for schizophrenia. 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 at that time was insufficient to demonstrate that TMS is effective in the treatment of schizophrenia. A 2015 Cochrane review 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.

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 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 2014 meta-analysis 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...
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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 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**

In 2016, Graef et al 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; 8 RCTs with sufficient data were included in the meta-analysis. These studies were considered to have a low-to-moderate risk of bias. In the overall analysis, there was no benefit of rTMS on upper-limb function or spasticity (SMD=0.03; 95% CI, -0.25 to 0.32).

**Section Summary: Stroke**

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

**Substance Abuse and Craving**

Jansen et al reported a 2013 meta-analysis evaluating the effect of rTMS and transcranial direct current stimulation of the DLPFC on substance dependence (alcohol, nicotine, cocaine, marijuana) or 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 rTMS, the evidence includes a large number of sham-controlled 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 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 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 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, OCD, panic disorder, Parkinson disease, PTSD, 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.

References
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05/16/2002 Medical Policy Committee review
06/05/2002 Managed Care Advisory Council approval
06/24/2002 Format revision. No substance change to policy.
06/01/2004 Medical Director review
06/15/2004 Medical Policy Committee review
06/28/2004 Managed Care Advisory Council approval
06/07/2006 Medical Director review
06/21/2006 Medical Policy Committee approval. Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
06/04/2008 Medical Director review
06/18/2008 Medical Policy Committee approval. No change to coverage eligibility.
06/04/2009 Medical Director review
06/17/2009 Medical Policy Committee approval. No change to coverage eligibility.
06/03/2010 Medical Policy Committee review
06/16/2010 Medical Policy Implementation Committee approval. No change to coverage eligibility.
12/31/2010 Coding updated.
06/02/2011 Medical Policy Committee review
06/15/2011 Medical Policy Implementation Committee approval. No change to coverage eligibility.
06/06/2012 Coding updated.
06/14/2012 Medical Policy Committee review
06/20/2012 Medical Policy Implementation Committee approval. No change to coverage eligibility. Added the word “neurologic” to the investigational statement.
06/06/2013 Medical Policy Committee review
07/10/2014 Medical Policy Committee review
07/16/2014 Medical Policy Implementation Committee approval. Coverage changed from investigational to eligible for coverage with criteria for transcranial magnetic stimulation of the brain for treatment-resistant depression. Continued treatment with transcranial magnetic stimulation of the brain as maintenance therapy and for all other psychiatric/neurologic disorders is investigational.
06/25/2015 Medical Policy Committee review
07/15/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/30/2016 Medical Policy Committee review
07/20/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis codes
09/07/2017 Medical Policy Committee review
09/20/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/02/2017 Medical Policy Committee review

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