

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

---

**Policy Number:**

MM.12.015

**Line(s) of Business:**

PPO; HMO; QUEST Integration

**Section:**

Other/Miscellaneous

**Place(s) of Service:**

Outpatient

**Original Effective Date:**

08/01/2014

**Current Effective Date:**

02/01/2018

### **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, resulting in electrical stimulation that affects neuronal function. Repetitive transcranial magnetic stimulation (rTMS) is being evaluated for the treatment of treatment-resistant depression (TRD) and a variety of other psychiatric or neurologic disorders.

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 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.

## II. Criteria/Guidelines

- A. TMS is covered (subject to Limitations and Administrative Guidelines) for use in adults with a confirmed diagnosis of severe treatment refractory major depressive disorder (MDD), when all of the following criteria are met:
  1. One or more of the following is met:
    - a. The patient is refractory to treatment as evidenced by a lack of a clinically significant response to a minimum of four distinct psychopharmacologic trials of therapy, each lasting at least eight weeks. The four trial must include both of the following:
      - i. 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.
      - ii. 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.
    - b. Inability to tolerate antidepressant medications as evidenced by four trials of such medications from at least two different classes, with distinct side effects.
    - c. History of refractoriness or intolerance to treatment as noted above and response to TMS in a previous depressive episode.
    - d. The patient has had ECT in the past, but cannot tolerate further treatment due to adverse effects.
  2. The patient has had a trial of evidence-based psychotherapy known to be effective in the treatment of MDD of an adequate frequency and duration without significant improvement in depressive symptoms.
  3. The patient has declined ECT.
  4. 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.
- B. Continuation of TMS beyond four weeks is covered when documentation, including results of evidence-based, validated depression monitoring scale, supports that the patient is responding to treatment.

### III. Limitations

- A. 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 acute or chronic psychotic symptoms or disorders (such as schizophrenia, schizophreniform or schizoaffective disorder) in the current depressive episode.
  3. Presence of an implanted magnetic-sensitive medical device located less than or equal to 30 centimeters from the TMS magnetic coil or other implanted metal items, including but not limited to a cochlear implant, implanted cardioverter defibrillator, pacemaker, vagus nerve stimulator, or metal aneurysm clips or coils, staples, or stents.
- B. TMS is not covered for all other psychiatric indications (e.g., bipolar disorder, anxiety disorders, mood disorders, schizophrenia) and neurologic indications as it is not known to be effective in improving health outcomes.
- C. TMS is not covered when used as maintenance therapy for MDD as it is not known to be effective in improving health outcomes.
- D. Treatments are limited to 30 treatments 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

- A. Precertification is required for the initial four weeks of treatment with rTMS. 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. 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.
  2. Documentation supporting trial and ineffectiveness of evidence-based psychotherapy.
  3. If applicable, documentation supporting that the patient was refractory to treatment and has had a response to rTMS during a previous depressive episode
  4. Documentation supporting that the patient has declined ECT
  5. Precertification is required for continuation of treatment beyond four weeks. Documentation from the medical record supporting that the patient is responding to treatment must be submitted.

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

## V. Scientific Background

### Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS), introduced in 1985 as a new method of noninvasive stimulation of the brain, involves placement of a small coil over the scalp, passing a rapidly alternating current through the coil wire, which produces a magnetic field that passes unimpeded through the scalp and bone, resulting in electrical stimulation of the cortex. TMS was initially used to investigate nerve conduction; 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 electroconvulsive therapy, TMS does not require general anesthesia and does not generally induce a convulsion.

### Repetitive TMS

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**

Device	Manufacturer	FDA Clearance No.	FDA Clearance Date
NeuroStar TMS	Neuronetics	DEN070003	2008
Brainsway™ H-Coil Deep TMS	Brainsway	K122288	2013
Rapid Therapy System	Magstim	K162935	2015
MagVita TMS Therapy System	Tonica Elektronik	K150641	2015
Neurosoft TMS	TeleEMG	K160309	2016

--	--	--	--

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 smaller size. The stimulation parameters are unchanged. The sTMS Mini (eNeura Therapeutics) received marketing clearance by the FDA in 2016. FDA product code: OKP.

## **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 April 25, 2017.

The following summary of the key literature to date focuses on systematic reviews of randomized controlled trials (RCTs). The evidence review on repetitive transcranial magnetic stimulation (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 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 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 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.

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  $\leq 7$  to  $\leq 10$  on the HAM-D). Meta-analysis showed a statistically significant improvement in depression scores compared with sham, with a weighted mean difference (WMD) of 2.31 (see Table 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 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**

Comparison	Favors	WMD (95% CI)	p	r Remission (95% CI)	p	for Response (95% CI)	p
rTMS vs sham	rTMS	2.3 (1.19 to 3.43)	<0.001	2.20 (1.44 to 3.38)	0.001	1.72 (1.13 to 2.62)	0.01
rTMS vs ECT	ECT	5.97 (0.94 to 11.0)	0.02	1.44 (0.64 to 3.23)	0.38	1.72 (0.95 to 3.11)	0.07

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

### 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 ( $d = -.54$ ). 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 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 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 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 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. 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 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 that 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 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, 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.

### **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."

#### **International Federation of Clinical Neurophysiology**

A group of European experts was commissioned to establish evidence-based guidelines on the therapeutic use of rTMS. Their 2014 guidelines included evidence published up until March 2014. For most indications, there was an absence of sufficient evidence, and the committee could provide no

recommendation. Indications that had a recommendation of a definite effect were neuropathic pain and depression. Indications that had a recommendation for a possible or probable effect included complex regional pain syndrome, Parkinson disease, motor stroke, hemispatial neglect, epilepsy, tinnitus, anxiety disorders, auditory hallucinations, a negative symptom of schizophrenia, as well as addiction and craving.

#### **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).

#### **Canadian Network for Mood and Anxiety Treatments**

The Canadian Network for Mood and Anxiety Treatments updated its clinical guidelines on neurostimulation therapies for the management of major depressive disorder in adults in 2009. The evidence reviewed supported ECT as a first-line treatment under specific circumstances; when used in patients who have failed to respond to one or more adequate antidepressant medication trials, ECT response rates have been estimated to be 50% to 60%. The guidelines considered rTMS to be a safe and well-tolerated treatment, with no evidence of cognitive impairment. Based on the 2008 meta-analysis by Lam et al, response (25%) and remission (17%) rates were found to be greater than sham but lower than for other interventions for treatment-resistant depression, leading to a recommendation for rTMS as a second-line treatment. The guidelines indicated that there was a major gap in the evidence base regarding maintenance rTMS, because only 1 open-label case series was identified.

#### **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](http://ClinicalTrials.gov) in May 2017 identified over 300 ongoing trials on rTMS.

## V. 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.

## VII. References

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcranial magnetic stimulation for depression. TEC Assessments. 2009;Volume 24:Tab 5.
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcranial magnetic stimulation for depression. TEC Assessments. 2011;Volume 26:Tab 3.
3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcranial magnetic stimulation for depression. TEC Assessments. 2013;Volume 28:Tab 9.
4. Gross M, Nakamura L, Pascual-Leone A, et al. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. *Acta Psychiatr Scand*. Sep 2007;116(3):165-173. PMID 17655557
5. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol Med*. Jan 2009;39(1):65-75. PMID 18447962
6. Gaynes B, Lux L, Lloyd S, et al. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Review No. 33 (AHRQ Publication No. 11-EHC056-EF). Rockville, MD: Agency for Healthcare Research and Quality; 2011.
7. Berlim MT, Van den Eynde F, Daskalakis ZJ. High-frequency repetitive transcranial magnetic stimulation accelerates and enhances the clinical response to antidepressants in major depression: a meta-analysis of randomized, double-blind, and sham-controlled trials. *J Clin Psychiatry*. Feb 2013;74(2):e122-129. PMID 23473357
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
9. Health Quality Ontario. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis of randomized controlled trials. *Ont Health Technol Assess Ser*. 2016;16(5):1-66. PMID 27099642
10. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. Dec 1 2007;62(11):1208-1216. PMID 17573044

11. Food and Drug Administration. 510(k) Summary: Brainsway deep TMS System. 2013; [http://www.accessdata.fda.gov/cdrh\\_docs/pdf12/k122288.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf12/k122288.pdf). Accessed May 19, 2017.
12. 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
13. Dunner DL, Aaronson ST, Sackeim HA, et al. A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1- year follow-up period. *J Clin Psychiatry*. Dec 2014;75(12):1394-1401. PMID 25271871
14. Richieri R, Guedj E, Michel P, et al. Maintenance transcranial magnetic stimulation reduces depression relapse: a propensity-adjusted analysis. *J Affect Disord*. Oct 2013;151(1):129-135. PMID 23790811
15. Connolly KR, Helmer A, Cristancho MA, et al. Effectiveness of transcranial magnetic stimulation in clinical practice post-FDA approval in the United States: results observed with the first 100 consecutive cases of depression at an academic medical center. *J Clin Psychiatry*. Apr 2012;73(4):e567-573. PMID 22579164
16. Janicak PG, Nahas Z, Lisanby SH, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. *Brain Stimul*. Oct 2010;3(4):187-199. PMID 20965447
17. Fang J, Zhou M, Yang M, et al. Repetitive transcranial magnetic stimulation for the treatment of amyotrophic lateral sclerosis or motor neuron disease. *Cochrane Database Syst Rev*. May 31 2013;5(5):CD008554. PMID 23728676
18. O'Connell NE, Wand BM, Marston L, et al. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev*. Apr 11 2014;4(4):CD008208. PMID 24729198
19. Chen R, Spencer DC, Weston J, et al. Transcranial magnetic stimulation for the treatment of epilepsy. *Cochrane Database Syst Rev*. Aug 11 2016(8):CD011025. PMID 27513825
20. Sun W, Mao W, Meng X, et al. Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy: a controlled clinical study. *Epilepsia*. Oct 2012;53(10):1782-1789. PMID 22950513
21. Saltychev M, Laimi K. Effectiveness of repetitive transcranial magnetic stimulation in patients with fibromyalgia: a meta-analysis. *Int J Rehabil Res*. Mar 2017;40(1):11-18. PMID 27977465
22. Food and Drug Administration. De Novo classification request for cerena transcranial magnetic stimulator (TMS) device. 2013; [http://www.accessdata.fda.gov/cdrh\\_docs/reviews/K130556.pdf](http://www.accessdata.fda.gov/cdrh_docs/reviews/K130556.pdf). Accessed May 19, 2017.
23. Berlim MT, Neufeld NH, Van den Eynde F. Repetitive transcranial magnetic stimulation (rTMS) for obsessive-compulsive disorder (OCD): an exploratory meta-analysis of randomized and sham-controlled trials. *J Psychiatr Res*. Aug 2013;47(8):999-1006. PMID 23615189
24. Trevizol AP, Shiozawa P, Cook IA, et al. Transcranial magnetic stimulation for obsessive-compulsive disorder: an updated systematic review and meta-analysis. *J ECT*. Dec 2016;32(4):262-266. PMID 27327557
25. Li H, Wang J, Li C, et al. Repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults. *Cochrane Database Syst Rev*. Sep 17 2014;9(9):CD009083. PMID 25230088
26. Mantovani A, Aly M, Dagan Y, et al. Randomized sham controlled trial of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for the treatment of panic disorder with comorbid major depression. *J Affect Disord*. Jan 10 2013;144(1-2):153-159. PMID 22858212

27. Chou YH, Hickey PT, Sundman M, et al. Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease: a systematic review and meta-analysis. *JAMA Neurol.* Apr 2015;72(4):432-440. PMID 25686212
28. Shirota Y, Ohtsu H, Hamada M, et al. Supplementary motor area stimulation for Parkinson disease: a randomized controlled study. *Neurology.* Apr 9 2013;80(15):1400-1405. PMID 23516319
29. Trevizol AP, Barros MD, Silva PO, et al. Transcranial magnetic stimulation for posttraumatic stress disorder: an updated systematic review and meta-analysis. *Trends Psychiatry Psychother.* Jan-Mar 2016;38(1):50-55. PMID 27074341
30. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcranial magnetic stimulation for the treatment of schizophrenia. *TEC Assessments.* 2011;Volume 26:Tab 6.
31. Dougall N, Maayan N, Soares-Weiser K, et al. Transcranial magnetic stimulation (TMS) for schizophrenia. *Cochrane Database Syst Rev.* Aug 20 2015;8(8):CD006081. PMID 26289586
32. Hao Z, Wang D, Zeng Y, et al. Repetitive transcranial magnetic stimulation for improving function after stroke. *Cochrane Database Syst Rev.* May 31 2013;5(5):CD008862. PMID 23728683
33. Le Q, Qu Y, Tao Y, et al. Effects of repetitive transcranial magnetic stimulation on hand function recovery and excitability of the motor cortex after stroke: a meta-analysis. *Am J Phys Med Rehabil.* May 2014;93(5):422-430. PMID 24429509
34. Li Y, Qu Y, Yuan M, et al. Low-frequency repetitive transcranial magnetic stimulation for patients with aphasia after stroke: A meta-analysis. *J Rehabil Med.* Sep 3 2015;47(8):675-681. PMID 26181486
35. Graef P, Dadalt ML, Rodrigues DA, et al. Transcranial magnetic stimulation combined with upper-limb training for improving function after stroke: A systematic review and meta-analysis. *J Neurol Sci.* Oct 15 2016;369:149-158. PMID 27653882
36. Jansen JM, Daams JG, Koeter MW, et al. Effects of non-invasive neurostimulation on craving: a meta-analysis. *Neurosci Biobehav Rev.* Dec 2013;37(10 Pt 2):2472-2480. PMID 23916527
37. American Psychiatric Association. Practice Guidelines for the treatment of patients with major depressive disorder. 2010; [http://psychiatryonline.org/pb/assets/raw/sitewide/practice\\_guidelines/guidelines/mdd.pdf](http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf). Accessed May 19, 2017.
38. American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. 2007; [http://psychiatryonline.org/pb/assets/raw/sitewide/practice\\_guidelines/guidelines/ocd.pdf](http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/ocd.pdf). Accessed May 19, 2017.
39. Lefaucheur JP, Andre-Obadia N, Antal A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol.* Nov 2014;125(11):2150-2206. PMID 25034472
40. Murphy TK, Lewin AB, Storch EA, et al. Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry.* Dec 2013;52(12):1341-1359. PMID 24290467
41. National Institute for Health and Care Excellence (NICE). Repetitive transcranial magnetic stimulation for depression [IPG-542]. 2015; <https://www.nice.org.uk/guidance/ipg542>. Accessed May 19, 2017.
42. National Institute for Health and Care Excellence (NICE). Transcranial magnetic stimulation for treating and preventing migraine [IPG477]. 2014; <https://www.nice.org.uk/guidance/ipg477>. Accessed May 19, 2017.
43. Miyasaki JM, Shannon K, Voon V, et al. Practice Parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* Apr 11 2006;66(7):996-1002. PMID 16606910

44. Kennedy SH, Milev R, Giacobbe P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. *J Affect Disord.* Oct 2009;117 Suppl 1:S44-53. PMID 19656575
45. Lam RW, Chan P, Wilkins-Ho M, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and metaanalysis. *Can J Psychiatry.* Sep 2008;53(9):621-631. PMID 18801225
46. Blue Cross Blue Shield. Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders. Policy # 2.01.50. July 2017.