

Medical Policy



An Independent Licensee of the
Blue Cross and Blue Shield Association

**Title: Transcranial Magnetic Stimulation (TMS) as a
Treatment of Depression and Other Psychiatric
Disorders**

See also: Vagus Nerve Stimulation
Treatment of Tinnitus

Professional

Original Effective Date: November 1, 2011

Revision Date(s): December 7, 2012;

May 7, 2013; October 15, 2014

Current Effective Date: October 15, 2014

Institutional

Original Effective Date: November 1, 2011

Revision Date(s): December 7, 2012;

May 7, 2013; October 15, 2014

Current Effective Date: October 15, 2014

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

Transcranial magnetic stimulation (TMS) is a noninvasive method of delivering electrical stimulation to the brain. A magnetic field is delivered through the skull where it induces electric currents that affect neuronal function. Repetitive TMS (rTMS) is being evaluated as a treatment of depression and other psychiatric/neurologic brain disorders.

Background

Transcranial magnetic stimulation (TMS) was first introduced in 1985 as a new method of noninvasive stimulation of the brain. The technique involves placement of a small coil over the scalp; passing a rapidly alternating current through the coil wire, which produces a magnetic field that passes unimpeded through the scalp and bone, resulting in electrical stimulation of the cortex. TMS was initially used to investigate nerve conduction; for example, TMS over the motor cortex will produce a contralateral muscular-evoked potential. The motor threshold, which is the minimum intensity of stimulation required to induce a motor response, is empirically determined for each individual by localizing the site on the scalp for optimal stimulation of a hand muscle, then gradually increasing the intensity of stimulation. The stimulation site for treatment is usually 5 cm anterior to the motor stimulation site.

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 showed 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 H1coil, are also being explored. In contrast to electroconvulsive therapy, TMS does not require anesthesia and does not induce a convulsion.

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

Regulatory Status

Devices for transcranial stimulation have received clearance by the U.S. Food and Drug Administration (FDA) for diagnostic uses. One device, NeoPulse (Neuronetics, Atlanta, GA), received approval in Canada, Israel, and the United States as a therapy for depression. Initially examined by the FDA under a traditional 510(k) application, the NeoPulse, now known as NeuroStar[®] TMS, received clearance for marketing as a "de novo" device in 2008. NeuroStar[®] TMS is indicated for the treatment of patients with depression who have failed one 6-week course of antidepressant medication.

The Brainsway[™] H-Coil Deep TMS device (Brainsway Ltd.) received FDA clearance in 2013. This device is indicated for the treatment of depression in patients who have failed to respond to antidepressant medications in their current episode of depression and is a

broader indication than that of the NeuroStar® TMS, which specifies the failure of 1 course of antidepressant medication (FDA product code: OBP).

Note: An FDA advisory panel met in January 2007 to determine if the risk-to-benefit profile for the NeoPulse was comparable to the risk-to-benefit profile of predicate electroconvulsive therapy (ECT) devices. The panel was not asked for a recommendation regarding the regulatory determination of substantial equivalence for this 510(k) submission. Materials presented at the Neurological Devices Panel meeting are posted online (www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4273b1_00-index.htm).

In 2013, the Cerena™ TMS device (Eneura Therapeutics) received de novo marketing clearance for the acute treatment of pain associated with migraine headache with aura. Warnings, precautions, and contraindications include the following:

- The device is only intended for use by patients experiencing the onset of pain associated with a migraine headache with aura.
- The device should not be used on headaches due to underlying pathology or trauma.
- The device should not be used for medication overuse headaches.
- The device has not been demonstrated as safe or effective when treating cluster headache or chronic migraine headache.
- The device has not been shown to be effective when treating during the aura phase.
- The device has not been demonstrated as effective in relieving the associated symptoms of migraine (photophobia, phonophobia, and nausea).
- Safety and effectiveness have not been established 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.

POLICY

A. Repetitive transcranial magnetic stimulation (rTMS) of the brain may be considered **medically necessary** as a treatment of major depressive disorder when all of the following conditions (1-3) have been met:

1. Confirmed diagnosis of severe major depressive disorder (single or recurrent) documented by standardized rating scales that reliably measure depressive symptoms;

AND

2. Any one of the following (a, b, c, or d):
 - a. Failure of 4 trials of psychopharmacologic agents including 2 different agent classes and 2 augmentation trials;

OR

- b. Inability to tolerate a therapeutic dose of medications as evidenced by 4 trials of psychopharmacologic agents with distinct side effects;

OR

- c. History of response to rTMS in a previous depressive episode (at least 3 months since the prior episode);

OR

- d. Is a candidate for electroconvulsive therapy (ECT) and ECT would not be clinically superior to rTMS (e.g., in cases with psychosis, acute suicidal risk, catatonia or life-threatening inanition rTMS should NOT be utilized);

AND

- 3. Failure of a trial of a psychotherapy known to be effective in the treatment of major depressive disorder of an adequate frequency and duration, without significant improvement in depressive symptoms, as documented by standardized rating scales that reliably measure depressive symptoms.

B. rTMS for major depressive disorder that does not meet the criteria listed above is considered **experimental / investigational**.

C. Continued treatment with rTMS of the brain as maintenance therapy is considered **experimental / investigational**.

Policy Guidelines

- 1. Repetitive transcranial magnetic stimulation should be performed using an FDA-cleared device in appropriately selected patients, by physicians who are adequately trained and experienced in the specific techniques used. A treatment course should not exceed 5 days a week for 6 weeks (total of 30 sessions), followed by a 3-week taper of 3 TMS treatments in week 1, 2 TMS treatments the next week, and 1 TMS treatment in the last week.
- 2. Contraindications to rTMS include:
 - a. Seizure disorder or any history of seizure with increased risk of future seizure;
OR
 - b. Presence of acute or chronic psychotic symptoms or disorders (such as schizophrenia, schizophreniform or schizoaffective disorder) in the current depressive episode;
OR
 - c. Neurologic conditions that include epilepsy, cerebrovascular disease, dementia, increased intracranial pressure, having a history of repetitive or severe head trauma, or with primary or secondary tumors in the central nervous system (CNS);
OR
 - d. Presence of an implanted magnetic-sensitive medical device located 30 centimeters or less from the TMS magnetic coil or other implanted metal items,

- including but not limited to a cochlear implant, implanted cardioverter defibrillator (ICD), pacemaker, vagus nerve stimulator, or metal aneurysm clips or coils, staples, or stents.
3. The following should be present for the administration of rTMS:
 - a. An attendant trained in basic cardiac life support and the management of complications such as seizures, as well as the use of the equipment must be present at all times;
AND
 - b. Adequate resuscitation equipment including, for example, suction and oxygen;
AND
 - c. The facility must maintain awareness of response times of emergency services (either fire/ambulance or "code team"), which should be available within five minutes. These relationships are reviewed on at least a one year basis and include mock drills.

RATIONALE

This policy was created in 2001 and updated periodically with searches of the MEDLINE database. At the time this policy was created, the U.S. Food and Drug Administration (FDA) had not cleared transcranial magnetic stimulation (TMS) as a therapeutic device for any neuropsychiatric disorder, including depression. In October 2008, the NeuroStar® TMS received U.S. Food and Drug Administration (FDA) marketing clearance as a de novo device for therapy of patients with treatment-resistant depression (TRD) who have failed one 6-week course of antidepressant medication.

The Blue Cross and Blue Shield Technology Evaluation Center (TEC) published assessments of repetitive TMS (rTMS) for depression in 2009, 2011, and 2013.(1-3) These TEC Assessments concluded that the available evidence does not permit conclusions regarding the effect of TMS on health outcomes. Limitations of the evidence include:

- Equivocal efficacy in the 3 largest sham-controlled trial of TMS,
- Uncertain clinical significance of the short-term anti-depressant effects found in meta-analyses, which are also at high risk of bias due to the inclusion of numerous small trials and potential for publication bias,
- Limited evidence beyond the acute period of treatment, and
- Lack of comparison with standard therapy (a second course of antidepressant therapy) in the population for whom TMS is indicated (patients who have failed one 6-week course of antidepressant medication).

In 2011, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review on nonpharmacologic interventions for TRD in adults.(4) Findings for the key questions (KQ) of the review follow.

Efficacy of Nonpharmacologic Interventions Against Other Nonpharmacologic Interventions (KQ 1a)

Direct Evidence: The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions for Tier 1 TRD was limited to 2 fair trials (both in major depressive disorder-only populations). One compared electroconvulsive therapy (ECT) and rTMS, and the other compared ECT and ECT plus rTMS. They showed, with low strength of evidence,

no differences between treatment options for depressive severity, response rates, and remission rates. No trial involved a direct comparison of psychotherapy with another nonpharmacologic intervention.

Indirect Evidence: They identified trials that compared a nonpharmacologic intervention, generally rTMS, vagus nerve stimulation (VNS), or psychotherapy, with a control or sham procedure in Tier 1 populations (ie, patients had 2 or more prior treatment failures with medications). The number of these trials with the same or similar control group was very small, so they could not pool them quantitatively. They assessed the potential benefits of nonpharmacologic interventions versus controls by calculating mean changes in depressive severity, relative risks of response, and relative risks of remission.

rTMS was beneficial relative to controls receiving a sham procedure for all 3 outcomes (severity of depressive symptoms, response rate, remission rate). rTMS produced a greater decrease in depressive severity (high strength of evidence). Specifically, rTMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than 5 points relative to sham control, and this change meets the minimum threshold of the 3-point HAM-D difference that is considered clinically meaningful. Response rates were greater with rTMS than sham (also high strength of evidence); those receiving rTMS were more than 3 times as likely to achieve a depressive response as patients receiving a sham procedure. Finally, rTMS was also more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving rTMS were more than 6 times as likely to achieve remission as those receiving the sham.

Efficacy of Nonpharmacologic Interventions Compared With Antidepressant Pharmacotherapies (KQ 1b)

Direct Evidence: No direct evidence was identified for rTMS.

Maintenance of Remission or Prevention of Relapse (KQ 2)

Direct Evidence: With respect to maintaining remission (or preventing relapse), there were no direct comparisons involving ECT, rTMS, VNS, or CBT.

Indirect Evidence: Three fair trials compared rTMS with a sham procedure and found no significant differences. However, too few patients were followed during the relapse prevention phases in 2 of the three studies, and patients in the third received a cointervention providing insufficient evidence for a conclusion.

AHRQ Authors' Conclusions: The evidence review suggests that comparative clinical research on nonpharmacologic interventions in a TRD population is early in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data is substantially hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence is for ECT and rTMS. However, even for the few comparisons of treatments that are supported by some evidence, the strength of evidence is low for benefits, reflecting low confidence that the evidence reflects the true effect and indicating that further research is likely to change our confidence in these findings. This finding of low strength is most notable in 2 cases: ECT and rTMS did not produce different clinical outcomes in TRD, and ECT produced better outcomes than pharmacotherapy. No trials directly compared the likelihood of maintaining remission for nonpharmacologic interventions. The few trials addressing adverse events, subpopulations, subtypes, and health-related outcomes provided low or insufficient

evidence of differences between nonpharmacologic interventions. The most urgent next steps for research are to apply a consistent definition of TRD, to conduct more head-to-head clinical trials comparing nonpharmacologic interventions with themselves and with pharmacologic treatments, and to delineate carefully the number of treatment failures following a treatment attempt of adequate dose and duration in the current episode.

Following is a summary of the key literature to date, focusing on randomized controlled trials (RCTs). The evidence review is divided by indication and by key differences in treatment protocols, specifically high-frequency left dorsolateral prefrontal cortex (DLPFC) stimulation, low-frequency (1-2 Hz) stimulation of the right DLPFC, combined high-frequency and low-frequency stimulation, and deep brain stimulation.

Depression

Studies published prior to 2008 are included if the study design was a randomized sham-controlled double-blind trial that enrolled at least 40 subjects; refer to the 2008 meta-analysis by Schutter for a summary of study characteristics and stimulation parameters used in these trials.⁽⁵⁾ Note that over the last decade, there has been a trend to increase the intensity, trains of pulses, total pulses per session, and number of sessions.⁽⁶⁾ Unless otherwise indicated in the trials described next, stimulation was set at 100% to 120% of motor threshold, clinical response was defined as an improvement of 50% or more on the HAM-D, and remission was considered to be a score of 7 or less on the HAM-D.

High-Frequency rTMS of the Left DLPFC for TRD

Lam et al conducted a meta-analysis of 24 RCTs comparing active versus sham rTMS in patients with TRD, although there were varying definitions of TRD.⁽⁷⁾ This analysis calculated a number needed to treat of 6, with a clinical response in 25% of active rTMS and 9% of sham rTMS patients. Remission was reported for 17% of active rTMS and 6% of sham rTMS patients.

The largest study (23 study sites) included in the meta-analysis was a double-blind multicenter trial with 325 TRD patients randomly assigned to daily sessions of high-frequency active or sham rTMS (Monday to Friday for 6 weeks) of the DLPFC.⁽⁸⁾ 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 study population failing to benefit from at least 2 treatments. Loss to follow-up was similar in the 2 groups, with 301 (92.6%) patients completing at least 1 postbaseline assessment and an additional 8% of patients from both groups dropping out before the 4-week assessment. Intention-to-treat (ITT) analysis showed a trend favoring the active rTMS group in the primary outcome measure (2 points on the Montgomery-Asberg Depression Rating Scale [MADRS]; $p=0.057$) and a modest (2-point) but significant improvement over sham treatment on the HAM-D. The authors reported that after 6 weeks of treatment, subjects in the active rTMS group were more likely to have achieved remission than the sham controls (14% vs 5%, respectively), although this finding is limited by loss to follow-up.

In 2010, George et al reported a randomized sham-controlled trial that involved 199 patients treated with left-prefrontal rTMS.⁽⁹⁾ This was a multicenter study involving patients with a moderate level of treatment resistance. The response rate using an ITT analysis was 14% for rTMS and 5% for sham ($p=0.02$). In this study, the site for stimulation was determined through pretreatment magnetic resonance imaging (MRI). Results from phase 2 (open treatment of nonresponders) and phase 3 (maintenance and follow-up) will be reported in the future.

Another randomized sham-controlled double-blind trial was conducted in 68 patients who had failed at least 2 courses of antidepressants.⁽¹⁰⁾ Three patients in each group did not complete the 15 treatment sessions or were excluded due to a change in medication during treatment, resulting in 91% follow-up. Independent raters found a clinical response in 31% (11 of 35) of the active rTMS patients and 6% (2 of 33) of the sham group. The average change in HAM-D was 7.8 for the active group and 3.7 for the control group. The Beck Depression Inventory (BDI) decreased by 11.3 points in the active rTMS group and 4.8 points in controls. Remission was observed in 7 patients (20%) in the active rTMS group and 1 patient (3%) in the control group. Regarding effectiveness of blinding; 15% of subjects in each group guessed they were receiving active TMS after the first session. After the 15th session, 58% of the rTMS group and 43% of the sham group guessed they had received active TMS; responders were more likely than nonresponders (85% vs 42%, respectively) to think that they had received the active treatment. The 11 responders were treated with antidepressant medication and followed up for 6 months. Of these, 1 was lost to follow-up, 5 (45%) relapsed, and 5 (45%) did not relapse.

Rossini et al randomly assigned 54 patients who had failed at least 2 adequate courses of antidepressants to sham control or active rTMS at 80% or 100% of motor threshold (MT) for 10 sessions over a 2-week period.⁽¹¹⁾ Double-blind evaluation found an intensity-dependent response with 6% (1/16) of the sham, 28% (5/18) of the 80% MT, and 61% (11/18) of the 100% MT groups showing improvement of 50% or more over a 5-week evaluation. All of the patients reported that they were unaware of the differences between sham and active stimulation.

In a 2008 report, Mogg et al randomly assigned 59 patients with major depression who had failed at least 1 course of pharmacotherapy for the index depressive episode.⁽¹²⁾ In this study population, 78% of the patients had failed 2 treatment courses and 53% had failed 3. The sham coil, which was provided by Magstim, was visually identical to the real coil and made the same clicking sound but did not deliver a magnetic field to scalp or cortex. Blinded assessments were performed 2 days after the fifth and final (tenth) sessions (97% follow-up), with additional assessments at 6 weeks (90% follow-up) and 4 months (83% follow-up). The mean group difference was estimated to be 0.3 points in HAM-D scores for the overall analysis. Interpretation of this finding is limited, because 7 sham patients (23%) were given a course of real rTMS after the 6-week assessment and analyzed as part of the sham group in the ITT analysis. The study was powered to detect a difference of 3.5 points in the HAM-D between the active and sham groups, and the 2.9-point group difference observed at the end of treatment was not significant. A higher percentage of patients in the active rTMS group achieved remission criteria of 8 points or less on the HAM-D (25% vs 10% control, respectively), and there was a trend for more patients to achieve clinical response in the active rTMS group (32% vs 10%, respectively, $p=0.06$). All of the 12 patients who met the criterion for clinical response (9 active, 3 sham) thought that they had received real rTMS, with more patients in the active group (70%) than the sham group (38%) guessing that they had received the real treatment. Interpretation of this finding is also limited, because the reason the subjects guessed that they had active treatment was not reported, and the subjects were not asked to guess before they began to show a clinical response.

A small double-blind randomized trial from 2009 suggests that specific targeting of Brodmann areas 9 and 46 may enhance the antidepressant response compared with the standard targeting procedure, ie, measuring 5 cm anterior from the motor cortex.⁽¹³⁾ Fifty-one patients who had failed at least two 6-week courses of antidepressant medication (average, 5.7 failed courses)

were randomly assigned to a standard localization procedure or to structural MRI-aided localization for 3 weeks (with 1-week extension if >25% reduction on the MADRS). Six patients in the targeted group and 10 in the standard group withdrew due to lack of response. A single patient in the targeted group and 5 in the standard group withdrew for other reasons, resulting in 17 patients in the targeted group and 12 in the standard group continuing for the full 4 weeks of treatment. To adjust for the imbalance in discontinuation rates, a mixed model statistical analysis was used. There was a significant difference between the groups in the overall mixed model analysis, and planned comparisons showed significant improvement in MADRS scores for the targeted group at 4 weeks. Response criteria were met by 42% of the targeted group and 18% of the standard group. Remission criteria were met by 30% of the targeted group and 11% of the standard group. Although encouraging, additional trials with a larger number of subjects are needed to evaluate this procedure.

Several studies have compared the outcomes of rTMS with those from ECT. In 1 study, 40 patients with nonpsychotic major depression were treated over the course of 1 month (20 total sessions) and evaluated with the HAM-D, in which a response was defined as a 50% decrease with a final score of 10 or less.(14) There was no difference in response rate between the 2 groups; 12 of 20 responded in the ECT group compared with 11 of 20 in the magnetic stimulation group. A United Kingdom National Institute for Health Research health technology assessment compared efficacy and cost effectiveness of rTMS and ECT.(15) Forty-six patients who had been referred for ECT were randomly assigned to either ECT (average, 6.3 sessions) or a 15-day course (5 treatments per week) of rTMS of the left DLPFC. ECT resulted in a 14-point improvement in the HAM-D and a 59% remission rate. Repetitive TMS was less effective than ECT (5-point improvement in HAM-D and a 17% remission rate). Another study reported no significant difference between ECT and rTMS in 42 patients with TRD; however, response rates for both groups were low.(16) The number of remissions (score ≤ 7 on HAM-D) totaled 3 (20%) for ECT and 2 (10%) for rTMS.

Deep TMS of the Left DLPFC for TRD

The RCT leading to 510(k) clearance of the Brainsway deep TMS system was conducted at 20 centers in the U.S. (n=13), Israel (n=4), Germany (n=2), and Canada (n=1).(17) The study 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. Per protocol analysis, which excluded 31 patients who did not receive adequate TMS treatment and 17 patients who did not meet the inclusion/exclusion criteria, showed a significant benefit for both response rate (38.4% vs 21.4%) and remission rate (32.6% vs 14.6%). Modified ITT analysis, which excluded the 17 patients who did not meet the inclusion/exclusion 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 by deep TMS. Remission rates were not reported. ITT analysis found no significant benefit of treatment at 4 or 16 weeks.

Low-Frequency rTMS of the Right DLPFC or Bilateral Stimulation for TRD

Fitzgerald et al randomly assigned 60 patients who had failed a minimum of at least two 6-week courses of antidepressant medications into 1 of 3 groups; high-frequency left rTMS, low-frequency right rTMS, or sham stimulation over 10 sessions.(18) All patients who entered the study completed the double-blind randomized phase, which showed no difference between the 2 active treatments (left, 13.5% reduction; right, 15% reduction) and greater improvements in the MADRS scores compared with the sham group (0.76% reduction). Only 1 patient achieved 50%

improvement during the initial 2 weeks. Then, only the subjects who showed at least 20% improvement at the end of the 10 sessions (15 active, 2 sham) continued treatment. Patients who did not respond by at least 20% were switched to a different active treatment. From week 2 to week 4, there was greater improvement in the low-frequency right rTMS group compared with the high-frequency left rTMS group (39% vs 14% improvement in MADRS, respectively). Seven patients (18% of 40) showed a clinical response of greater than 50% by the end of the 4 weeks.

In a subsequent study, Fitzgerald et al randomly assigned 50 patients with TRD to sequential bilateral active or sham rTMS. (19) After 2 weeks of treatment, 3 subjects had dropped out of the sham treatment group, and there was a slight but nonsignificant improvement favoring the active group for the MADRS (26.2 vs 30.9, respectively) and the BDI (18.3 vs 21.6, respectively). At this time point, 60% of subjects receiving active rTMS and 50% of subjects receiving sham treatment guessed that they were in the active group. The clinical response was reported by subjects as the major reason for their guess, with 11 of 13 responders (9 active, 2 sham) guessing that they were in the active group. As in the earlier study, only the subjects who showed at least 20% improvement at the end of each week continued treatment. Treatment on week 3 was continued for 15 subjects in the active group and 7 subjects in the sham group. By week 6, 11 subjects in the active rTMS remained in the study, with no control subjects remaining. Final ratings for the 11 subjects who continued to respond through week 6 were 8.9 on the MADRS and 9.2 on the BDI.

Another multicenter double-blind trial randomly assigned 130 patients with TRD to 5 sessions per week of either 1- or 2-Hz rTMS over the right DLPFC.(20) Sixty-eight patients (52%) completed 4 weeks of treatment; there was an approximate 30% improvement in depression scales, with no differences between the 1- or 2-Hz groups. Due to the potential for placebo effects for this type of intervention, the absence of a sham control group limits interpretation.

A small randomized sham-controlled trial was published in 2010 that involved either right or left rTMS in 48 patients with TRD.(21) Overall reductions in the HAM-D-24 from baseline to 3 months were not significantly different between rTMS and sham treatment groups. In this small study, right cranial stimulation was significantly more effective than left cranial stimulation (sham or rTMS).

rTMS as an Adjunctive Treatment for Moderate to Severe Depression

Schutter conducted a meta-analysis of 30 double-blind randomized sham-controlled trials (1164 patients) of high-frequency rTMS over the left DLPFC in patients with major depression.(5) The pooled weighted mean effect size for treatment was calculated with Hedges g, a standardized mean difference that adjusts for sampling variance, to be 0.39 (95% confidence interval, 0.25 to 0.54), which is considered moderate. For 27% of the population, rTMS was used as a primary/adjunctive treatment; 3 trials were included that used rTMS as a primary/adjunctive treatment for depression and enrolled more than 40 subjects.(22-24) rTMS has also been examined in patients with clinical evidence of cerebrovascular disease and late-life depression.(25)

A 2012 study examined the efficacy of ultra-high-frequency (30 Hz) rTMS over the left prefrontal cortex in moderate to severely depressed patients who were taking medication.(26) Sham treatment consisted of low-frequency stimulation to the left prefrontal cortex. No benefit of rTMS for depressive symptoms was found when lithium was added as a covariate. Ultra-high-frequency rTMS was found to improve performance on the Trail-Making Test, which covaried with

improvement of psychomotor retardation. Additional research on whether adjunctive rTMS can improve response to pharmacologic treatment as a first-line therapy is needed.

Maintenance Therapy

Demirtas-Tatlidede et al reported durability of the antidepressant response to rTMS and efficacy of retreatment for relapses in a prospective series of 16 patients.(27) Patients who initially had clinically significant antidepressant responses to rTMS were enrolled in the study and followed for 4 years. During this period, there were 64 episodes of relapse. Relapses were treated with a 10-day course of rTMS, with an average of 4 treatment courses per patient (range, 2-10) and a mean treatment interval of 4.9 months (range, 1.5-24.0). About half of patients had a clinically significant response to repeated courses of rTMS and continued in the study. These patients had a medication-free interval of 33 months (range, 26-43 months) and a mean response on the HAM-D of 64.8%. Other subjects terminated the study due to nonresponse after the second (n=3), third (n=1), fourth (n=2), or fifth (n=1) treatment course.

A variety of maintenance schedules are being studied. Richieri et al used propensity-adjusted analysis of observational data and found that the group of patients who had maintenance rTMS tapered over 20 weeks (from 3 times per week to once a month) had a significantly reduced relapse rate compared with patients who had no additional treatment (37.8% vs 81.8%).(28) Connolly et al reported that in the first 100 cases treated at their institution the response rate was 50.6% and the remission rate was 24.7%.(29) At 6 months after the initial rTMS treatment, 26 of 42 patients (62%) who received tapered maintenance therapy (from 2 sessions per week for the first 3 weeks to monthly) maintained their response. In another study, patients who met criteria for partial response during either a sham-controlled or open-label phase of a prior study were tapered from rTMS and simultaneously started on maintenance antidepressant monotherapy.(30) 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.

Fitzgerald et al reported a prospective open-label trial of clustered maintenance rTMS for patients with refractory depression.(31) All patients had received a second successful course of rTMS following relapse and were then treated with monthly maintenance therapy consisting of 5 rTMS treatments over a 2.5-day period (Friday evening, Saturday, and Sunday). Of 35 patients, 25 (71%) relapsed at a mean of 10.2 months (range, 2-48 months).

Additional data are needed related to durability of effect and to maintenance therapy.

Alzheimer's Disease

Ahmed et al randomized 45 patients with probable Alzheimer's disease to 5 sessions of bilateral high-frequency rTMS, bilateral low-frequency rTMS, or sham TMS over the DLPFC.(32) Thirty-two patients had mild to moderate dementia and 13 had severe dementia. There were no significant differences between groups at baseline. Measures of cortical excitability immediately after the last treatment session showed that treatment with high-frequency rTMS reduced the duration of transcallosal inhibition. At 3 months after treatment, the high-frequency rTMS group improved significantly more than the other 2 groups in standard rating scales, and subgroup analysis showed that this was due primarily to improvements in patients with mild/moderate dementia. Patients in the subgroup of mild to moderate dementia who were treated with high-frequency rTMS improved from 18.4 to 22.6 on the Mini Mental State Examination, from 20.1 to 24.7 on the Instrumental Daily Living Activity scale, and from 5.9 to 2.6 on the Geriatric Depression Scale.

Rabey et al reported an industry-sponsored randomized double-blind trial of rTMS with cognitive training (NeuroAD system) in 15 patients with probable mild to moderate Alzheimer's disease.⁽³³⁾ Patients received 5 sessions per week for 6 weeks over 6 different brain areas, followed by biweekly sessions for 3 months. Specific cognitive tasks were designed for the 6 targeted brain regions. These included syntax and grammar for Broca area, comprehension and categorization for Wernicke area, action naming, object naming and spatial memory tasks for the right and left DLPFC, and spatial attention tasks for the right and left somatosensory association cortex. After 6 weeks of treatment, there was an improvement in the average Alzheimer's Disease Assessment Scale, cognitive subsection (ADAS-cog) score of 3.76 points in the rTMS group compared with 0.47 in the placebo group. After 4.5 months of treatment, the ADAS-cog score in the rTMS group had improved by 3.52 points compared with a worsening of 0.38 in the placebo group. The Clinical Global Impression of Change improved significantly by an average of 3.57 after 6 weeks and 3.67 after 4.5 months compared with 4.25 and 4.29, respectively, in the placebo group.

Attention-Deficit/Hyperactivity Disorder

In 2012, Weaver et al reported a randomized sham-controlled crossover study of rTMS in 9 adolescents/young adults with attention deficit/hyperactivity disorder (ADHD).⁽³⁴⁾ rTMS was administered in 10 sessions over 2 weeks, with 1 week of no TMS between the active and sham phases. The clinical global impression and ADHD-IV scales improved in both conditions over the course of the study, with no significant differences between the active and sham phases.

Bulimia Nervosa

In 2008, Walpoth et al reported no evidence of efficacy of rTMS in a small trial (n=14) of patients with bulimia nervosa.⁽³⁵⁾

Dysphagia

rTMS for the treatment of dysphagia following stroke has been examined in small RCTs. One study randomized 26 patients to rTMS or sham over the affected esophageal motor area of the cortex.⁽³⁶⁾ Ten minutes of rTMS over 5 days reduced both dysphagia on the Dysphagic Outcome and Severity scale and disability measured by the Barthel Index. There was a trend for improved hand grip strength in the rTMS group. Blinded assessment showed that the effects were maintained at 1-month and 2-month follow-up. Another study randomized 30 patients with dysphagia following stroke or traumatic brain injury to high-frequency rTMS, low-frequency rTMS, or sham stimulation.⁽³⁷⁾ Active or sham rTMS was administered bilaterally over the anterolateral scalp over a period of 2 weeks. Swallowing scale scores improved in both the low-frequency and sham groups. Improvement in videofluoroscopic evaluation was greater in the low-frequency rTMS group than the other 2 groups. Blinding of evaluators was not described.

Study in a larger number of subjects is needed to determine the efficacy of this treatment with greater certainty.

Epilepsy

In 2012, Sun et al reported a randomized double-blind controlled trial of low-frequency rTMS to the epileptogenic zone for refractory partial epilepsy.⁽³⁸⁾ Sixty patients were randomized into 2 groups; one group received 2 weeks of rTMS at 90% of resting motor threshold, and the other group received rTMS at 20% of resting motor threshold. Outcomes were measured for 8 weeks after the end of treatment. With intent-to-treat analysis, high-intensity rTMS resulted in a significant decrease in seizures when compared with baseline (from 8.9 per week at baseline to 1.8 per week at follow-up) and when compared with low-intensity rTMS (from 8.6 at baseline to

8.4 per week at follow-up). High-intensity rTMS also decreased interictal discharges (from 75.1 to 33.6 per hour) and improved ratings on the Symptom Checklist–90. These initial results are promising, but require substantiation in additional trials.

Fibromyalgia

A 2012 systematic review included 4 studies on transcranial direct current stimulation and 5 on rTMS for treatment of fibromyalgia pain.(39) Three of the 5 trials were considered to be high quality. Four of the 5 were double-blind RCTs; the fifth included study was a case series of 4 patients who were blinded to treatment. Quantitative meta-analysis was not conducted due to variability in brain site, stimulation frequency/intensity, total number of sessions, and follow-up intervals, but 4 of the 5 studies on rTMS reported significant decreases in pain. Greater durability of pain reduction was observed with stimulation of the primary motor cortex compared with the DLPFC.

One of the studies included in the systematic review was a small 2011 trial that was conducted in the U.S. by Short et al.(40) Twenty patients with fibromyalgia, defined by the American College of Rheumatology criteria, were randomized to 10 sessions of left prefrontal rTMS or sham TMS along with their standard medications. At 2 weeks after treatment, there was a significant change from baseline in average visual analog scale (VAS) for pain in the rTMS group (from 5.60 to 4.41) but not in the sham-treated group (from 5.34 to 5.37). There was also a significant improvement in depression symptoms in the active group compared with baseline (from 21.8 to 14.10) but not in the sham group (from 17.6 to 16.4). There were no statistically significant differences between the groups in this small trial.

A 2013 report evaluated the effect of very low-intensity rTMS in a randomized sham-controlled double-blinded trial of 54 patients with fibromyalgia.(41) Six weeks of rTMS (once per week) with 33 magnetic coils around the head resulted in a significant improvement in pain thresholds (+28%) across the 8 sessions and in the ability to perform daily activities (11%), perceived chronic pain (-39%) and sleep quality (75%) beginning at week 6. Fatigue, anxiety, depression, and severity of headaches were unaffected by treatment.

Additional study is needed to determine effective treatment parameters in a larger number of subjects and to evaluate durability of the effect.

Migraine Headache

A pivotal randomized, double-blind, multicenter, sham-controlled trial was performed with the Cerena™ TMS device to demonstrate safety and effectiveness for the de novo application.(42) Enrolled in the study 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 baseline phase to establish the frequency and severity of 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, 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™ and 16.67% for sham, $p=0.018$) and for the

proportion of subjects who were pain free after 24 hours (33.96% for Cerena™ and 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 noninferior to sham for the proportion of subjects free of nausea and phonophobia.

These results are limited by the 46% drop-out 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 when treating migraine headache during the aura phase. The device has not been demonstrated as effective in relieving the associated symptoms of migraine (photophobia, phonophobia, nausea).(42)

Obsessive-Compulsive Disorder

A 2013 meta-analysis included 10 small RCTs totaling 282 patients with obsessive-compulsive disorder.(43) Response rates of rTMS augmentation therapy were 35% for active and 13% for sham rTMS. The pooled odds ratio was 3.39, and the number needed to treat was 5. There was no evidence of publication bias. Exploratory subgroup analysis suggested that the 2 most promising stimulation parameters were low-frequency rTMS and non-DLPFC regions (ie, orbitofrontal cortex or supplementary motor area). Further study focusing on these stimulation parameters is needed.

Panic Disorder

In 2013, Mantovani et al reported a randomized, double-blind, sham-controlled trial of low-frequency rTMS to the right DLPFC in 21 patients with panic disorder with comorbid major depression.(44) Response was defined as a 40% or greater decrease on the Panic Disorder Severity Scale and a 50% or greater decrease on HAM-D. After 4 weeks of treatment, the response rate for panic was 50% with active rTMS and 8% with sham. There was no significant difference in the response rate for depressive symptoms (25% active rTMS vs 8% for sham). After an additional 4 weeks of open-label treatment, the response rate was 67% for panic and 50% for depressive symptoms. Five of 12 responders returned for 6-month follow-up and showed sustained improvement.

Parkinson Disease

A systematic review from 2009 included 10 RCTs with a total of 275 patients with Parkinson disease.(45) Seven of the studies were double-blind, 1 was not blinded, and 2 of the studies did not specify whether the raters were blinded. In studies that used high-frequency rTMS there was a significant improvement on the Unified Parkinson's Disease Rating Scale (UPDRS) with a moderate effect size of -0.58. For low-frequency rTMS, the results were heterogeneous and did not significantly reduce the UPDRS. The analyzed studies varied in outcomes reported, rTMS protocol, patient selection criteria, demographics, stages of Parkinson disease and duration of follow-up, which ranged from immediate to 16 weeks after treatment

In 2012, Benninger et al. reported a randomized double-blind sham-controlled trial of brief (6 sec) very-high-frequency (50 Hz) rTMS over the motor cortex in 26 patients with mild to moderate Parkinson disease.(46) Eight sessions of 50-Hz rTMS did not improve gait, bradykinesia, or global and motor scores on the UPDRS compared with the sham-treated group. Activities of daily living were significantly improved a day after the intervention, but the effect was no longer evident at 1 month after treatment. Functional status and self-reported well-being were not affected by the treatment. No adverse effects of the very high-frequency stimulation were identified.

Another study from 2012 randomized 20 patients with Parkinson disease to 12 brief sessions (6 minutes) of high-frequency (5-Hz) rTMS or sham rTMS over the leg area of the motor cortex followed by treadmill training.(47) Blinded evaluation showed a significant effect of rTMS combined with treadmill training on neurophysiologic measures, and change in fast walking speed and the timed up and go task. Mean treadmill speed improved to a similar extent in the active and sham rTMS groups.

A 2013 exploratory multicenter double-blind trial randomized 106 patients to 8 weeks of 1-Hz rTMS, 10 Hz rTMS, or sham stimulation over the supplementary motor area.(48) At 9 weeks, all groups showed a similar amount of improvement. At the 20-week follow-up, only the 1 Hz group showed a significant improvement (6.84 points) in the primary outcome measure, the UPDRS part III. There was no significant improvement in other outcome measures.

Additional study with a larger number of subjects and longer follow-up is needed to determine if rTMS improves motor symptoms in patients with Parkinson disease.

Postpartum Depression

Myczkowski et al conducted a double-blind, sham-controlled study of 14 patients with postpartum depression randomized to 20 sessions of active or sham rTMS over the left DLPFC.(49) A positive response to treatment was defined as a reduction of at least 30% in the HAM-D and Edinburgh Postnatal Depression Scale (EPDS). At 2 weeks after the end of treatment, the active rTMS group showed significant improvements in the HAM-D, Global Assessment Scale, Clinical Global Impression and Social Adjustment Scale. The difference in the EPDS (reduction of 39.4% vs 6.2% for sham) did not reach statistical significance in this small study, and there were marginal cognitive and social improvements. In addition, results were presented as mean values, rather than by the proportion of patients who showed clinically meaningful improvement.

Posttraumatic Stress Disorder

The efficacy of rTMS for posttraumatic stress disorder (PTSD) has been examined in several small RCTs.

A 2004 study randomized 24 patients with PTSD to 10 sessions of low-frequency (1-Hz), high-frequency (10-Hz), or sham rTMS over the right DLPFC.(50) Blinded assessment 2 weeks after the intervention found that high-frequency rTMS improved the self-reported PTSD checklist (PCL) by 29.3%, the clinician evaluation on the Treatment Outcome PTSD scale by 39.0%, the HAM-D by 25.9%, and the Hamilton Anxiety Rating Scale by 44.1%. Scores for the sham and low-frequency group were not significantly improved.

In 2012, Watts et al reported a double-blind trial with 20 patients randomized to low-frequency rTMS or sham over the right DLPFC.(51) Blinded evaluation at the end of treatment showed clinically significant improvements in the Clinician Administered PTSD Scale (CAPS) and the PCL compared with sham. Depressive and anxiety symptoms also improved in the rTMS group. Six of the 10 rTMS patients showed a degradation of symptoms between the immediate post-treatment assessment and the 2-month post-treatment follow-up.

In another double-blind trial, 30 patients with PTSD were randomized to deep, high-frequency rTMS after brief exposure to a script of the traumatic event, rTMS after a script of a nontraumatic event, or sham stimulation after a brief script of the traumatic event.(52) Patients received 3

treatment sessions per week for 4 weeks, and response was defined as a 50% or greater improvement in CAPS score. Intent-to-treat analysis showed a significant improvement in the total CAPS score in the exposure + stimulation group (24.3) compared with rTMS alone (7.9) or traumatic exposure with sham rTMS (9.1). The greatest improvement was in the intrusive component of the CAPS scale. Heart rate responses to the traumatic script were also reduced over the 4 weeks of treatment. The proportion of patients who showed a response to treatment was not reported and the durability of the response was not assessed.

Section Summary

Several small RCTs have reported improvement of PTSD with rTMS over the right dorsolateral cortex. Results of high-frequency versus low-frequency stimulation are conflicting, and durability of the response has not been assessed. Additional study is needed.

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 published an Assessment of TMS as an adjunct treatment for schizophrenia.(53) Five meta-analyses were reviewed, along with RCTs in which measurements were carried out beyond the treatment period. A meta-analysis of the effect of TMS on positive symptoms of schizophrenia (hallucinations, delusions, disorganized speech and behavior) did not find a significant effect of TMS. Four meta-analyses that looked specifically at auditory hallucinations showed a significant effect of TMS. It was noted that outcomes were evaluated at the end of treatment, and the durability of the effect is unknown. The Assessment concluded that the available evidence is insufficient to demonstrate that TMS is effective in the treatment of schizophrenia.

A 2012 meta-analysis included 17 randomized, double-blind, sham-controlled trials (N=337) of the effect of rTMS on auditory hallucinations.(54) When measured at the end of treatment, the mean effect size of rTMS directed at the left temporoparietal area was 0.40 (moderate), and the effect size of rTMS directed at all brain regions was 0.33 (small). For the 5 trials that examined outcomes of rTMS 1 month after treatment, the effect was no longer significant.

Blumberger et al examined the efficacy of priming stimulation (6 Hz) before low-frequency stimulation (1 Hz) of Heschl gyrus within the left temporoparietal cortex.(55) Fifty-four patients with medication-resistant auditory hallucinations were randomized to receive 20 sessions of left-sided stimulation, priming, or sham rTMS. Response rates on the Psychotic Symptoms Rating Scale did not differ between the 3 treatment groups.

A small (n=18) double-blind, randomized, sham-controlled trial from 2012 found no significant effect of deep rTMS with an H1 coil on auditory hallucinations.(56)

Section Summary

The evidence on rTMS for the treatment of auditory hallucinations in schizophrenia consists of a number of small RCTs. Evidence to date shows small to moderate effects on hallucinations when measured at the end of treatment, but evidence suggests that the effect is not durable.

Stroke

A 2013 Cochrane review included 19 trials with a total of 588 participants on the effect of TMS for improving function after stroke.(57) The 2 largest trials showed that rTMS was not associated

with a significant improvement in function. The review concluded that current evidence does not support the routine use of rTMS for the treatment of stroke.

Hsu et al reported a meta-analysis of the effect of rTMS on upper limb motor function in patients with stroke in 2012.⁽⁵⁸⁾ Eighteen RCTs with a total of 392 patients were included in the meta-analysis. Most of the studies were double blind (n=11) or single blind (n=3). Eight studies applied low-frequency (1-Hz) rTMS over the unaffected hemisphere, 5 applied high-frequency (5-Hz) rTMS over the affected hemisphere, and 2 used both low- and high-frequency stimulation. Outcomes included kinematic motion analyses (5 trials), hand grip (2 trials), and the Wolf Motor Function Test (2 trials). Meta-analysis of results showed a moderate effect size (0.55) for rTMS on motor outcome, with a greater effect size of rTMS in patients with subcortical stroke (mean effect size, 0.73) compared with nonspecified lesion sites (mean effect size, 0.45), and for studies applying low-frequency rTMS (mean effect size, 0.69) compared with high-frequency rTMS (effect size, 0.41). Effect size of 0.5 or greater was considered to be clinically meaningful.

In 2012, Seniow et al reported a randomized, double-blind sham-controlled pilot study of low-frequency rTMS (1 Hz at 90% of resting motor threshold for 30 min) to the contralesional motor cortex combined with physical therapy in patients with moderate upper-extremity hemiparesis following stroke.⁽⁵⁹⁾ Power analysis indicated that a sample size of 129 patients would be required to detect changes in functional motor ability, but only 40 patients met eligibility criteria over the 4 years of the study. Blinded analysis showed no significant difference in hand function or level of neurologic deficit between active or sham rTMS when measured either immediately after the 3-week intervention or at 3-month follow-up.

Section Summary

Evidence consists of a number of RCTs and a meta-analysis of 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 is needed to determine whether rTMS facilitates standard physical therapy in patients with stroke.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers

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

In response to requests, input was received from 1 physician specialty society and 3 academic medical centers while this policy was under review in 2014. The reviewers considered rTMS to be medically necessary for TRD. Input agreed with the proposed criteria for treatment of TRD with rTMS, as included in the policy statement.

SUMMARY

Transcranial magnetic stimulation (TMS) 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. The literature on repetitive TMS (rTMS) for treatment-resistant

depression (TRD) includes numerous double-blind, randomized sham-controlled short-term trials. Results of these trials show mean improvements of uncertain clinical significance across groups as a whole. The percentage of subjects who show a clinically significant response is reported at approximately 2 to 3 times that of sham controls, with approximately 15% to 25% of patients meeting the definition of clinical response. (26) Based on the short-term benefit observed in randomized controlled trials, clinical input, and the lack of alternative treatments aside from electroconvulsive therapy (ECT) in patients with TRD, rTMS may be considered medically necessary in patients with TRD who meet specific criteria.

For other psychiatric/neurologic conditions, the evidence is insufficient to determine whether rTMS leads to improved outcomes. The available clinical trials are small and report mixed results for a variety of conditions other than depression. There are no large, high-quality trials for any of these other conditions. Therefore, rTMS is considered investigational for other psychiatric/neurologic conditions.

Practice Guidelines and Position Statements

The American Psychiatric Association 2010 practice guidelines for the treatment of patients with major depressive disorder states that treatment in the acute phase should be aimed at inducing remission of the major depressive episode and achieving a full return to the patient's baseline level of functioning [I, 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 ECT, TMS, or light therapy. A number of strategies are available when a change in the treatment plan seems necessary.... Transdermal selegiline, a relatively selective MAO B inhibitor with fewer dietary and medication restrictions, or transcranial magnetic stimulation could also be considered [II, Recommended with moderate clinical confidence].(60)

In 2007 the National Institute for Health and Care Excellence (NICE) published an Interventional Procedure Guideline (IPG) 242, which stated that current evidence suggests no major safety concerns for the use of TMS in the treatment of depression. There was uncertainty related to the clinical efficacy of TMS, which may depend on a number of factors such as higher intensity, greater frequency, bilateral application, and/or longer treatment durations than have appeared in evidence to date. TMS should be performed in research studies designed to evaluate these factors.(61) The opinion was repeated in the NICE 2009 Clinical Guideline 90.(62)

NICE guidance in 2006 on the management of bipolar disorder in adults, children, and adolescents in primary and secondary care states that TMS should not be routinely used for acute depressive episodes in people with bipolar disorder. The guidance states that TMS is not of proven efficacy for bipolar disorder and that when compared with sham TMS, the participants receiving sham treatment had lower end point mania symptom scores.(63)

2006 Practice Guidelines on the evaluation and treatment of depression, psychosis, and dementia in Parkinson disease from the American Academy of Neurology concluded that there is insufficient evidence 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). (64)

The Canadian Network for Mood and Anxiety Treatments updated their clinical guidelines on neurostimulation therapies for the management of major depressive disorder in adults.(65) The evidence reviewed supported ECT as a first-line treatment under specific circumstances; when used in patients who have failed to respond to 1 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 TRD, leading to a recommendation for rTMS as a second-line treatment. The guidelines indicated that there is a major gap in the evidence base regarding maintenance rTMS, as only 1 open-label case series was identified.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

- 90867 Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management
- 90868 Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent deliver and management, per session
- 90869 Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold redetermination with delivery and management
Code 90867 is reported once per course of treatment, and codes 90868 and 90869 cannot be reported for the same session.

ICD-9 Diagnoses

- 296.23 Major depressive disorder, single episode, severe, without mention of psychotic behavior
- 296.33 Major depressive disorder, recurrent episode, severe, without mention of psychotic behavior

ICD-10 Diagnoses (Effective October 1, 2015)

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

REVISIONS

12-07-2012	Policy added to the bcbsks.com web site.
05-07-2013	Updated Description section.
	Updated Rationale section.
	Updated Reference section.
10-15-2014	<p>Updated Description section.</p> <p>In Policy section: Removed the following, "Transcranial magnetic stimulation of the brain is considered investigational as a treatment of all other psychiatric/neurologic disorders, including but not limited to bipolar disorder, schizophrenia, obsessive-compulsive disorder, or migraine headaches." And added: A. Repetitive transcranial magnetic stimulation (rTMS) of the brain may be considered medically necessary as a treatment of major depressive disorder when all of the following conditions (1-3) have been met: 1. Confirmed diagnosis of severe major depressive disorder (single or recurrent) documented by standardized rating scales that reliably measure depressive symptoms; AND 2. Any one of the following (a, b, c, or d): a. Failure of 4 trials of psychopharmacologic agents including 2 different agent classes and 2 augmentation trials; OR b. Inability to tolerate a therapeutic dose of medications as evidenced by 4 trials of psychopharmacologic agents with distinct side effects; OR c. History of response to rTMS in a previous depressive episode (at least 3 months since the prior episode); OR d. Is a candidate for electroconvulsive therapy (ECT) and ECT would not be clinically superior to rTMS (e.g., in cases with psychosis, acute suicidal risk, catatonia or life-threatening inanition rTMS should NOT be utilized); AND 3. Failure of a trial of a psychotherapy known to be effective in the treatment of major depressive disorder of an adequate frequency and duration, without significant improvement in depressive symptoms, as documented by standardized rating scales that reliably measure depressive symptoms.</p>

	<p>B. rTMS for major depressive disorder that does not meet the criteria listed above is considered experimental / investigational.</p> <p>C. Continued treatment with rTMS of the brain as maintenance therapy is considered experimental / investigational.</p>
	Added Policy Guideline section.
	<p>In Coding section:</p> <ul style="list-style-type: none"> • Added ICD-9 diagnoses: 296.23, 296.33 • Added ICD-10 diagnoses: F32.2, F33.2
	Updated Rationale section.
	Updated References section.

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. Gaynes B, Lux L, Lloyd S et al. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Review No. 33. (Prepared by RTI International-University of North Carolina (RTI-UNC) Evidence based Practice Center under Contract No. 290-02-00161.) AHRQ Publication No. 11-EHC056- EF. Rockville, MD: Agency for Healthcare Research and Quality. 2011. Available online at: http://www.effectivehealthcare.ahrq.gov/ehc/products/76/792/TRD_CER33_2011110.pdf. Last accessed April, 2014.
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* 2009; 39(1):65-75.
6. 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* 2007; 116(3):165-73.
7. 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* 2008; 53(9):621-31.
8. 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* 2007; 62(11):1208-16.

9. George MS, Lisanby SH, Avery D et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 2010; 67(5):507-16.
10. Avery DH, Holtzheimer PE, 3rd, Fawaz W et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biol Psychiatry* 2006; 59(2):187-94.
11. Rossini D, Lucca A, Zanardi R et al. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. *Psychiatry Res* 2005; 137(1-2):1-10.
12. Mogg A, Pluck G, Eranti SV et al. A randomized controlled trial with 4-month follow-up of adjunctive repetitive transcranial magnetic stimulation of the left prefrontal cortex for depression. *Psychol Med* 2008; 38(3):323-33.
13. Fitzgerald PB, Hoy K, McQueen S et al. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. *Neuropsychopharmacology* 2009; 34(5):1255-62.
14. Grunhaus L, Schreiber S, Dolberg OT et al. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biol Psychiatry* 2003; 53(4):324-31.
15. McLoughlin DM, Mogg A, Eranti S et al. The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis. *Health Technol Assess* 2007; 11(24):1-54.
16. Rosa MA, Gattaz WF, Pascual-Leone A et al. Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. *Int J Neuropsychopharmacol* 2006; 9(6):667-76.
17. U.S. Food and Drug Administration. 510(k) Summary: Brainsway deep TMS System. 2013. Available online at: http://www.accessdata.fda.gov/cdrh_docs/pdf12/k122288.pdf. Last accessed February, 2014.
18. Fitzgerald PB, Brown TL, Marston NA et al. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 2003; 60(10):1002-8.
19. Fitzgerald PB, Benitez J, de Castella A et al. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry* 2006; 163(1):88-94.
20. Fitzgerald PB, Huntsman S, Gunewardene R et al. A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. *Int J Neuropsychopharmacol* 2006; 9(6):655-66.
21. Triggs WJ, Ricciuti N, Ward HE et al. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: a randomized, sham-controlled trial. *Psychiatry Res* 2010; 178(3):467-74.

22. Koerselman F, Laman DM, van Duijn H et al. A 3-month, follow-up, randomized, placebo-controlled study of repetitive transcranial magnetic stimulation in depression. *J Clin Psychiatry* 2004; 65(10):1323-8.
23. Rumi DO, Gattaz WF, Rigonatti SP et al. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. *Biol Psychiatry* 2005; 57(2):162-6.
24. Herwig U, Fallgatter AJ, Hoppner J et al. Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. *Br J Psychiatry* 2007; 191:441-8.
25. Jorge RE, Moser DJ, Acion L et al. Treatment of vascular depression using repetitive transcranial magnetic stimulation. *Arch Gen Psychiatry* 2008; 65(3):268-76.
26. Ullrich H, Kranaster L, Sigges E et al. Ultra-high-frequency left prefrontal transcranial magnetic stimulation as augmentation in severely ill patients with depression: a naturalistic sham-controlled, double-blind, randomized trial. *Neuropsychobiology* 2012; 66(3):141-8.
27. Demirtas-Tatlidede A, Mechanic-Hamilton D, Press DZ et al. An open-label, prospective study of repetitive transcranial magnetic stimulation (rTMS) in the long-term treatment of refractory depression: reproducibility and duration of the antidepressant effect in medication-free patients. *J Clin Psychiatry* 2008; 69(6):930-4.
28. Richieri R, Guedj E, Michel P et al. Maintenance transcranial magnetic stimulation reduces depression relapse: a propensity-adjusted analysis. *J Affect Disord* 2013; 151(1):129-35.
29. 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* 2012; 73(4):e567-73.
30. 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* 2010; 3(4):187-99.
31. Fitzgerald PB, Grace N, Hoy KE et al. An open label trial of clustered maintenance rTMS for patients with refractory depression. *Brain Stimul* 2012.
32. Ahmed MA, Darwish ES, Khedr EM et al. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. *J Neurol* 2011.
33. Rabey JM, Dobronevsky E, Aichenbaum S et al. Repetitive transcranial magnetic stimulation combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: a randomized, double-blind study. *J Neural Transm* 2012.

34. Weaver L, Rostain AL, Mace W et al. Transcranial magnetic stimulation (TMS) in the treatment of attention-deficit/hyperactivity disorder in adolescents and young adults: a pilot study. *J ECT* 2012; 28(2):98-103.
35. Walpoth M, Hoertnagl C, Mangweth-Matzek B et al. Repetitive transcranial magnetic stimulation in bulimia nervosa: preliminary results of a single-centre, randomised, double-blind, sham-controlled trial in female outpatients. *Psychother Psychosom* 2008; 77(1):57-60.
36. Khedr EM, Abo-Elfetoh N, Rothwell JC. Treatment of post-stroke dysphagia with repetitive transcranial magnetic stimulation. *Acta Neurol Scand* 2009; 119(3):155-61.
37. Kim L, Chun MH, Kim BR et al. Effect of repetitive transcranial magnetic stimulation on patients with brain injury and Dysphagia. *Ann Rehabil Med* 2011; 35(6):765-71.
38. 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* 2012; 53(10):1782-9.
39. Marlow NM, Bonilha HS, Short EB. Efficacy of Transcranial Direct Current Stimulation and Repetitive Transcranial Magnetic Stimulation for Treating Fibromyalgia Syndrome: A Systematic Review. *Pain Pract* 2012.
40. Short EB, Borckardt JJ, Anderson BS et al. Ten sessions of adjunctive left prefrontal rTMS significantly reduces fibromyalgia pain: A randomized, controlled pilot study. *Pain* 2011; 152(11):2477-84.
41. Maestu C, Blanco M, Nevado A et al. Reduction of pain thresholds in fibromyalgia after very low-intensity magnetic stimulation: A double-blinded, randomized placebo-controlled clinical trial. *Pain Res Manag* 2013; 18(6):e101-6.
42. U.S. Food and Drug Administration. De Novo classification request for cerena transcranial magnetic stimulator (TMS) device. 2013. Available online at: http://www.accessdata.fda.gov/cdrh_docs/reviews/K130556.pdf. Last accessed April, 2014.
43. 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* 2013; 47(8):999-1006.
44. 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* 2013; 144(1-2):153-9.
45. Elahi B, Elahi B, Chen R. Effect of transcranial magnetic stimulation on Parkinson motor function--systematic review of controlled clinical trials. *Mov Disord* 2009; 24(3):357-63.
46. Benninger DH, Iseki K, Kranick S et al. Controlled study of 50-Hz repetitive transcranial magnetic stimulation for the treatment of Parkinson disease. *Neurorehabil Neural Repair* 2012; 26(9):1096-105.

47. Yang YR, Tseng CY, Chiou SY et al. Combination of rTMS and Treadmill Training Modulates Corticomotor Inhibition and Improves Walking in Parkinson Disease: A Randomized Trial. *Neurorehabil Neural Repair* 2012.
48. Shirota Y, Ohtsu H, Hamada M et al. Supplementary motor area stimulation for Parkinson disease: a randomized controlled study. *Neurology* 2013; 80(15):1400-5.
49. Myczkowski ML, Dias AM, Luvisotto T et al. Effects of repetitive transcranial magnetic stimulation on clinical, social, and cognitive performance in postpartum depression. *Neuropsychiatr Dis Treat* 2012; 8:491-500.
50. Cohen H, Kaplan Z, Kotler M et al. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. *Am J Psychiatry* 2004; 161(3):515-24.
51. Watts BV, Landon B, Groft A et al. A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. *Brain Stimul* 2012; 5(1):38-43.
52. Isserles M, Shalev AY, Roth Y et al. Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder - A pilot study. *Brain Stimul* 2012.
53. 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.
54. Slotema CW, Aleman A, Daskalakis ZJ et al. Meta-analysis of repetitive transcranial magnetic stimulation in the treatment of auditory verbal hallucinations: Update and effects after one month. *Schizophr Res* 2012; 142(1-3):40-5.
55. Blumberger DM, Christensen BK, Zipursky RB et al. MRI-targeted repetitive transcranial magnetic stimulation of Heschl's gyrus for refractory auditory hallucinations. *Brain Stimul* 2012; 5(4):577-85.
56. Rosenberg O, Gersner R, Klein LD et al. Deep transcranial magnetic stimulation add-on for the treatment of auditory hallucinations: a double-blind study. *Ann Gen Psychiatry* 2012; 11:13.
57. Hao Z, Wang D, Zeng Y et al. Repetitive transcranial magnetic stimulation for improving function after stroke. *Cochrane Database Syst Rev* 2013; 5:CD008862.
58. Hsu WY, Cheng CH, Liao KK et al. Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke: a meta-analysis. *Stroke* 2012; 43(7):1849-57.
59. Seniow J, Bilik M, Lesniak M et al. Transcranial magnetic stimulation combined with physiotherapy in rehabilitation of poststroke hemiparesis: a randomized, double-blind, placebo-controlled study. *Neurorehabil Neural Repair* 2012; 26(9):1072-9.
60. American Psychiatric Association. Practice Guidelines for the treatment of patients with major depressive disorder. 2010. Available online at: http://psychiatryonline.org/data/Books/prac/PG_Depression3rdEd.pdf. Last accessed February, 2014.
61. National Institute for Health and Care Excellence. Interventional Procedure Guideline (IPG) 214 Transcranial magnetic stimulation for severe depression. 2007.

- Available online at: <http://publications.nice.org.uk/transcranial-magnetic-stimulation-for-severe-depression-ipg242>. Last accessed February, 2014.
62. National Institute for Health and Care Excellence. Clinical Practice Guideline (CG) 90 Depression in adults: The treatment and management of depression in adults. 2009. Available online at: <http://publications.nice.org.uk/depression-in-adults-cg90>. Last accessed February, 2014.
 63. National Institute for Health and Care Excellence. Bipolar disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. 2006. Available online at: <http://www.nice.org.uk/nicemedia/live/10990/30194/30194.pdf>. Last accessed April, 2014.
 64. 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* 66(7):996-1002. [Practice Guideline]. 2006; 2006/04/12. Available online at: <http://www.neurology.org/content/66/7/996.full.pdf+html>. Last accessed April, 2014.
 65. 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* 2009; 117 Suppl 1:S44-53.

Other References

1. Blue Cross and Blue Shield of Kansas Behavioral Health Liaison Committee, June 2012; June 2014.
2. BCBSKS Medical Consultant, Practicing Board Certified Psychiatrist, November 2012.