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

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 H1 coil are also being explored.

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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 one course of antidepressant medication.

On July 26, 2011, the FDA issued Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems. It states that a repetitive transcranial magnetic stimulation (rTMS) system is an external device that delivers repetitive pulsed magnetic fields of sufficient magnitude to induce neural action potentials in the prefrontal cortex to treat the symptoms of major depressive disorder (MDD) without inducing seizure in patients who have failed at least one antidepressant medication and are currently not on any antidepressant therapy. This document can be accessed online at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265269.htm#11>. Effective August 25, 2011, the Food and Drug Administration (FDA) classified the repetitive transcranial magnetic stimulation (rTMS) system into class II (special controls). The Agency classified "this device type into class II (special controls) in order to provide a reasonable assurance of safety and effectiveness of these devices." This document can be accessed online at: <http://www.gpo.gov/fdsys/pkg/FR-2011-07-26/html/2011-18806.htm>

Related Policies

[7.01.20 Vagus Nerve Stimulation](#)

8.01.39 Treatment of Tinnitus

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Policy

**This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Transcranial magnetic stimulation (TMS) of the brain may be considered **medically necessary** to treat the symptoms of major depressive disorder (MDD) in patients with treatment-resistant depression (TRD) who have failed at least one antidepressant medication and are currently not on any antidepressant therapy.

Transcranial magnetic stimulation (TMS) is **not medically necessary** for all other indications including schizophrenia, fibromyalgia, obsessive compulsive disorder, dysphasia, post-traumatic stress disorder, stroke or Parkinson's disease.

Policy Guidelines

rTMS therapy involves a series of treatment sessions. Treatment sessions may be approximately 40 minutes each, and administered 5 days a week. A typical course of rTMS may be 4 to 6 weeks. However, this can vary depending on an individual's response to treatment. Further research is needed to provide some information about whether maintenance treatments are needed, and which types of maintenance treatment are most effective.

Rationale

This policy is based in part on the Blue Cross and Blue Shield Technology Evaluation Center (TEC) assessment of repetitive TMS (rTMS) for depression in 2009 (1) along with searches of the MEDLINE database, and the 2011 Agency for Healthcare Research and Quality (AHRQ) review.

The TEC Assessment concluded that the available evidence did not permit conclusions regarding the effect of TMS on health outcomes. Limitations of the evidence included:

- Equivocal efficacy in the largest sham-controlled trial of TMS,
- Uncertain clinical significance of the short-term anti-depressant effects found in meta-analyses,
- A lack of information 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).

TEC published an updated Assessment of TMS for depression in 2011. (2) Included were 6 recent meta-analyses, the largest of which evaluated 30 double-blind sham-controlled trials with a total of 1,383 patients. Recent clinical trials were also reviewed. The 2011 TEC Assessment reached the following conclusions:

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- The meta-analyses and recent clinical trials of TMS generally show statistically significant effects on depression outcomes at the end of the TMS treatment period.
- The largest randomized clinical trial showed a greater effect in patients with only one prior treatment failure, with possibly minimal or no effect in patients with greater than one prior treatment failure. Based on current evidence, it cannot be determined whether TMS after one treatment failure would be as effective as the current standard of a second course of antidepressant therapy.
- Also identified as gaps in current knowledge are whether TMS is effective as an adjunctive treatment and whether retreatment is effective.

The Agency for Healthcare Research and Quality (AHRQ) review (Gaynes, 2011) determined that, in general, existing evidence is still insufficient to draw conclusions regarding the comparative effectiveness of nonpharmacologic therapies such as rTMS and ECT. The outcomes associated with these strategies and with usual care were determined by data from the relatively few studies that were feasible to quantitatively analyze in the AHRQ review. The strongest evidence was for the relative outcomes of rTMS compared with usual care based on the meta-analyzed data in the report. In the report there were two Tier 1 trials reviewed (Tier 1 evidence is defined as: studies in which treatment-resistant depression (TRD) patients specifically had two or more prior treatment failures with medications.) (3) The trials compared rTMS with sham. All findings provided low strength of evidence. For young adults (ages 18–37), one trial found that rTMS produced a greater decrease in depressive severity and a greater response rate than sham. A second trial, conducted in older adults with post-stroke depression, found that rTMS produced a greater decrease in depressive severity and a greater response rate but no difference in remission rates compared with a sham control. rTMS was beneficial relative to controls receiving a sham procedure for all three 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 three 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 six times as likely to achieve remission as those receiving the sham.

The New England Comparative Effectiveness Public Advisory Council (CEPAC) Coverage Policy Analysis on repetitive transcranial magnetic stimulation (rTMS), reviewed the AHRQ evidence review on rTMS along with supplementary information on utilization, costs, and cost-effectiveness. CEPAC voted that the evidence was adequate to demonstrate that (rTMS), was as good as or better than usual care for patients with treatment-resistant depression. (4)

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 stimulation (DLPFC), low-frequency (1-2 Hz)

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stimulation of the right dorsolateral prefrontal cortex, or combined high-frequency and low-frequency 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 below, stimulation was set at 100% to 120% of motor threshold, clinical response was defined as an improvement of 50% or more on the Hamilton Depression Rating Scale (HAM-D), and remission was considered to be a score of 7 or less on the HAM-D.

High Frequency rTMS of the Left Dorsolateral Prefrontal Cortex for Treatment-Resistant Depression

Lam and colleagues conducted a meta-analysis of 24 randomized controlled trials (RCTs) comparing active versus sham repetitive TMS (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 left dorsolateral prefrontal cortex (DLPFC). (8) Treatment-resistant depression 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 post-baseline assessment and an additional 8% of patients from both groups dropping out before the 4-week assessment. Intent-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 multi-centered 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 pre-treatment magnetic resonance imaging (MRI). Results from Phase 2 (open treatment of non-responders) and Phase 3 (maintenance and follow-up) will be reported in the future.

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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 that 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 that they had received active TMS; responders were more likely than non-responders (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 and colleagues 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 of 16) of the sham, 28% (5 of 18) of the 80% MT, and 61% (11 of 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 measured 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, since 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 and 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, since 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 anti-depressant response compared with the standard targeting procedure, i.e., measuring 5 cm anterior from the motor cortex. (13) Fifty-one patients who had failed at least two

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6-week courses of antidepressant medication (average 5.7 failed courses) were randomly assigned to a standard localization procedure or to structural magnetic resonance imaging (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.

Several studies have compared the outcomes of rTMS with those from electroconvulsive therapy. In one 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 less than or equal to 10. (14) There was no difference in response rate between the 2 groups; 12 of 20 responded in the electroconvulsive therapy group compared to 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 electroconvulsive therapy. (15) Forty-six patients who had been referred for electroconvulsive therapy were randomly assigned to either electroconvulsive therapy (average of 6.3 sessions) or a 15-day course (5 treatments per week) of rTMS of the left DLPFC. Electroconvulsive therapy resulted in a 14-point improvement in the HAM-D and a 59% remission rate. Repetitive TMS was less effective than electroconvulsive therapy (5-point improvement in HAM-D and a 17% remission rate). Another study reported no significant difference between electroconvulsive therapy and rTMS in 42 patients with TRD; however, response rates for both groups were low. (16) The number of remissions (score of 7 or less on the HAM-D) totaled 3 (20%) for electroconvulsive therapy and 2 (10%) for rTMS.

In a randomized sham-controlled study, Schaller and colleagues studied the influence on mood of a series of 9 High Frequency (HF) rTMS stimulations of the left dorsolateral prefrontal cortex (DLPFC). (17) Forty-four young healthy male volunteers were randomly assigned to receive 9 sessions of active HF-rTMS (n = 22) or sham rTMS (n = 22) over the left DLPFC. Each session consisted of 15 trains of 25 Hz starting with 100% of motor threshold. The sham stimulation was performed using a sham coil. The variables of interest consisted of six Visual Analogue Scales (VAS) and the Beck Depression Inventory (BDI). A significant reduction of the BDI sum score in the active group (GLM, $p < 0.001$) was noted whereas no significant changes of the BDI sum score resulted from sham stimulation (GLM, $p = 0.109$). The BDI single item analyses revealed within and between group differences supporting the modifying effect of rTMS on BDI. The authors conclude that a 9-day long series of HF-rTMS of the left DLPFC improved mood, analysed by BDI in healthy young men. No significant long-term changes were noted in VAS.

With results published in 2011, Hadley and colleagues enrolled 19 patients who were in a current major depressive episode with treatment-resistant unipolar or bipolar depression and treated them in their acute episode and in a maintenance fashion for 18 months. (18) The patients received daily left

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prefrontal rTMS at 120% resting motor threshold, 10 Hz, 5 seconds on, and 10 seconds off and for a mean of 6800 stimuli per session (34,000 stimuli per week), more than twice the dose delivered in the pivotal FDA trial. All patients continued antidepressant medication throughout the rTMS treatment; thus rTMS was an adjunctive treatment. The higher rTMS doses were well tolerated without significant adverse effects or adverse events. All measured dimensions (depression, quality of life, suicidal ideation, social and physical functioning), showed improvement; many showing improvement in 1 to 2 weeks. Notably, suicidal ideation diminished in 67% of the patients after just 1 week. The researchers concluded that higher doses of daily left prefrontal rTMS may safely be used in outpatients with major depressive episode even as an adjunctive treatment.

High Frequency rTMS as an Adjunctive Treatment for Moderate to Severe Depression

Schutter conducted a meta-analysis of 30 double-blind randomized sham-controlled trials (1,164 patients) of high-frequency rTMS over the left dorsolateral prefrontal cortex 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 [CI]: 0.25–0.54), 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. (19-21) Repetitive TMS has also been examined in patients with clinical evidence of cerebrovascular disease and late-life depression. (22)

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. (23) 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.

Low Frequency rTMS of the Right Dorsolateral Prefrontal Cortex or Bilateral Stimulation for Treatment- Resistant Depression

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. (24) 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 to 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 and 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%

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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 and colleagues randomly assigned 50 patients with TRD to sequential bilateral active or sham rTMS. (25) After 2 weeks of treatment, 3 subjects had dropped out of the sham treatment group, and there was a slight but non-significant 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 and 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 dorsolateral prefrontal cortex. (26) 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. (27) 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).

Maintenance Therapy

Fitzgerald et al. reported a prospective open-label trial of clustered maintenance rTMS for patients with refractory depression. (28) 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). Patients were treated with maintenance therapy of the same type that they had initially received (14 high frequency to the left dorsolateral prefrontal cortex, 12 low frequency to the right dorsolateral prefrontal cortex, and 9 bilateral). The primary outcome was the mean duration until clinical relapse, addition or change of antidepressant medication, or withdrawal from maintenance treatment to pursue other treatment options. Of 35 patients, 25 (71%) relapsed at a mean of 10.2 months (range, 2 to 48 months), which was substantially shorter than the interval (<3 months) for relapse from the initial treatment.

Janicak and colleagues reported on assessment of relapse during a multisite, open-label study. (29) In this 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. They were then followed for 24 weeks. Ten of 99 patients relapsed.

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Thirty-eight patients had symptom worsening, and 32 of these (84%) had symptomatic benefit with adjunctive rTMS.

A retrospective study that included maintenance rTMS was reported by Connolly et al. in 2012. (30) Out of the first 100 cases treated at their institution, 42 received maintenance rTMS. Most of the patients had failed more than 1 adequate antidepressant trial and were treated with high-frequency rTMS over the dorsolateral prefrontal cortex. Low-frequency rTMS to the right dorsolateral prefrontal cortex was given in patients with a family or personal history of seizures and in some patients who were also receiving high-frequency rTMS. The response rate was 50.6% of the first 100 cases and the remission rate was 24.7%. Maintenance treatment (42 patients) was tapered gradually from 2 sessions per week for the first 3 weeks to monthly. At 6 months after the initial rTMS treatment, 26 of the 42 patients (62%) maintained their response.

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

Alzheimer's Disease

Ahmed et al. randomized 45 patients with probable Alzheimer's disease to 5 sessions of bi-lateral high-frequency rTMS, bi-lateral low-frequency rTMS, or sham TMS over the dorsolateral prefrontal cortex. (31) 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 (MMSE), from 20.1 to 24.7 on the Instrumental Daily Living Activity (IADL) scale and from 5.9 to 2.6 on the Geriatric Depression Scale (GDS).

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. (32) 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's area, comprehension and categorization for Wernicke's area, action naming, object naming and spatial memory tasks for the right and left dorsolateral prefrontal cortex, 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 Disease Assessment Scale, cognitive subsection (ADAS-cog) score of 3.76 points in the rTMS group compared to 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 to 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 to 4.25 and 4.29 in the placebo group.

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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).(33) 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. (34)

Dysphagia

rTMS for the treatment of dysphagia following stroke has been examined in small randomized controlled trials. One study randomized 26 patients to rTMS or sham over the affected esophageal motor area of the cortex.(35) 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. (36) 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.(37) 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 to baseline (from 8.9 per week at baseline to 1.8 per week at follow-up) and when compared to 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.

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Fibromyalgia

A 2012 systematic review included 4 studies on transcranial direct current stimulation and 5 on rTMS for treatment of fibromyalgia pain.(38) Three of the 5 trials were considered to be high quality. Four of the 5 were double-blind randomized controlled trials; the 5th 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 to the dorsolateral prefrontal cortex.

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. (39) 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 to 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.

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

Obsessive Compulsive Disorder

Two small (n=18 and 30) randomized sham-controlled trials found no evidence of efficacy for treatment of obsessive compulsive disorder (OCD), although another small sham-controlled trial (n=21) reported promising results with bilateral stimulation of the supplementary motor area. (40-42)

Panic Disorder

In 2013, Mantovani et al. reported a randomized double-blind sham-controlled trial of low frequency rTMS to the right dorsolateral prefrontal cortex in 21 patients with panic disorder with comorbid major depression. (43) Response was defined as a 40% or greater decrease on the panic disorder severity scale (PDSS) and a 50% or greater decrease on the 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 randomized controlled trials with a total of 275 patients with Parkinson disease.(44) Seven of the studies were double-blind, one was not blinded and 2 of the

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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. (45) Eight sessions of 50 Hz rTMS did not improve gait, bradykinesia, or global and motor scores on the UPDRS compared to 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 min) of high frequency (5-Hz) rTMS or sham rTMS over the leg area of the motor cortex followed by treadmill training.(46) Blinded evaluation showed a significant effect of rTMS combined with treadmill training on neurophysiological 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.

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 dorsolateral prefrontal cortex.(47) 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 randomized controlled trials.

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 dorsolateral prefrontal cortex.(48) Blinded assessment 2 weeks after the intervention found that high frequency rTMS improved the self-reported PTSD

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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 dorsolateral prefrontal cortex.(49) 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 non-traumatic event, or sham stimulation after a brief script of the traumatic event. (50) 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 to 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.

Conclusions: Several small randomized controlled trials 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. (51) Five meta-analyses were reviewed, along with randomized controlled trials (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, and 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.(52) 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 one month after treatment, the effect was no longer significant.

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Blumberger et al. examined the efficacy of priming stimulation (6 Hz) prior to low frequency stimulation (1 Hz) of Heschl's gyrus within the left temporoparietal cortex. (53) 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. (54)

Conclusions: The evidence on rTMS for the treatment of auditory hallucinations in schizophrenia consists of a number of small randomized controlled trials. 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

Hsu et al. reported a meta-analysis of the effect of rTMS on upper limb motor function in patients with stroke in 2012. (55) Eighteen randomized-controlled trials 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 to non-specified lesion sites (mean effect size, 0.45), and for studies applying low frequency rTMS (mean effect size, 0.69) compared to 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 physiotherapy in patients with moderate upper extremity hemiparesis following stroke. (56) 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 neurological deficit between active or sham rTMS when measured either immediately after the 3-week intervention or at 3-month follow-up.

Conclusions: Evidence consists of a number of randomized controlled trials 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 physiotherapy in patients with stroke.

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Clinical Trials

Numerous studies regarding rTMS are listed online at:
<http://clinicaltrials.gov/ct2/results?term=transcranial+magnetic+stimulation>.

Practice Guidelines and Position Statements

The Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines on neurostimulation therapies for the management of major depressive disorder in adults (57) The evidence reviewed supported electroconvulsive therapy (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 50–60%. 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., (5) 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 one open-label case series was identified.

The Movement Disorder Society published an evidence-based review of treatments for the non-motor symptoms of Parkinson's disease in 2011. (58) The review found insufficient evidence to make adequate conclusions on the efficacy rTMS for the treatment of depression in Parkinson's disease.

Summary

The clinical trials of Transcranial magnetic stimulation (TMS) generally show statistically significant effects on depression outcomes at the end of the TMS treatment period. TMS is FDA approved to treat the symptoms of major depressive disorder (MDD) in patients who have failed at least one antidepressant medication and are currently not on any antidepressant therapy, subsequently, rTMS may be considered **medically necessary** for this indication. Although further research is needed to determine which of the locations and treatment parameters examined to date are most effective to guide the number of sessions needed to elicit a clinically significant response, to determine whether the response is durable with or without anti-depressant medications, and to provide some information about whether maintenance treatments are needed, and which types of maintenance treatment are most effective.

Transcranial magnetic stimulation (TMS) is only FDA approved for the indication in the treatment of treatment-resistant depression. The available evidence on rTMS for other psychiatric / neurologic disorders is insufficient to permit conclusions regarding the effect of this technology on health outcomes. Therefore, for all other indications, rTMS remains **not medically necessary**.

Medicare National Coverage

No national coverage determination was identified.

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| Section: | Medicine | Effective Date: | April 1, 2013 |
| Subsection: | Medicine | Original Policy Date: | September 13, 2012 |
| Subject: | Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders | Page: | 21 of 21 |

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Policy History

| Date | Action | Reason |
|----------------|----------------|---|
| September 2012 | New Policy | |
| March 2013 | Updated Policy | Policy reviewed and rationale updated for non-FDA approved indications. No change in policy statement. New FDA approved device added. |

Keywords

Depression, Transcranial Magnetic Stimulation
Magnetic Stimulation, Transcranial
NeoPulse, Transcranial Magnetic Stimulation
NeuroStar, Transcranial Magnetic Stimulation
Transcranial Magnetic Stimulation, Depression
Repetitive Transcranial Magnetic Stimulation, Depression
Brainsway H-Coil Deep TMS Device

This policy was approved by the FEP Pharmacy and Medical Policy Committee on March 8, 2013 and is effective April 1, 2013.

Signature on file

Deborah M. Smith, MD, MPH