



# CIGNA MEDICAL COVERAGE POLICY

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**Subject Transcranial Magnetic Stimulation**

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## Table of Contents

Coverage Policy .....	1
General Background .....	1
Coding/Billing Information .....	16
References .....	17
Policy History .....	23

## Hyperlink to Related Coverage Policies

- Complementary and Alternative Medicine
- Deep Brain and Motor Cortex Stimulation
- Electrical Stimulators
- Light Therapy for Seasonal Affective Disorder (SAD)
- Vagus Nerve Stimulation (VNS)

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## Coverage Policy

**CIGNA does not cover transcranial magnetic stimulation (TMS) for any indication, including depression or other psychiatric disorders, because it is considered experimental, investigational or unproven.**

## General Background

Though the majority of individuals treated for depression respond to standard treatments for depression, some do not benefit, or cannot tolerate, interventions such as psychotherapy, pharmacotherapy, or electroconvulsive therapy (ECT). Alternate approaches to treat depression are being investigated, including transcranial magnetic stimulation (TMS), vagal nerve stimulation, cranial electrical stimulation and herbal/homeopathic remedies (Rutherford and Roose, 2009; Miniussi, et al., 2005).

TMS was first used in 1985 as a neurophysiological investigational method to study brain-behavior relationships and was applied clinically in a neurosurgical context. Brief pulses of magnetic energy are applied to the scalp via a large electromagnetic coil to generate low levels of electrical current in underlying brain tissue. The goal of repetitive trains of stimulation (rTMS) is to stimulate areas of the brain involved in mood regulation in order to lessen the duration or severity of depressive episodes. In the course of its use, mood effects have been observed, and interest in developing TMS as a treatment followed, along with interest in continued use to probe neural pathways related to mood disorders. TMS may be delivered as a single pulse, in paired pulses, or as

rTMS. rTMS is described by the number of pulses per second or frequency in hertz (Hz). Effects of rTMS on cortical excitability and inhibition outlast the stimulation itself, from minutes to hours, a characteristic that could lead to therapeutic applications (Gooch and Pullman, 2005).

The earliest studies used single-pulse TMS at low frequencies. It is now known that lower frequencies are inhibitory and that higher frequencies are excitatory, and low- and high-frequency rTMS have been studied. Over time, improvements in coil design have allowed more focal stimulation, and the prefrontal cortex has been the region of interest in many recent studies in which rTMS was used in the treatment of mood disorders. With rTMS, the electrical current generates a focused magnetic field that passes through the scalp and is largely unimpeded by bone or tissue. The magnetic field, in turn, depolarizes brain cells to a depth of 2 cm from the coil. The fact that the skull is transparent to magnetic stimulation has led to speculation about, and exploration of, enhancing control of the site and intensity of stimulation delivered by using rTMS. Individuals are usually fully awake and sitting during TMS therapy, with sessions lasting from 20 minutes to one hour. If multiple sessions are required, they occur daily on consecutive weekdays for a number of weeks (Prudic, 2005; Peselow, 2005; Burt, et al., 2002).

While the majority of clinical trials on TMS have evaluated its use in depression, other conditions have also been studied, including, but not limited to, Parkinson's disease, post-traumatic stress disorder, acute ischemic stroke, obsessive-compulsive disorders and schizophrenia, alcohol dependence, tinnitus, migraines, chronic neuropathic pain, spinal cord injury. Ongoing research supports continued investigation of the usefulness of rTMS in the treatment of depression, although effect sizes vary and are modest. Studies have typically used high-frequency rTMS for a minimum of two weeks. Study designs have been both open and sham-controlled. Sample sizes have been relatively small. Few patients were without psychotropics or were followed for any substantial period. There have been a few direct comparisons of ECT and rTMS. Such comparisons have not favored rTMS. Studies have not shown the intervention to be effective for psychotic illness. As well, it may be less effective in elderly patients because of increased distance of brain tissue (associated with age) from the skull and, hence, from the magnetic field generated. rTMS has the advantages of being a subconvulsive and focal treatment, thus eliminating the need for anesthesia, and having minimal to no noticeable cognitive side effects. It has been reported that TMS does carry a very small risk of seizures, and it is recommended that patients be monitored for this adverse effect during the procedure (Machii, et al., 2006; Prudic, 2005; Gooch and Pullman, 2005).

### **U.S. Food and Drug Administration (FDA)**

On October 8, 2008, a TMS device, NeuroStar™ TMS System from Neuronetics, Inc. (Malvern, PA) has been approved for use by the FDA. The FDA determined that the NeuroStar TMS System is indicated for the treatment of Major Depressive Disorder (MDD) in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode and can be classified in class II with the establishment of special controls. The FDA states that class II special controls provide reasonable assurance of the safety and effectiveness of the device type. Risks involved with the use of the device type include (FDA, 2008):

- usage outside of labeled patient population
- ineffective treatment
- seizure
- scalp discomfort, scalp burn or other adverse events
- magnetic field effects on functioning of other medical devices
- adverse tissue reaction
- hazards associated with electrical equipment
- hazards caused by electromagnetic interference and electrostatic discharge hazards
- hearing loss

### **Literature Review–Depression**

Published clinical trials evaluating the efficacy of TMS to date have generally involved small numbers of patients with major depression as the focus of treatment. The studies include varied diagnostic groups on and off pharmacotherapy. Studies have varied in terms of interval of treatment, degree and placement of stimulation and tend to be of short duration with limited follow-up intervals.

In a prospective study, Janicak et al. (2010) assessed the durability of antidepressant effect after acute response to TMS in patients with major depressive disorder (MDD) using protocol-specified maintenance antidepressant monotherapy. Three hundred one patients were randomly assigned to active or sham TMS in a 6-week, controlled trial. Nonresponders could enroll in a second, 6-week, open-label study. Patients who met criteria for partial response (i.e., >25% decrease from the baseline HAMD 17) during either the sham-controlled or open-label study (n=142) were tapered off TMS over three weeks, while simultaneously starting maintenance antidepressant monotherapy. Patients were then followed for 24 weeks in a naturalistic follow-up study examining the long-term durability of TMS. During this durability study, TMS was readministered if patients met prespecified criteria for symptom worsening (i.e., a change of at least one point on the CGI-S scale for two consecutive weeks). Relapse was the primary outcome measure. Ten of 99 (10%; Kaplan-Meier survival estimate =12.9%) patients relapsed. Thirty-eight (38.4%) patients met criteria for symptom worsening and 32/38 (84.2%) re-achieved symptomatic benefit with adjunctive TMS. Safety and tolerability were similar to acute TMS monotherapy. Limitations of this study include the lack of a controlled comparison. The two groups were no longer fully randomized after entry in the long-term trial, inferential statistical comparisons are not appropriate. Further, all patients, regardless of whether they benefited from active or sham TMS during acute treatment, were continued on antidepressant medication monotherapy as a primary maintenance strategy during the 24-week follow-up. Hence, the acute sham responder group was not followed as a “pure” sham responder (or no treatment) extension cohort, because these patients may have received clinical benefit from the introduction of antidepressant medication.

In a prospective, multi-site, randomized, active sham-controlled (1:1 randomization) study, George et al. (2010) examined if daily left pre-frontal rTMS safely and effectively treats major depressive disorder. Approximately 860 outpatients were screened, yielding 199 antidepressant drug-free patients with unipolar non-psychotic major depressive disorder. The researchers delivered rTMS to the left pre-frontal cortex at 120 % motor threshold (10 Hz, 4-second train duration, and 26-second intertrain interval) for 37.5 minutes (3000 pulses per session) using a figure-eight solid-core coil. Sham rTMS used a similar coil with a metal insert blocking the magnetic field and scalp electrodes that delivered matched somatosensory sensations. In the intention-to-treat sample (n=190), remission rates were compared for the two treatment arms using logistic regression and controlling for site, treatment resistance, age, and duration of the current depressive episode. Patients, treaters, and raters were effectively masked. Minimal adverse effects did not differ by treatment arm, with an 88% retention rate (90% sham and 86% active). Primary efficacy analysis revealed a significant effect of treatment on the proportion of remitters (14.1% active rTMS versus 5.1% sham) (p=0.02). The odds of attaining remission were 4.2 times greater with active rTMS than with sham (95% CI, 1.32-13.24). The number needed to treat was 12. Most remitters had low antidepressant treatment resistance. Almost 30% of patients remitted in the open-label follow-up (30.2% originally active and 29.6% sham). There are several limitations reported with the study. As a consequence of the extensive work in designing a sham system, which delayed the start of the trial, the study failed to enroll the projected 240 subjects suggested by the initial power analysis. This power issue may be the reason why the treatment condition effect on remission rate in the fully adherent sample analysis was not statistically significant. Treaters were able to guess randomization assignment better than chance, without much confidence, which was not explained by covarying for clinical benefit. Although the treatment effect was statistically significant on a clinically meaningful variable (remission), the overall number of remitters and responders was less than one would like with a treatment that requires daily intervention for three weeks or more, and it is unclear how long the clinical benefit lasts once achieved.

In a three-group, three week double-blind, randomized controlled trial, Pallanti et al. (2010) compared unilateral low frequency, sequential bilateral rTMS treatment and sham in patients with treatment resistant depression (TRD) under stable pharmacological treatment. Sixty patients were assigned to receive either low-frequency rTMS over the right dorsolateral prefrontal cortex (DLPFC) (140s x1 Hz) followed by contralateral sham (unilateral group, n=20), low frequency right DLPFC rTMS followed by left DLPFC high frequency rTMS (5s x 10 Hz) (bilateral group, n=20), or bilateral sham (sham group, n=20). The primary outcome variable was the score on Hamilton Depression Scale (HAM-D). Low frequency right-sided and sequential bilateral stimulation showed different antidepressant efficacy at three weeks and across the full duration of the study, only the unilateral method appearing significantly more effective than sham at the end of the trial, and correlated to the higher percent of remitters (30% of the group versus 10% -bilateral- and 5% -sham). Unilateral stimulation, but not bilateral, showed higher antidepressant efficacy compared to sham stimulation. The data suggest that right-sided low frequency stimulation may be a first line treatment alternative in resistant depression. The authors report that to confirm and extend these findings further studies require a longer follow-up period.

Mogg et al. (2008) conducted a randomized clinical trial with four month follow-up to evaluate the effectiveness of rTMS for major depression. Fifty-nine patients with major depression were randomly assigned to a 10-day course of either real (n=29) or sham (n=30) rTMS of the left dorsolateral prefrontal cortex. Primary outcome measures were the 17-item Hamilton Depression Rating Scale (HAMD) and proportions of patients meeting criteria for response ( $\geq 50\%$  reduction in HAMD) and remission ( $\text{HAMD} \leq 8$ ) after treatment. Secondary outcomes included mood self-ratings on Beck Depression Inventory-II and visual analogue mood scales, Brief Psychiatric Rating Scale (BPRS) score, and both self-reported and observer-rated cognitive changes. Patients had six-week and four-month follow-ups. Overall, HAMD scores were modestly reduced in both groups but with no significant group x time interaction ( $p=0.09$ ) or group main effect ( $p=0.85$ ); the mean difference in HAMD change scores was  $-0.3$  (95% CI  $-3.4$  to  $2.8$ ). At end-of-treatment time-point, 32% of the real group were responders compared with 10% of the sham group ( $p=0.06$ ); 25% of the real group met the remission criterion compared with 10% of the sham group ( $p=0.2$ ); the mean difference in HAMD change scores was  $2.9$  (95% CI  $-0.7$  to  $6.5$ ). There were no significant differences between the two groups on any secondary outcome measures. Blinding was difficult to maintain for both patients and raters. Four patients did not complete the full treatment course, of whom two were lost to follow-up. The authors reported that adjunctive rTMS of the left dorsolateral prefrontal cortex could not be shown to be more effective than sham rTMS for treating depression.

O'Reardon et al. (2007) conducted a multi-site, randomized, double-blind, controlled study examining whether TMS over the left dorsolateral prefrontal cortex (DLPFC) is effective and safe in the acute treatment of major depression. In this multicenter study, 301 medication-free patients with major depression who had not benefited from prior treatment were randomized to active (n=155) or sham TMS (n=146) conditions. The patients had a current episode duration of three years or less. Patients were required to have failed at least one but no more than four adequate antidepressant treatments in this or the most recent episode. Patients were eligible if they had marked intolerance to antidepressants as indicated by four failed attempts to tolerate an adequate medication trial during their lifetime. Exclusionary criteria for study participation included a lifetime history of psychosis, bipolar disorder, or obsessive-compulsive disorder; posttraumatic stress disorder and eating disorders (if present in the past year); lack of response to an adequate trial of ECT; prior treatment with TMS or a vagus nerve stimulator implant; pregnancy; a personal or close family history of a seizure disorder; presence of neurologic disorder or medication therapy known to alter seizure threshold; or presence of ferromagnetic material in or in close proximity to the head.

The study had three phases: a one week lead in phase with no treatment, a six week acute treatment phase with daily treatment with sham or TMS, and a taper phase consisting of three weeks of reduced frequency of TMS or sham and start of antidepressant. Sessions were conducted five times per week with TMS at 10 pulses/sec, 120% of motor threshold, 3000 pulses/session, for 4–6 weeks. Primary outcome was the symptom score change as assessed at week four with the Montgomery-Asberg Depression Rating Scale (MADRS). Response was defined as at least 50% reduction from baseline score. Remission was defined by an absolute scale-specific score. Secondary outcomes included changes on the 17- and 24-item HAMD and response and remission rates with the MADRS and HAMD.

Loss to follow-up was similar in the two groups, with 301 (92.6%) patients completing at least one post-baseline assessment and an additional 8% of patients from both groups dropping out before the four week assessment, which then become an open-label study. A dropout rate of 4.5% was reported for transient scalp discomfort or pain. Subjects in the TMS group exhibited improvement on several secondary outcome measures, but antidepressant effects did not reach statistical significance for the primary outcome measure, the MADRS. Baseline symptom scores MADRS (active 32.8 versus sham 33.9,  $p=0.36$ ). Week four symptom scores MADRS (active 27 versus sham 29.8,  $p=0.57$ ). Week six symptom scores MADRS (active 26.8 versus sham 30,  $p=0.58$ ). There was no long-term follow-up in this study. No outcomes were reported beyond six weeks.

Avery et al. (2008) provided further analysis of the open-label extension study of active rTMS for patients from the O'Reardon et al. (2007) study who did not benefit from the initial four week course of rTMS. As with O'Reardon's study, Avery used a sham-controlled design. They noted that patients who had failed only one adequate trial of an antidepressant were more likely to achieve a favorable response than those who had more than one treatment prior to rTMS. In those patients who received sham in the preceding randomized controlled trial (n=85), the mean reduction in MADRS scores after six weeks of open-label active TMS was  $-17.0$  (95% CI =  $-14.0$  to  $-19.9$ ). Further, at six weeks, 36 (42.4%) of these patients achieved response on the MADRS, and 17 patients (20.0%) remitted (MADRS score  $< 10$ ). For those patients who received and did not respond to active TMS in the preceding randomized controlled trial (n=73), the mean reduction in MADRS scores was  $-12.5$  (95%

CI = -9.7 to -15.4), and response and remission rates were 26.0% and 11.0%, respectively, after 6 weeks of additional open-label TMS treatment. The authors acknowledged that the response and remission rates at six weeks were probably higher than they actually were given that it was an open-label extension study, and there likely was a placebo effect related to expectations of a positive treatment outcome. Avery compared the data with the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) results (Rush, et al., 2006), also an open-label trial. They compared remission rates after 1–2 unsuccessful courses of antidepressants to be similar to those of the current study of TMS, and conclude that their data suggested the efficacy of rTMS to be comparable to that of second or third line pharmaceutical strategies. Avery did not note that the STAR\*D study had a much larger sample size (n=4041 versus 158), or that they were comparing data that included two full 6 week courses of rTMS for 73 patients. The lack of a control treatment condition limits the interpretation of the data.

In a randomized clinical trial, Herwig et al. (2007) evaluated whether the application of rTMS in a routine clinical setting as an additional strategy to standard antidepressant medication would enhance the clinical improvement of depression compared with sham treatment with regard to the number of responders and the decrease in depression rating scores. A total of 127 patients were randomized to rTMS group (n=62) duration of current episode eight weeks or less in 25 pts, longer in 36 patients. The sham group (n=65) duration of current episode eight weeks or less in 24 patients, longer in 41 patients. The patients ranged in age from 18–75 years with a diagnosis of major depressive episode with Diagnostic and Statistical Manual of Mental Disorders Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria including bipolar affective disorder, score of  $\geq 18$  points on at least two of three depression rating scales. rTMS used as adjunct to venlafaxine or mirtazapine therapy or as monotherapy when no medication was possible. Patients stable on lithium therapy for at least three months prior to study entry were allowed to continue taking lithium. The rTMS group, received rTMS on the left side (position F3 according to international 10–20 system for electroencephalography electrode placement) with frequency 10 Hz and intensity 110% motor threshold (MT); 2000 stimuli/session times 15 daily sessions. The sham group received therapy with the coil placed 5 cm lateral to position F3 at an angle of 45°; intensity reduced to 90% MT for 15 daily sessions. Outcomes were measured at baseline, weeks one, two, three, and six. Response rate (response defined as  $\geq 50\%$  improvement in scores on at least two depression scales [MADRS; HAMD, Beck Depression Inventory (BDI)] after three wks of therapy); secondary outcome was overall change in depression rating score. Remission was defined as a score of 10 points or below in all three scales. No difference was found in the responder rates of the real and the sham treatment groups (31% in each) or in the decrease of the scores on the depression rating scales. The authors reported that the data do not support previous reports from smaller samples indicating an augmenting or accelerating antidepressant effect of rTMS.

Loo et al. (2007) studied the efficacy and safety of twice-daily rTMS over two weeks. A total of 38 patients with depression enrolled in a sham-controlled trial of twice-daily rTMS (left prefrontal cortex, 10 Hz, 110% intensity, 1500 stimuli per session) over two weeks. Mood and neuropsychological functioning were assessed weekly by blind raters, using the MADRS as the primary outcome measure, plus HAMD and self-report measures. Two subjects, one sham and one active, withdrew before completion of the two-week blind phase. After the blind period, 22 subjects continued with once-daily rTMS to receive a total of six weeks of active rTMS. The patients were moderately treatment-resistant. Active treatment resulted in significantly greater improvement than sham over the two-week blind period on one outcome measure only (MADRS  $p < 0.05$ ). Subjects showed further improvement over the six weeks of active rTMS. Neuropsychological test scores did not change significantly. The authors reported a limitation of this study is the direct lack of comparison with rTMS given once daily. Also, subjects in this study were not medication-free, although the antidepressants during the trial were medications to which the subjects had failed to respond and were maintained at stable doses over the study period. The authors reported that rTMS given twice daily was effective and safe, with no adverse neuropsychological effects, although further investigations are needed to compare the efficacy of once daily and twice daily rTMS within a single study.

In a six-week randomized sham-controlled trial (n=50) Fitzgerald et al. (2006a) studied the efficacy of sequential bilateral rTMS combining both high-frequency left-sided stimulation (i.e., 15 trains of five seconds' duration at 10 Hz) with low-frequency right-side rTMS (i.e., three trains of 140 seconds' duration at 1 Hz). Forty-two patients had a diagnosis of major depressive episode (unipolar), and eight had a diagnosis of bipolar I disorder, depressive episode (four in each group). Twenty-five patients were in each arm of the study. All patients (unipolar and bipolar) had failed to respond to a minimum of two courses of antidepressant medications for at least six weeks. These courses were required to be at a standard minimum effective dose (e.g., 20 mg/day of

fluoxetine, paroxetine, or citalopram; 150 mg/day of a tricyclic antidepressant; or 125 mg/day of venlafaxine). There was no difference in the proportions of patients taking any of the medication types between the two groups. Patients were not withdrawn from medication prior to treatment. Their dosage of medication was not allowed to change four weeks prior to and during treatment. Twenty patients reported at least one previous ECT treatment course. Half of these patients reported a previously favorable response to ECT, seven reported no response, and three reported a course limited by cognitive side effects. Patients with significant medical illness, neurological disorders, or other axis I psychotic disorders were excluded. For five consecutive days per week, all patients received ten outpatient treatment sessions. After the tenth session, a blind assessment was made classifying patients as initial responders if they achieved a > 20% reduction in score on the MADRS. If the patients met the > 20% reduction in MADRS score, they received another week of rTMS. The patients were assessed on a weekly basis and received further rTMS if they achieved an additional 10% reduction in MADRS score up to a maximum of six weeks of total treatments. Open-label active rTMS under the same treatment conditions was offered for those patients receiving sham stimulation. Five patients in the active group and two patients in the sham group reported a brief headache after one or more treatment sessions. In the active group, three patients reported brief nausea. No adverse events were reported. In the active group, 10/25 patients finished after two weeks, two continued for three weeks, two for four weeks, and 11 for the full six weeks. In the sham group, only seven continued for longer than 2 weeks. Two of these continued into week four, but none progressed further than week four in the study. The response rate in the active group was 44% (11/25) and 8% in the sham group (2/25); ( $p < 0.05$ ). Clinical remission in the active group was 6% (9/25) and in the sham group 0% (0/25); ( $p = 0.005$ ). Therapeutic response increased over a period of six weeks. The study limitations included: small sample size; lack of long-term follow-up period; heterogeneous patient population; slow-responding patients were excluded after two weeks; there was not good information as to the integrity of the blinding after two weeks of treatment, and the clinicians providing treatment were not blind to group; interpretation of the results of this study is complicated by the concurrent medication treatment of most subjects.

Fitzgerald et al. (2006b) conducted a randomized controlled trial of the efficacy of 1 Hz versus 2 Hz right prefrontal cortex rTMS. A total of 130 patients with treatment-resistant depression were randomized to either 1 or 2 Hz rTMS over the right prefrontal cortex for two weeks with a possible further two-week extension. Nonresponders were randomized to either 5 or 10 Hz left prefrontal cortex rTMS. Overall, 66 patients (51%) achieved response and 35 (27%) remission criteria. For right-sided treatment, depression significantly improved, but there was no between-group difference. Twenty-eight (42%) patients in the 1 Hz group and 33 (53%) patients in the 2 Hz group achieved response criteria ( $p > 0.05$ ). Depression symptom scores also improved for patients who crossed over to left-sided treatment, but there was no significant difference in response between 5 and 10 Hz rTMS. The authors reported that, despite a heterogeneous sample, a significant proportion of patients met clinical response criteria following treatment, but response to 1 and 2 Hz did not differ. Two Hz right prefrontal cortex rTMS has antidepressant properties but offers no advantage over 1 Hz despite doubling pulse number.

In a sham-controlled study, Avery et al. (2006) investigated the clinical efficacy of TMS using a more aggressive treatment protocol than was used in previous sham-controlled studies by utilizing a greater intensity of stimulation, greater number of sessions and total pulses. An Investigational Device Exemption was received from the FDA. There were multiple patient exclusions including, but not limited to: patients with active suicide ideation or recent suicide attempt; patients with a history of ECT therapy nonresponse; and chronically depressed patients. Patients had to be age 21–65 and have a diagnosis of major depressive disorder. The patients had to have failed, or been unable to respond to, at least two previous antidepressant trials. Patients had to have a 17-item HAMD score of 17 or more at both screening and treatment day one with a decrease of no more than 20% between these two visits. There were no significant differences between subjects randomized to receive TMS ( $n = 35$ ) and those randomized to receive sham ( $n = 33$ ). The patients received 15 sessions of active or sham rTMS delivered to the left dorsolateral prefrontal cortex at 110% the estimated prefrontal threshold. Each session consisted of 32 trains of 10 Hz rTMS delivered in five-second trains. The primary end point was treatment response defined as a  $\geq 50\%$  decrease in HAMD score at one and two weeks following the final rTMS treatment. Remission was defined as an HAMD score less than eight. Forty-one percent of the TMS group reported pain at the site of stimulation. The response time for the TMS group was 30.6% (11/35) greater than the 6.1% (2/33) rate in the sham group ( $p = 0.008$ ). The remission rate for the TMS group was 20% (7/35) greater than the 3% (1/33) for the sham group ( $p = 0.033$ ). Of the 11 responders to TMS, five did not relapse during the six-month follow-up. Mean HAMD score at six months was 4.6. Of the five active TMS responders, one each relapsed at months one, two, three, four, and five. The authors reported that with this study, and the following study by Fitzgerald et al. (2003), clinically relevant antidepressant responses can be

obtained in TMS studies if higher intensities and more sessions are used. The authors do state more research is needed with larger sample sizes and higher intensities to determine the efficacy of TMS treatment.

Miniussi et al. (2005) studied the efficacy of a five-day treatment regimen with high and low TMS rates in a population of depressed patients. Additionally, the TMS-induced changes in plasma levels of neurotransmitters were evaluated. Seventy-one drug-resistant depressed patients were randomly assigned to low (1 Hz) or high (17 Hz) rate TMS, applied for five days over the left dorsolateral prefrontal cortex. Two study designs were used. One group of 20 patients received active treatment, while the other group entered a double-blind, placebo-controlled, crossover design. Pre- and post-treatment blood samples were taken to evaluate plasma levels of serotonin and dopamine. The authors reported that using the treatment schedule of one week, rTMS produced an antidepressant effect that is not distinguishable from a placebo effect. Also, differences in the type of treatment or clinical response do not correlate with changes in plasma levels of neurotransmitters implicated in mood control. The authors stated that further studies with larger patient populations, and for longer treatment periods, are required to assess the potential benefit of TMS in the treatment of depression.

In a five-week, randomized placebo-controlled trial, Rossini et al. (2005) investigated the efficacy of high frequency rTMS directed to the left prefrontal cortex in drug-resistant depressed patients. Fifty-four patients were randomized to 10 daily applications of real or sham rTMS. Subjects receiving active stimulation were further randomized into subgroups according to the intensity of stimulation: 80% versus 100% of motor threshold. Two patients dropped out of the study due to withdrawal and the other, from the 80% sham group, due to worsening of clinical condition during the first week of treatment. At the end of the study, the response rates were 61.1%, 27.8%, and 6.2% for the 100% motor threshold group, 80% motor threshold group, and sham group, respectively. A significant difference was found between the sham and 100% motor threshold groups, while the 80% motor threshold group did not differ significantly from the sham group.

In a single-center, prospective, double-blind, sham-controlled "add on" trial, Hausmann et al. (2004) concluded that rTMS as an "add on" in the stimulation of depression did not exert an additional antidepressant effect. The efficacy of high-frequency, left-sided repetitive TMS and low-frequency, right-sided TMS to the right prefrontal cortex in treatment-resistant depression was evaluated in a double-blind, randomized, sham-controlled trial conducted by Fitzgerald et al. (2003). Sixty patients were divided into three groups of 20 that did not differ in age, sex, or any other clinical variables. The researchers reported a significant difference in response among the three groups, with a substantial difference between the high-frequency, left-sided repetitive TMS and low-frequency, right-sided TMS groups and the sham group but not between the treatment groups.

In a double-blind controlled study, Loo et al. (1999) examined the efficacy and safety of left prefrontal rTMS for treating resistant major depression. Eighteen subjects were randomly assigned to two weeks of real or sham rTMS, and then permitted up to four weeks of real rTMS. Mood, electroencephalogram (EEG), hearing and neuropsychological function were assessed. The results after two weeks showed no significant difference between groups. The researchers found that four weeks of rTMS yielded progressive improvement and was safe.

**TMS and ECT:** A randomized clinical trial conducted for the National Coordinating Center for Health Technology Assessment (NCCHTA) found that ECT is a more effective antidepressant treatment than three weeks of rTMS (McLoughlin, et al., 2007). Forty-six patients with major depression were randomized to receive a 15-day course of rTMS (n=24) or a course of ECT (n=22). One patient was lost to follow-up at end of treatment and another eight at six months. The end-of-treatment HRSD scores were lower for ECT (95% confidence interval (CI) 3.40–14.05,  $p=0.002$ ), with 13 (59%) achieving remission compared with four (17%) in the rTMS group ( $p=0.005$ ). However, HRSD scores did not differ between groups at six months. Beck Depression Inventory-II, visual analogue mood scales (VAMS), and Brief Psychiatric Rating Scale scores were lower for ECT at the end of treatment and remained lower after six months. Improvement in subjective reports of side-effects following ECT correlated with antidepressant response. There was no difference between the two groups before or after treatment on global measures of cognition. The investigators reported that there was also no difference in gain in quality adjusted life years (QALYs) for ECT and rTMS patients. It should be noted that rater blinding was not maintained and is a potential source of bias. However, similar results were obtained on both observer- and self-rated measures. The optimal parameters for administering rTMS to achieve an antidepressant effect are not yet known.

In a randomized single-blind study, Rosa et al. (2006) compared the efficacy of rTMS and ECT. Forty-two patients between 18 and 65 years of age, referred to ECT due to unipolar non-psychotic depression refractoriness, entered the trial. They were randomly assigned to receive either rTMS or ECT. Depressive symptom changes were blindly measured by HAMD, visual analogue scale for depression and Clinical Global Impression at baseline, after two and four weeks of treatment. There was no difference in the antidepressant efficacy of ECT and rTMS. Response rates were relatively low in both groups (40% and 50% respectively), with no significant difference between them ( $p=0.55$ ). Remission rates were also low for both groups (20% and 10% respectively), also with no significant difference ( $p=0.631$ ). There was no significant difference in the neuropsychological test performance after either one of these therapies. The authors reported that both treatments were associated with a degree of improvement in refractory depression and therefore add to the literature that rTMS can be an effective option to ECT. The authors reported that the limitations of this study were the lack of a placebo group, small sample size, and their neuropsychological battery might not have been adequate to detect memory changes following ECT treatment, especially with unilateral ECT (deficits of orientation, anterograde memory and delayed recall of non-verbal material), or the sample was too small to show this difference.

Eranti et al. (2006) conducted a multicenter randomized controlled trial to test the equivalence of rTMS with ECT. A total of 107 patients met the inclusion criteria with 61 patients declining participation in the study due to clinical decision or they did not want to participate in research. Forty-six patients with major depression referred for ECT were randomly assigned to either a 15-day course of rTMS of the left dorsolateral prefrontal cortex ( $n=24$ ) or a standard course of ECT ( $n=22$ ). The primary outcome measures were the score on the 17-item HAMD and the proportion of patients with remissions (Hamilton score,  $\leq 8$ ) at the end of treatment. Secondary outcomes included mood self-ratings on the Beck Depression Inventory-II and visual analogue mood scales, Brief Psychiatric Rating Scale score, and both self-reported and observer-rated cognitive changes. Follow-up was after six months. Five of the rTMS patients stopped treatment within two weeks because of a perceived lack of benefit. A total of 23 patients were analyzed for primary outcome in the rTMS group. Two patients were lost to follow-up, and one death was noted due to previously diagnosed prostate cancer. A total of 22 patients were analyzed for primary outcome in the ECT group. Six patients were lost to follow-up. The HAMD scores at the end of treatment were significantly lower for ECT, with 13 patients (59.1%) achieving remission in the ECT group and four (16.7%) in the rTMS group. However, at six months, the HAMD scores did not differ between groups. Beck scale, visual analogue mood scale, and Brief Psychiatric Rating Scale scores were lower for ECT at the end of treatment and remained lower after six months. Self- and observer-rated cognitive measures were similar in the two groups. The authors reported that rTMS was not as effective as ECT, and ECT was substantially more effective for the short-term treatment of depression.

Janicak et al. (2002) compared rTMS to ECT in severely ill, depressed patients in a randomized clinical trial. Twenty-five patients with major depression (i.e., unipolar or bipolar) were randomly assigned to rTMS or a course of ECT. The primary outcome measure was the 24-item HAMD. The authors reported that rTMS and ECT had comparable therapeutic effects. Similar conclusions were reported in studies by Grunhaus et al. (2003) and Pridmore et al. (2000).

**Literature Review-Safety of TMS:** Machii et al. (2006) conducted a review of the literature and their own data to assess the safety of rTMS to non-motor areas. The authors identified 173 articles, published between 1998 and 2003, that applied rTMS to non-motor areas. Also, they analyzed data on 249 patients from their own studies between 1997 and 2003. The authors found 74 articles in which the authors reported the presence or absence of adverse events. Overall, headache was the most common adverse event, occurring in 23% of the patients, and more frequently with frontal rTMS. Serious adverse events were rare and consisted of four cases of psychotic symptoms and two seizures induced by rTMS to the dorsolateral prefrontal cortex in patients with depression. The authors concluded that rTMS, as currently applied to non-motor areas, appears to be safe with few adverse events.

**Institute for Clinical Systems Improvement (ICSI):** The 2010 ICSI healthcare guideline titled Major Depression in Adults in Primary Care discusses other therapies for major depression stating that based on work group consensus, the following other strategies are in order of the likely clinical judgment and decision process of a primary care provider (light therapy, ECT, vagus nerve stimulation, rTMS, magnetic seizure therapy, deep brain stimulation, acupuncture). The authors report on the evidence for rTMS stating that "older studies used a protocol of four weeks of rTMS and had more variable results. More recent studies had better results with a longer (six week) protocol." The guideline concludes "at this time it appears there probably is enough evidence

to consider rTMS (as implemented with a protocol that utilizes a six-week standardized protocol) an evidence-based treatment for treatment-resistant depression in adults. It is not a first-line treatment, and there is ongoing lack of clarity about which patient populations should be targeted first-line treatment, and there is ongoing lack of clarity about which patient populations should be targeted (Lisanby, 2009)".

**National Institute for Health and Clinical Excellence (NICE):** In November 2007, the NICE (United Kingdom) issued an interventional procedural guidance document on TMS for severe depression. The authors reported that there are no major safety concerns about TMS. However, there are uncertainties about how to achieve the best results from this procedure, in terms of what intensity of electromagnetic energy should be used, how frequently the procedure should be carried out, how long treatment sessions should last and whether both sides of the brain should be stimulated. For these reasons, NICE has reported that this procedure should only be carried out as part of a research or clinical study that looks at these questions. NICE reports that these research studies should consider how to decide whether the procedure is suitable for certain types of patients, whether other treatments patients are taking affect the results of the procedure, and the long term outcomes of electromagnetic stimulation of the brain.

**Meta-analyses and Reviews:** In a meta-analysis, Slotema et al. (2010) examined if rTMS is effective for various psychiatric disorders. A literature search was performed from 1966 through October 2008. Data were obtained from randomized, sham-controlled studies of rTMS treatment for depression (34 studies, n=751 rTMS and n=632 sham), auditory verbal hallucinations (AVH, seven studies), negative symptoms in schizophrenia (seven studies), and obsessive-compulsive disorder (OCD, three studies). Studies of rTMS versus electroconvulsive therapy (ECT, six studies) for depression. Standardized mean effect sizes of rTMS versus sham were computed based on pre-treatment versus post-treatment comparisons. The mean weighted effect size of rTMS versus sham for depression was 0.55 ( $p < 0.001$ ). Monotherapy with rTMS was more effective than rTMS as adjunctive to antidepressant medication. ECT was superior to rTMS in the treatment of depression (mean weighted effect size -0.47,  $p = 0.004$ ). In the treatment of AVH, rTMS was superior to sham treatment, with a mean weighted effect size of 0.54 ( $p < 0.001$ ). The mean weighted effect size for rTMS versus sham in the treatment of negative symptoms in schizophrenia was 0.39 ( $p = 0.11$ ) and for OCD, 0.15 ( $p = 0.52$ ). Side effects were mild, yet more prevalent with high-frequency rTMS at frontal locations. The authors stated that although the efficacy of rTMS in the treatment of depression and AVH may be considered proven, the duration of the effect is as yet unknown. Effect sizes were measured immediately after the cessation of rTMS treatment. There are indications that the effects of rTMS may last for several weeks to months. The authors reported that although rTMS cannot replace ECT in depressive patients, there may be subgroups in which rTMS can replace antidepressant medication.

A random effects meta-analysis by Schutter et al. (2009) was performed to investigate the clinical efficacy of rTMS over the left dorsolateral prefrontal cortex (DLPFC) in depression. This meta-analysis included 30 double-blind sham-controlled trials with 1164 patients. The clinical trial by O'Reardon et al. (2007) was included in this assessment and is included in this meta-analysis contributing to over one-fourth of the total number of patients. The authors concluded that, "The results show that fast frequency rTMS over the left DLPFC is superior to sham and may be as effective as at least a subset of commercially available antidepressant medications. In addition, TMS is a safe method and because of its few side-effects is well tolerated by patients. However, at this point caution should be exercised because the integrity of blinding and the lack of a proper control condition are considered limitations of rTMS trials. In addition, age bias, medication, suboptimal stimulation parameters, lack of biological information and follow-up assessments may stand in the way of exploiting the effects of rTMS. Nevertheless, ongoing methodological innovations and technological advancements in the field will without doubt further improve the quality and therapeutic efficacy of future rTMS trials. All in all, the present findings suggest that rTMS treatment may be an alternative for patients suffering from major (non-psychotic) depression, and especially for those patients who do not tolerate the side-effects associated with regular pharmacological treatment."

Lam et al. (2008) conducted a systematic review of randomized controlled trials of active rTMS compared with a sham in patients with treatment resistant depression (i.e., at least one failed trial). The primary outcome was clinical response as determined from global ratings, or 50% or greater improvement on a rating scale. Other outcomes included remission and standardized mean differences in end point scores. Meta-analysis was conducted for absolute risk differences using random effects models. Sensitivity and subgroup analyses were also conducted to explore heterogeneity and robustness of results. A total of 24 studies (n=1092 patients) met criteria for quantitative synthesis. Active rTMS was significantly superior to sham conditions in producing clinical response, with a risk difference of 17% and a number-needed-to-treat of 6. The pooled response and remission

rates were 25% and 17%, and 9% and 6% for active rTMS and sham conditions, respectively. Sensitivity and subgroup analyses did not significantly affect these results. Dropouts and withdrawals owing to adverse events were very low. For patients with treatment resistant depression, rTMS appears to provide significant benefits in short-term treatment studies. However, the relatively low response and remission rates, the short durations of treatment, and the relative lack of systematic follow-up studies suggest that further studies are needed before rTMS can be considered as a first-line monotherapy treatment for treatment resistant depression or less refractory cases of depression.

Gross et al. (2007) performed a systematic review and a meta-analysis of the rTMS studies on depression published in the past 12 months comparing these results with an earlier meta-analysis that analyzed the results of the initial rTMS studies on depression. The inclusion criteria included the meta-analysis of Martin et al. (2003) that included 13 studies (324 patients) and five studies for the recent meta-analysis (274 patients). The pooled effect size (standardized mean difference between pretreatment versus post-treatment) from the random effects model was -0.76 (95% confidence interval, CI, -1.01 to -0.51). This result was significantly larger than that of the earlier meta-analysis -0.35, (95% CI) -0.66 to -0.04). The authors concluded that the recent rTMS clinical trials have shown larger antidepressant effects when compared with the earlier studies but larger multicenter studies are still necessary to confirm these trends.

Hermann et al. (2006) conducted a meta-analysis that included prospective studies investigating the effects of rTMS on depressive symptoms in patients. Thirty-three studies met the inclusion criteria. Studies had to be randomized parallel or crossover design with sham control, with both patients and investigators unaware of whether patients were receiving real or sham rTMS. Patients were required to have a diagnosis of depression (i.e., major depressive disorder or bipolar disorder). The studies were required to report their findings using either the HAMD or the MADRS. The authors concluded that studies that have examined rTMS efficacy in the treatment of depression are heterogeneous in terms of outcome, sample characteristics, and treatment parameters. Most of the studies have a small number of participants. Strict double-blinding often cannot be guaranteed because of sham conditions that may be detected by patients. The authors reported that there is as yet no compelling evidence regarding the most effective combination of rTMS parameters and that larger controlled trials are needed with more knowledge regarding the characteristics of patients who benefit from this treatment and the size and persistence of clinical outcomes.

A 2003 Cochrane review assessed the efficacy of rTMS in treating depression. After a systematic review and meta-analysis of published randomized controlled trials comparing rTMS with sham in patients with depression, a total of 16 trials were included in the review, with 14 containing data in a suitable form for quantitative analysis. The HAMD showed an effect that favored rTMS compared to sham after two weeks of treatment, but this was not significant at the two-week follow-up. The authors concluded that current trials are of low quality and provide insufficient evidence to support the use of rTMS in the treatment of depression (Martin, et al., 2003). The Cochrane review conclusion is in accordance with the conclusions from the systematic and meta-analysis of TMS for the treatment of depression conducted by Couturier (2005) and Gershon et al. (2003).

Kozel and George (2002) conducted a meta-analysis to determine whether the literature supports the use of left prefrontal rTMS as a treatment option for depression. Ten of 14 studies (n=230) were suitable for analysis. The authors concluded that, as of the date of this meta-analysis, double-blind published rTMS literature supports the use of left prefrontal rTMS to improve depressive symptoms. The authors discuss that multiple TMS parameters have been used with varying protocol designs. It is not known which TMS parameters maximize effectiveness. The duration of improvement after acute treatment, or whether maintenance rTMS could be used to prolong the benefits of rTMS, is unknown. Also, the relationship between medication use and rTMS is unknown.

McNamara et al. (2001) conducted a meta-analysis to evaluate the effectiveness of repetitive TMS in mood disorders and schizophrenia. Included in the study were five randomized control trials (n=81) and one randomized nonplacebo-controlled trial of patients with mania and a placebo-controlled trial of patients with schizophrenia. The authors concluded that rTMS showed a beneficial effect compared to placebo, although the extent and duration of the antidepressant effect of rTMS needs to be defined. With regard to the treatment of mood disorders and schizophrenia, further studies are needed to evaluate the role of rTMS.

### **Technology Assessment**

In 2010, ECRI updated the 2009 emerging evidence report on repetitive transcranial magnetic stimulation (NeuroStar System) for major depressive disorder. The literature search identified four clinical studies related to

a single multicenter randomized controlled trial (RCT) assessing the NeuroStar TMS Therapy System for major depressive disorder (MDD): a RCT (O'Reardon, et al., 2007); an open-label extension study from the RCT (Avery, et al., 2008); an analysis of clinical predictors of rTMS outcome from the RCT and the open-label extension study (Lisanby, et al., 2009), and an analysis of safety data from the RCT, the open-label extension study, and a six-month durability-of-effect study (Janicak, et al., 2008). Based on this evidence, the report addressed four key clinical questions concluding that, "The data are too limited (one randomized controlled trial [RCT] with a too brief follow-up) to definitively determine whether rTMS is better than sham rTMS for second-line treatment of MDD. At 4 weeks, about 18% of patients receiving rTMS had a 50% or greater reduction in symptoms compared to 11% of patients receiving sham rTMS." The report concludes that no published data are available to determine if rTMS (i.e., NeuroStar TMS Therapy System) significantly reduce symptoms or improve the remission rate compared to other second-line treatments for MDD (i.e., psychotherapy + antidepressant; combination antidepressants; other medications [i.e., lithium, thyroid hormone, stimulants, antipsychotic medications] used to augment the effects of antidepressants). The question if rTMS (i.e., NeuroStar TMS Therapy System) improves response and remission rates in patients with MDD who have not responded to first-line therapy and what are the characteristics of those patients could not be determined because of an insufficient quality and quantity of data. The last key clinical question was what adverse events (AEs) are associated with rTMS (i.e., NeuroStar TMS Therapy System) when used as a second-line treatment for patients with MDD that has not responded to initial therapy. The report concluded that common mild-to-moderate AEs associated with the NeuroStar TMS Therapy System and reported in the studies included application-site pain or discomfort, muscle twitching, toothache, skin pain, facial pain, and eye pain. The overall discontinuation rate at four weeks in the RCT was 7.7% in the active treatment group and 8.2% in the sham treatment group. In the open-label study, the all-cause discontinuation rate was 17.7%, with 9.4% due to AEs (all of which occurred in patients who had been in the sham RCT group and then crossed over to active treatment). Potentially serious AEs that could occur include tissue reaction, seizure, and hearing loss; however, these AEs did not occur in the clinical trials assessed. No evidence was found to suggest that rTMS is associated with the occurrence of treatment-emergent suicidal ideation (ECRI, 2009).

In November 2009, the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) published a Technology Assessment on TMS for depression. A search of the peer-reviewed literature was completed for the period up through May 2009. The literature search was intended to review sham-controlled studies of TMS which included meta-analyses of such trials (Schutter, 2009; Lam, et al., 2008, Gross, et al., 2007; Couturier, 2005, Martin, et al., 2003). The five most recent meta-analyses were selected as was the O'Reardon et al. (2007) clinical trial of the NeuroStar TMS Therapy System. The authors concluded that TMS for the treatment of depression does not meet the technology assessment criteria (BCBSA, 2009).

### **Professional Societies/Organizations**

The updated American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Major Depressive Disorder states that evidence for TMS is currently insufficient to support its use in the initial treatment of major depressive disorder. Electroconvulsive therapy (ECT) remains the treatment of best established efficacy against which other stimulation treatments (e.g., VNS, deep brain stimulation, TMS, other electromagnetic stimulation therapies) should be compared. A substantial number of studies of TMS have been conducted, but most have had small sample sizes, and the studies overall have yielded heterogeneous results. Further complicating the interpretation of the TMS literature is the variability in stimulation intensities (relative to the motor threshold), stimulus parameters (e.g., pulses/second, pulses/session), anatomical localization of stimulation, and number of TMS sessions in the treatment course. As an initial treatment in the acute phase of major depression the guideline reports, "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. 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" (Gelenberg, et al., 2010).

The Canadian network for mood and anxiety treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults recommends that rTMS is a second line therapy to ECT (Kennedy, et al., 2009).

### **Literature Review—Other Psychiatric or Neurological Disorders**

There have been a number of studies and meta-analyses exploring the efficacy of TMS for a selection of neuropsychiatric-related disorders including, but not limited to, the treatment of auditory hallucinations in

schizophrenia (Freitas, et al., 2010; Dlabac-de Lange, et al., 2010; Fitzgerald, et al., 2005, Shonefildt-Lecuona, et al., 2004; Hoffman, et al., 2003; Aleman, et al., 2007), alcohol dependence (Mishra, et al., 2010), chronic pain (O'Connell, et al., 2010), post-traumatic stress disorder (Boggio, et al., 2010; Cohen, et al., 2004), obsessive-compulsive disorder (Rodriguez-Martin, et al., 2003), Parkinson's disease (Filipović, et al., 2010; Fregni, et al., 2004), chronic tinnitus (Marcondes, et al., 2010; Langrebe, et al., 2008; Khedr, et al., 2008), postoperative pain (Borckardt, et al., 2006; Khedr, et al., 2005), acute ischemic stroke (Khedr, et al., 2009, 2010; Fregni, et al., 2006), migraine (Lipton, et al., 2010), spinal cord injury (Kumru, et al., 2010). Some of the methodological limitations of these studies include small sample size, limited follow-up intervals and varied diagnostic groups on and off pharmacotherapy. Therefore, the role of TMS in the treatment of other psychiatric or neurological disorders has not been clearly established. The FDA has not yet cleared or approved for marketing any rTMS device for treatment purposes other than depression (ECRI, 2010).

**Alcohol Dependence:** In a prospective, single-blind, sham-controlled study, Mishra et al. (2010) studied the anticraving efficacy of high-frequency repetitive transcranial magnetic stimulation (rTMS) of the right dorsolateral pre-frontal cortex (DLPFC) in patients with alcohol dependence. A total of 45 patients with alcohol dependence syndrome (according to ICD-10 DCR), with Clinical Institute of Withdrawal Assessment in Alcohol Withdrawal (CIWA-Ar) scores  $\leq 10$ . Patients were allocated to active and sham rTMS in a 2:1 ratio, such that 30 patients received active and 15 patients sham rTMS to the right DLPFC (10 Hz frequency, 4.9 seconds per train, inter-train interval of 30 seconds, 20 trains per session, total 10 sessions). The Alcohol Craving Questionnaire (ACQ-NOW) was administered to measure the severity of alcohol craving at baseline, after the last rTMS session and after one month of the last rTMS session. Two-way repeated-measures analysis of variance (ANOVA) showed significant reduction in the post-rTMS ACQ-NOW total score and factor scores in the group allocated active rTMS compared to the sham stimulation. The effect size for treatment with time interaction was moderate ( $\eta^2 = 0.401$ ). The authors reported that further studies are required to optimize TMS parameters such as frequency of stimulation, number of trains, duration of each train, intertrain interval and number of sessions which will be effective in alcoholism without producing other adverse events.

**Auditory Hallucinations and Schizophrenia:** In a randomized double-blind trial, Fitzgerald et al. (2005) studied 33 patients with treatment-resistant auditory hallucinations. rTMS was applied for 10 consecutive days for 15 minutes at 1 Hz and 90% of the resting motor threshold. It was reported that active treatment did not result in a greater therapeutic effect than sham on any measure except for the loudness of the hallucinations, with a reduction in the active versus the sham group. The authors reported that the study did not support the effectiveness of rTMS using the stimulation parameters provided.

In a cross-over sham controlled study (n=12), Shonefildt-Lecuona et al. (2004) explored the efficacy of stereotaxic rTMS for treating medication-resistant auditory hallucinations in schizophrenia. The authors concluded there was no significant reduction of hallucinations after stereotaxic rTMS.

In a randomized, placebo-controlled, double-blind trial, Hoffman et al. (2003) studied daily TMS to the left temporoparietal lobe for nine days with schizophrenia and schizoaffective disorder (n=24). The authors concluded that rTMS can be administered safely to patients with active schizophrenia and schizoaffective disorder, but further studies are needed regarding possible treatment for patients with auditory hallucinations. Also, additional studies are needed evaluating the interaction of rTMS with psychotropic drugs, and the efficacy of extended protocols that include maintenance rTMS.

Freitas et al. (2010) performed a meta-analysis of all prospective studies of the therapeutic application of rTMS in refractory schizophrenia assessing the effects of high-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC) to treat negative symptoms, and low-frequency rTMS to the left temporo-parietal cortex (TPC) to treat auditory hallucinations (AH) and overall positive symptoms. When analyzing controlled (active arms) and uncontrolled studies together, the effect sizes showed significant and moderate effects of rTMS on negative and positive symptoms (based on PANSS-N or SANS, and PANSS-P or SAPS, respectively). However, the analysis for the sham-controlled studies revealed a small non-significant effect size for negative (0.27,  $p=0.417$ ) and for positive symptoms (0.17,  $p=0.129$ ). When specifically analyzing AH (based on AHRS, HCS or SAH), the effect size for the sham-controlled studies was large and significant (1.04;  $p=0.002$ ). The authors reported that these meta-analyses support the need for further controlled, larger trials to assess the clinical efficacy of rTMS on negative and positive symptoms of schizophrenia, while suggesting the need for exploration for alternative stimulation protocols.

Diabac-de Lange et al. (2010) conducted a meta-analysis to investigate the efficacy of prefrontal rTMS for treating negative symptoms of schizophrenia. A literature search was performed in for the years 1985 through July 2008. Nine randomized controlled trials involving 213 patients were included in the meta-analysis. The overall mean weighted effect size for rTMS versus sham was in the small-to-medium range and statistically significant ( $d = 0.43$ ; 95% CI, 0.05-0.80). When including only the studies using a frequency of stimulation of 10 Hz, the mean effect size increased to 0.63 (95% CI, 0.11-1.15). When including only the studies requiring participants to be on a stable drug regimen before and during the study, the mean weighted effect size decreased to 0.34 (95% CI, 0.01-0.67). Studies with a longer duration of treatment ( $> \text{ or } = 3$  weeks) had a larger mean effect size when compared to studies with a shorter treatment duration:  $d = 0.58$  (95% CI, 0.19-0.97) and  $d = 0.32$  (95% CI, -0.3 to 0.95), respectively. The authors reported that results from this meta-analysis warrant further study of rTMS as a potential treatment of negative symptoms of schizophrenia.

Aleman et al. (2007) conducted a meta-analysis to investigate the efficacy of rTMS treatment of hallucinations. A total of 15 studies were identified that reported empirical data regarding rTMS treatment of auditory hallucinations. Ten of the studies met the inclusion criteria with a total of 212 patients. The authors concluded that rTMS may prove to be a promising method for reducing the frequency and intensity of auditory hallucinations in treatment-resistant patients, but larger clinical trials with follow-up are needed to establish the clinical efficacy of this treatment.

**Migraine:** Lipton et al. (2010) conducted a multi-center, randomized, double-blind, parallel-group, two-phase, sham-controlled study to assess the efficacy and safety of a new portable hand held sTMS device for acute treatment of migraine with aura. A total of 267 adults were enrolled into phase one. All individuals had to meet international criteria for migraine with aura, with visual aura preceding at least 30% of migraines followed by moderate or severe headache in more than 90% of those attacks. A total of 66 patients dropped out during phase one. In phase two, 201 individuals were randomly allocated by computer to either sham stimulation ( $n=99$ ) or sTMS ( $n=102$ ). Participants were instructed to treat up to three attacks over three months while experiencing aura. The primary outcome was pain-free response 2 hours after the first attack, and co-primary outcomes were non-inferiority at 2 hours for nausea, photophobia, and phonophobia. A total of 37 patients did not treat a migraine attack and were excluded from outcome analyses. A total of 164 patients treated at least one attack with sTMS ( $n=82$ ) or sham stimulation ( $n=82$ ; modified intention-to-treat analysis set). Pain-free response rates after 2 hours were significantly higher with sTMS (32/82 [39%]) than with sham stimulation (18/82 [22%]), for a therapeutic gain of 17% (95% CI 3–31%;  $p=0.0179$ ). Sustained pain-free response rates significantly favored sTMS at 24 hours and 48 hours post-treatment. Non-inferiority was shown for nausea, photophobia, and phonophobia. No device-related serious adverse events were recorded, and incidence and severity of adverse events were similar between sTMS and sham groups. The authors report a number of limitations with the study including optimum patterns of use need to be established.

**Post-Traumatic Stress Disorder:** Boggio et al. (2010) conducted a double-blind, placebo-controlled phase II trial. A total of 30 patients with DSM-IV-diagnosed post-traumatic stress disorder (PTSD) were randomly assigned to receive one of the following treatments: active 20 Hz rTMS of the right DLPFC, active 20 Hz rTMS of the left DLPFC, or sham rTMS. Treatments were administered in 10 daily sessions over two weeks. A blinded rater assessed severity of core PTSD symptoms, depression, and anxiety before, during, and after completion of the treatment protocol. In addition, a battery of neuropsychological tests was measured before and after treatment. Results show that both active conditions-20 Hz rTMS of left and right DLPFC-induced a significant decrease in PTSD symptoms as indexed by the PTSD Checklist and Treatment Outcome PTSD Scale; however, right rTMS induced a larger effect as compared to left rTMS. In addition, there was a significant improvement of mood after left rTMS and a significant reduction of anxiety following right rTMS. Improvements in PTSD symptoms were long lasting; effects were still significant at the 3-month follow-up. Neuropsychological evaluation showed that active 20 Hz rTMS is not associated with cognitive worsening and is safe for use in patients with PTSD.

Cohen et al. (2004) studied the efficacy of rTMS of the right prefrontal cortex in patients with (PTSD). For 10 daily sessions over two weeks, 24 patients were randomly assigned to receive rTMS at low frequency (1 Hz) or high frequency (10 Hz). The severity of the PTSD, anxiety, and depression were blindly assessed before, during, and after treatment. The authors concluded that high-frequency rTMS had greater therapeutic effects than sham or low- frequency rTMS.

**Acute Ischemic Stroke:** Khedr et al. (2010) conducted a randomized controlled trial to evaluate the effect of two different frequencies of rTMS on motor recovery and on cortical excitability up to one year post-treatment. Forty-eight patients with acute ischemic stroke were randomly classified into three groups. The first two groups received real rTMS over motor cortex (3 and 10 Hz respectively) of the affected hemisphere and the third group received sham stimulation of the same site, daily for five consecutive days. Disability was assessed before, after fifth sessions, and then after 1, 2, 3 and 12 months. Cortical excitability was assessed for both hemispheres before and after the second and fifth sessions, significant 'rTMS x time' interaction was obtained indicating that real and sham rTMS had different effects on rating scales. This was because real rTMS produced greater improvement than sham that was evident even at one year follow-up. These improvements were associated with changes in cortical excitability over the period of treatment. This is a preliminary study limited by small sample size.

Khedr et al. (2009) conducted a randomized controlled trial to investigate the therapeutic effect of repetitive transcranial magnetic stimulation (rTMS) on post-stroke dysphagia. Twenty-six patients with post-stroke dysphagia due to monohemispheric stroke were randomly allocated to receive real (n=14) or sham (n=12) rTMS of the affected motor cortex. Each patient received a total of 300 rTMS pulses at an intensity of 120% hand motor threshold for five consecutive days. Clinical ratings of dysphagia and motor disability were assessed before and immediately after the last session and then again after one and two months. The amplitude of the motor-evoked potential (MEP) evoked by single-pulse TMS was also assessed before and at one month in 16 of the patients. There were no significant differences between patients who received real rTMS and the sham group in age, hand grip strength, Barthel Index or degree of dysphagia at the baseline assessment. Real rTMS led to a significantly greater improvement compared with sham in dysphagia and motor disability that was maintained over two months of follow-up. This was accompanied by a significant increase in the amplitude of the oesophageal MEP evoked from either the stroke or non-stroke hemisphere. The authors reported that further exploration of stimulus parameters is necessary since the chances that they chose parameters that are optimal in all patients with any type of stroke are very small.

Fregni et al. (2006) conducted a randomized, sham-controlled phase II trial to evaluate the safety and efficacy of five sessions of low-frequency rTMS in stroke patients. Fifteen patients with chronic stroke were randomized to receive active or sham rTMS of the unaffected hemisphere. A blinded rater assessed motor function and corticospinal excitability at baseline, during and after two weeks of treatment. Safety was assessed using a neuropsychologic battery and electroencephalogram. The authors reported that active rTMS resulted in a significant improvement of the motor function performance in the affected hand that lasted for two weeks. These effects were not observed in the sham rTMS group (affected and unaffected hand) and in the unaffected hand in the active rTMS group. Corticospinal excitability decreased in the stimulated, unaffected hemisphere and increased in the affected hemisphere. There was a significant correlation between motor function improvement and corticospinal excitability change in the affected hemisphere. Cognitive performance and electroencephalogram were not changed significantly throughout the trial in both groups of treatment. The authors concluded that these results support and extend the findings of previous studies on rTMS in stroke patients because five consecutive sessions of rTMS increased the magnitude and duration of the motor effects. The authors noted that this increased dose of rTMS is not associated with cognitive adverse effects and/or epileptogenic activity. The authors stated that further studies are needed to investigate stroke patients with different demographic and clinical characteristics.

rTMS or sham stimulation was administered over the motor cortex for 10 days to randomly assigned groups of 26 patients with acute ischemic stroke. Patients also continued their normal treatment. Disability scores before rTMS, at the end of rTMS treatment, and 10 days later showed rTMS improved patients' scores over the sham group. The authors stated further studies are needed with longer follow-up to assess the benefits of rTMS (Khedr, et al., 2005).

**Parkinson's Disease:** In a placebo-controlled, crossover study, with two treatment arms, Filipović et al. (2010) evaluated the delayed (24hour) effects of the left frontal left frontal-rTMS treatment on physiological measures of excitability of the motor cortex. Nine patients with Parkinson's Disease in Hoehn and Yahr stages 2 or 3 and prominent medication-induced dyskinesia were studied. In each of the treatment arms, rTMS (1800 pulses; 1 Hz rate; intensity of the real stimuli just-below the active motor threshold) was delivered over the motor cortex for four consecutive days. Motor cortex excitability was evaluated at the beginning of the study and the next day following each of the four-day rTMS series (real and sham) with patients first in the practically defined "off" state, following 12h withdrawal of medication, and subsequently in a typical "on" state following usual morning

medication dose. Low-frequency rTMS delivered over several consecutive days changes the excitability of motor cortex by increasing the excitability of inhibitory circuits. The effects persist for at least a day after rTMS. The authors reported a need for further studies that would systematically evaluate relevant methodological features able to establish more prominent and longer lasting effects. That is, clinical trials that would involve not only stronger TMS stimuli, but also more days of rTMS and bilateral stimulation.

Fregni et al. (2004) studied the efficacy of TMS in depression in the context of Parkinson's disease. Forty-two patients received 15 Hz plus placebo, or 20 mg/day of fluoxetine plus sham, during 10 days. Both groups showed the same response with regard to mood. TMS showed an effect on depression for eight weeks after the end of the protocol. TMS did not show any motor side effects attributed to fluoxetine. The authors stated that suitable stimulation parameters (i.e., number of stimuli per session, number of sessions per week, and optimum length of a course of stimulation) need to be investigated.

**Obsessive-Compulsive Disorder:** A 2003 Cochrane review of the clinical efficacy of TMS from randomized control trials in the treatment of obsessive-compulsive disorder included three trials with only two suitable for analysis. No difference was seen between rTMS and sham TMS using the Yale-Brown Obsessive-Compulsive Scale or the HAMD. No conclusion could be made due to insufficient data (Martin, et al., 2003).

**Chronic Pain:** In a Cochrane review, O'Connell et al. (2010) evaluated the efficacy of non-invasive brain stimulation techniques in chronic pain. The selection criteria included randomized and quasi-randomized studies of rTMS, if they employed a sham stimulation control group, recruited patients over the age of 18 with pain of three months duration or more and measured pain as a primary outcome. Studies of rTMS (368 participants) demonstrated significant heterogeneity. Pre-specified subgroup analyses suggest that low frequency stimulation is ineffective. A short-term effect on pain of active high-frequency stimulation of the motor cortex in single-dose studies was suggested (standardized mean difference (SMD) -0.40, 95% confidence interval (CI) -0.26–0.54,  $p < 0.00001$ ). This equates to a 15% (95% CI 10%–20%) reduction in pain which does not clearly exceed the pre-established criteria for a minimally clinically important difference (>15%).

**Postoperative Pain:** Twenty gastric bypass surgery patients were randomly assigned to receive 20 minutes of either active or sham left prefrontal rTMS immediately after surgery. Patient-controlled analgesia pump use was tracked, and patients also rated pain and mood twice per day using visual analog scales. Groups were similar at baseline in terms of body mass index, age, mood ratings, pain ratings, surgery duration, time under anesthesia, and surgical anesthesia methods. Significant effects were observed for surgery type (open versus laparoscopic) and condition (active versus sham TMS) on the cumulative amount of patient-delivered morphine during the 44 hours after surgery. Active prefrontal rTMS was associated with a 40% reduction in total morphine use compared to sham during the 44 hours after surgery. The effect seemed to be most prominent during the first 24 hours after cortical stimulation delivery. No effects were observed for rTMS on mood ratings. The authors reported that a single session of postoperative prefrontal rTMS was associated with a reduction in patient-controlled analgesia pump use in gastric bypass surgery patients. The authors reported this is a preliminary study and that additional well-designed studies with larger sample sizes are needed (Borckardt, et al., 2006).

**Spinal Cord Injury:** Kumru et al. (2010) conducted a randomized, double-blind, sham-controlled trial to examine whether the modulation of excitability of the primary motor cortex with high frequency rTMS could modify lower limb spasticity in patients with incomplete spinal cord injury (SCI). Patients were assessed by the Modified Ashworth Scale, Visual Analogue Scale, and the Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET) and neurophysiologically with measures of corticospinal and segmental excitability by the Hmax/Mmax, T reflex, and withdrawal reflex. Fifteen patients received five days of daily sessions of active (n 14) or sham (n 7) rTMS to the leg motor area (20 trains of 40 pulses at 20 Hz and an intensity of 90% of resting motor threshold for the biceps brachii muscle). A significant clinical improvement in lower limb spasticity was observed in patients following active rTMS but not after sham stimulation. This improvement lasted for at least one week following the intervention. Neurophysiological studies did not change.

**Chronic Tinnitus:** TMS is being investigated for the treatment of patients with chronic tinnitus (Marcondes, et al., 2010; Langrebe, et al., 2008; Khedr, et al., 2008).

Marcondes et al., (2010) conducted a double-blind placebo controlled study investigating both immediate and long-term effects of low frequency (1 Hz) rTMS in patients with tinnitus and normal hearing. Using a parallel design, 20 patients were randomized to receive either active or placebo stimulation over the left temporoparietal

cortex for five consecutive days. Treatment results were assessed by using the Tinnitus Handicap Inventory. Ethyl cysteinyl dimethyl single photon emission computed tomography (SPECT) imaging was performed before and 14 days after rTMS. After active rTMS there was significant improvement of the tinnitus score as compared to sham rTMS for up to six months after stimulation. SPECT measurements demonstrated a reduction of metabolic activity in the inferior left temporal lobe after active rTMS. The reported limitation of this study was the control condition. As the sham coil only mimics the sound of active rTMS but lacks the somatosensory sensation, it is not an optimal control condition.

### Professional Societies/Organizations

The American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder states that the use of somatic treatments such as TMS needs additional investigation (Koran, et al., 2007). There has been no update to this practice guideline since 2007.

The APA Practice Guideline for the Treatment of Patients with Schizophrenia states that although rTMS may share beneficial features of ECT and studies with rTMS have shown promising results in decreasing auditory hallucinations, rTMS has a lack of approval by the FDA for the treatment of psychosis, and additional research is recommended before its use in clinical practice (Lehman, et al., 2004). The updated APA Guideline Watch for the Treatment of Patients with Schizophrenia does not mention TMS (Dixon, et al., 2009).

The American Academy of Neurology evidence-based practice parameter for the evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (2006) concludes that there is insufficient evidence to support or refute the efficacy of TMS or ECT in the treatment of depression associated with Parkinson disease (Miyasaki, et al., 2006). There has been no update to this practice parameter since 2006.

### Summary

Studies have been performed assessing TMS for the treatment of major depression disorder (MDD), schizophrenia and other psychiatric and neurological disorders. Evidence in the peer-reviewed literature has concluded that TMS is safe with few adverse events. While TMS is safe, the efficacy of TMS as compared to other treatments (e.g., psychotherapy, pharmacotherapy, electroconvulsive therapy) has not been established for any indication, including depression or other psychiatric disorders. The majority of clinical trials to assess TMS, including sham-controlled trials, have involved small numbers of patients with MDD as the focus of treatment. The majority of studies to date are not consistent in interval of treatment, degree and placement of stimulation and study length, tend to be of short duration with limited follow-up intervals and include varied diagnostic groups on and off pharmacotherapy. There is a lack of published data to determine if TMS significantly reduce symptoms or improve the remission rate compared to other second-line treatments for MDD. As well, no professional organizations have adopted standards for the administration of this treatment and do not recommend its use in routine clinical practice. Therefore, the role of TMS in the treatment of depression, or other psychiatric or neurological disorders, has not been clearly established.

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

### Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
90867	Therapeutic repetitive transcranial magnetic stimulation treatment; planning (code effective 01/01/2011)
90868	Therapeutic repetitive transcranial magnetic stimulation treatment; delivery and management, per session (code effective 01/01/2011)
0160T	Therapeutic repetitive transcranial magnetic stimulation treatment planning (code deleted 12/31/2010)
0161T	Therapeutic repetitive transcranial magnetic stimulation treatment delivery and management, per session (code deleted 12/31/2010)

ICD-9-CM	Description
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<b>Diagnosis Codes</b>	
	All codes

**\*Current Procedural Terminology (CPT®) ©2010 American Medical Association: Chicago, IL.**

## References

1. Aleman A, Sommer IE, Kahn RS. Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis. *J Clin Psychiatry*. 2007 Mar;68(3):416-21.
2. Alonso P, Pujol J, Cardoner N, Benlloch L, Deus J, Menchon JM, et al. Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2001 Jul;158(7):1143-5.
3. American Psychiatric Association (APA) Practice Guidelines. Accessed November 24, 2010. Available at URL address: [http://www.psych.org/psych\\_pract/treatg/pg/prac\\_guide.cfm](http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm)
4. Avery DH, Isenberg KE, Sampson SM, Janicak PG, Lisanby SH, Maixner DF, Loo C, Thase ME, et al. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. *J Clin Psychiatry*. 2008 Mar;69(3):441-51.
5. Avery DH, Holtzheimer PE 3rd, Fawaz W, Russo J, Neumaier J, Dunner DL, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biol Psychiatry*. 2006 Jan 15;59(2):187-94. Epub 2005 Sep 1.
6. Belmaker B, Fitzgerald P, George MS, Lisanby HS, Pascual-Leone A, Schlaepfer TE, Wasserman E. Managing the risks of repetitive stimulation. *CNS Spectrums*. 2003 July;8(7):489.
7. BlueCross BlueShield Association Technology Evaluation Center. Transcranial Magnetic Stimulation for Depression. Assessment Program. 24(5). October 2009. Accessed November 24, 2010. Available at URL address: <http://www.bcbs.com/blueresources/tec/press/transcranial-magnetic-stimulation-depression.html>
8. Boggio PS, Rocha M, Oliveira MO, Fecteau S, Cohen RB, Campanhã C, et al. Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. *J Clin Psychiatry*. 2010 Aug;71(8):992-9.
9. Borckardt JJ, Weinstein M, Reeves ST, Kozel FA, Nahas Z, Smith AR, et al. Postoperative left prefrontal repetitive transcranial magnetic stimulation reduces patient-controlled analgesia use. *Anesthesiology*. 2006 Sep;105(3):557-62.
10. Bretlau LG, Lunde M, Lindberg L, Undén M, Dissing S, Bech P. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. *Pharmacopsychiatry*. 2008 Mar;41(2):41-7.
11. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int J Neuropsychopharmacol*. 2002 Mar;5(1):73-103.
12. Cohen H, Kaplan Z, Kotler M, Kouperman I, Moisa R, Grisaru N. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2004 Mar;161(3):515-24.

13. Couturier JL. Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: a systematic review and meta-analysis. *J Psychiatry Neurosci*. 2005 Mar;30(2):83-90.
14. Dlabac-de Lange JJ, Knegtering R, Aleman A. Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: review and meta-analysis. *J Clin Psychiatry*. 2010 Apr;71(4):411-8.
15. Dixon L, Perkins D, Calmes C. Guideline Watch (November 2009) Practice Guideline for the Treatment of Patients with Schizophrenia. Accessed November 24, 2010. Available at URL address: [http://www.psychiatryonline.com/pracGuide/pracGuideTopic\\_6.aspx](http://www.psychiatryonline.com/pracGuide/pracGuideTopic_6.aspx)
16. Dougherty DD, Rauch SL. Somatic therapies for treatment-resistant depression: new neurotherapeutic interventions. *Psychiatr Clin North Am*. 2007 Mar;30(1):31-7.
17. ECRI Institute. Hotline Response [database online]. Plymouth Meeting (PA): ECRI Institute; 2010 May 13. rTMS for treatment of various movement disorders. Available at URL address: <http://www.ecri.org>
18. ECRI Institute. Repetitive transcranial magnetic stimulation (NeuroStar System) for major depressive disorder. [Emerging Technology evidence report]. Plymouth Meeting (PA): ECRI Institute; updated 2010 September 21. Available at URL address: <http://www.ecri.org>
19. Elata Foundation [website]. TMS—Frequently Asked Questions. 2007. Accessed December 7, 2010. Available at: <http://www.elata.org/tms-faq.shtml>
20. Eranti S, Mogg A, Pluck G, Landau S, Purvis R, Brown RG, et al. A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. *Am J Psychiatry*. 2007 Jan;164(1):73-81.
21. Filipović SR, Rothwell JC, Bhatia K. Slow (1 Hz) repetitive transcranial magnetic stimulation (rTMS) induces a sustained change in cortical excitability in patients with Parkinson's disease. *Clin Neurophysiol*. 2010 Jul;121(7):1129-37.
22. Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry*. 2006a Jan;163(1):88-94.
23. Fitzgerald PB, Huntsman S, Gunewardene R, Kulkarni J, Daskalakis ZJ. A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. *Int J Neuropsychopharmacol*. 2006b Dec;9(6):655-66.
24. Fitzgerald PB, Benitez J, Daskalakis JZ, Brown TL, Marston NA, de Castella A, Kulkarni J. A double-blind sham-controlled trial of repetitive transcranial magnetic stimulation in the treatment of refractory auditory hallucinations. *J Clin Psychopharmacol*. 2005 Aug;25(4):358-62.
25. Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, De Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 2003 Oct;60(10):1002-8.
26. Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, Ferreira MJ, et al. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. *Stroke*. 2006 Aug;37(8):2115-22.
27. Fregni F, Santos CM, Myczkowski ML, Rigolino R, Gallucci-Neto J, Barbosa ER, et al. Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2004 Aug;75(8):1171-4.
28. Freitas C, Fregni F, Pascual-Leone A. Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia. *Schizophr Res*. 2009 Mar;108(1-3):11-24.

29. Gelenberg AJ, Freeman MP, Markowitz JC, Rosenbaum JF, Thase ME, Trivedi MH, et al. American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3<sup>rd</sup> Edition. October 2010. Accessed December 7, 2010. Available at URL address: <http://www.psych.org/guidelines/mdd2010>
30. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry*. 2010 May;67(5):507-16.
31. Gooch CL, Brannagan TH, Pullman SL, Weimer LH. Electromyography, nerve conduction studies, and magnetic stimulation. In: Rowland LP, editor. *Merritt's Neurology*. 12<sup>th</sup> ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010. Ch. 16.
32. Grisar N, Chudakov B, Yaroslavsky Y, Belmaker RH. Transcranial magnetic stimulation in mania: a controlled study. *Am J Psychiatry*. 1998 Nov;155(11):1608-10.
33. Gross M, Nakamura L, Pascual-Leone A, Fregni F. 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 Sep;116(3):165-73.
34. Grunhaus L, Schreiber S, Dolberg OT, Polak D, Dannon PN. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biol Psychiatry*. 2003 Feb 15;53(4):324-31.
35. Hausmann A, Kemmler G, Walpoth M, Mechtcheriakov S, Kramer-Reinstadler KK, Lechner T et al. No benefit derived from repetitive transcranial magnetic stimulation in depression: a prospective, single center, randomized, double blind, sham controlled "add on" trial. *J Neurol Neurosurg Psychiatry*. 2004;75:320-2.
36. Herwig U, Fallgatter AJ, Höppner J, Eschweiler GW, Kron M, Hajak G, et al. Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. *Br J Psychiatry*. 2007 Nov;191:441-8.
37. Hoffman RE, Hawkins KA, Guorguieva R, Boutros NN, Rachid F, Carroll K et al. Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. *Arch Gen Psychiatry*. 2003 Jan;60:49-56.
38. Institute for Clinical Systems Improvement (ICSI). Health care guideline. Major depression in adults in primary care. 13<sup>th</sup> ed. May 2010. Accessed December 7, 2010. Available at URL address: <http://www.icsi.org/index.aspx>
39. Janicak PG, Nahas Z, Lisanby SH, Solvason HB, Sampson SM, McDonald WM, 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 Oct;3(4):187-99
40. Janicak PG, Dowd SM, Martis B, Alam D, Beedle D, Krasuski J, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. *Biol Psychiatry*. 2002; 51:659-67.
41. Janicak PG, O'Reardon JP, Sampson SM, Husain MM, Lisanby SH, Rado JT, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *J Clin Psychiatry*. 2008 Feb;69(2):222-32.
42. Kennedy SH, Milev R, Giacobbe P, Ramasubbu R, Lam RW, Parikh SV, et al; Canadian Network for Mood and Anxiety Treatments (CANMAT). 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 Oct;117 Suppl 1:S44-53.

43. Khedr EM, Ahmed MA, Fathy N, Rothwell JC. Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. *Neurology*. 2005 Aug 9;65(3):466-8.
44. Khedr EM, Rothwell JC, Ahmed MA, El-Atar A. Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: comparison of different stimulus frequencies. *J Neurol Neurosurg Psychiatry*. 2008 Feb;79(2):212-5.
45. Khedr EM, Etraby AE, Hemeda M, Nasef AM, Razek AA. Long-term effect of repetitive transcranial magnetic stimulation on motor function recovery after acute ischemic stroke. *Acta Neurol Scand*. 2010 Jan;121(1):30-7.
46. Khedr EM, Abo-Elfetoh N, Rothwell JC. Treatment of post-stroke dysphagia with repetitive transcranial magnetic stimulation. *Acta Neurol Scand*. 2009 Mar;119(3):155-61.
47. Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB; American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. *Am J Psychiatry*. 2007 Jul;164(7 Suppl):5-53.
48. Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *J Psychiatr Pract*. 2002 Sep;8(5):270-5.
49. Kumru H, Murillo N, Samsó JV, Valls-Sole J, Edwards D, Pelayo R, et al. Reduction of spasticity with repetitive transcranial magnetic stimulation in patients with spinal cord injury. *Neurorehabil Neural Repair*. 2010 Jun;24(5):435-41
50. Lam RW, Chan P, Wilkins-Ho M, Yatham LN. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and metaanalysis. *Can J Psychiatry*. 2008 Sep;53(9):621-31.
51. Landgrebe M, Binder H, Koller M, Eberl Y, Kleinjung T, Eichhammer P, et al. Design of a placebo-controlled, randomized study of the efficacy of repetitive transcranial magnetic stimulation for the treatment of chronic tinnitus. *BMC Psychiatry*. 2008 Apr 15;8:23.
52. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, Kreyenbuhl J; American Psychiatric Association; Steering Committee on Practice Guidelines. Practice guideline for the treatment of patients with schizophrenia, second edition. Accessed December 8, 2010. Available at URL address: [http://www.psych.org/psych\\_pract/treatg/pg/prac\\_guide.cfm](http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm)
53. Lipton RB, Dodick DW, Silberstein SD, Saper JR, Aurora SK, Pearlman SH, et al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. *Lancet Neurol*. 2010 Apr;9(4):373-80.
54. Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*. 2009 Jan;34(2):522-34.
55. Loo CK, Mitchell PB, McFarquhar TF, Malhi GS, Sachdev PS. A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. *Psychol Med*. 2007 Mar;37(3):341-9.
56. Loo CK, Mitchell PB, Croker VM, Malhi GS, Wen W, Gandevia SC, Sachdev PS. Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression. *Psychol Med*. 2003 Jan;33(1):33-40.

57. Loo C, Mitchell P, Sachdev P, McDarmont B, Parker G, Gandevia S. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *Am J Psychiatry*. 1999 June;156(6):946-8.
58. McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, 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 Jul;11(24):1-54.
59. McNamara B, Ray JL, Arthurs OJ, Boniface S. Transcranial magnetic stimulation for depression and other psychiatric disorders. *Psychol Med*. 2001;31(7):1141-6.
60. Machii K, Cohen D, Ramos-Estebanez C, Pascual-Leone A. Safety of rTMS to non-motor cortical areas in healthy participants and patients. *Clin Neurophysiol*. 2006 Feb;117(2):455-71. Epub 2006 Jan 4.
61. Marcondes RA, Sanchez TG, Kii MA, Ono CR, Buchpiguel CA, Langguth B, Marcolin MA. Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: a double-blind controlled, clinical and neuroimaging outcome study. *Eur J Neurol*. 2010 Jan;17(1):38-44.
62. Martin JLR, Barbanoj MJ, Schaelpfer TE, Thompson E, Pérez V, Kulisevsky J. Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis. *Br J Psychiatry*. 2003b;182:480-91.
63. Mayo Clinic. Transcranial Magnetic Stimulation. October 19, 2009. Accessed December 7, 2010. Available at URL address: [http://www.mayoclinic.org/transcranial-magnetic-stimulation/?mc\\_id=comlinkpilot&placement=bottom](http://www.mayoclinic.org/transcranial-magnetic-stimulation/?mc_id=comlinkpilot&placement=bottom)
64. Miniussi C, Bonato C, Bignotti S, Gazzoli A, Gennarelli M, Pasqualetti P, et al. Repetitive transcranial magnetic stimulation (rTMS) at high and low frequency: an efficacious therapy for major drug-resistant depression? *Clin Neurophysiol*. 2005 May;116(5):1062-71.
65. Mishra BR, Nizamie SH, Das B, Praharaj SK. Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: a sham-controlled study. *Addiction*. 2010 Jan;105(1):49-55.
66. Miyasaki JM, Shannon K, Voon V, Ravina B, Kleiner-Fisman G, Anderson K, et al.; Quality Standards Subcommittee of the American Academy of Neurology. 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*. 2006 Apr 11;66(7):996-1002.
67. Mogg A, Pluck G, Eranti SV, Landau S, Purvis R, Brown RG, 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 Mar;38(3):323-33. Epub 2007 Oct 15.
68. National Alliance on Mental Illness. Transcranial Magnetic Stimulation (TMS). October 2009. Accessed December 8, 2010. Available at URL address: [http://www.nami.org/Content/ContentGroups/Helpline1/Transcranial\\_Magnetic\\_Stimulation\\_\(rTMS\).htm](http://www.nami.org/Content/ContentGroups/Helpline1/Transcranial_Magnetic_Stimulation_(rTMS).htm)
69. National Institute for Excellence (NICE). Transcranial magnetic stimulation for severe depression. Interventional Procedure (IP) Number: 346 IP Guidance Number: IPG242. November 28, 2007. Accessed December 8, 2010. Available at URL address: <http://www.nice.org.uk/>
70. NeuroStar TMS Therapy® Accessed December 7, 2010. Available at URL address: <http://www.neurostartms.com/Home.aspx>
71. O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev*. 2010 Sep 8;(9):CD008208.

72. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. 2007 Dec 1;62(11):1208-16. Epub 2007 Jun 14.
73. Pallanti S, Bernardi S, Di Rollo A, Antonini S, Quercioli L. Unilateral low frequency versus sequential bilateral repetitive transcranial magnetic stimulation: is simpler better for treatment of resistant depression? *Neuroscience*. 2010 May 5;167(2):323-8.
74. Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *Int J Neuropsychopharmacol*. 2000 Jun;3(2):129-134.
75. Rowny SB, Lisanby SH. Other brain stimulation methods. In: Sadock BJ, Sadock VA, editors. *Kaplan Sadock Psychiatry*. 9<sup>th</sup> ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009. Part 31.34b
76. Rodriguez-Martin JL, Barbanoj JM, Pérez V, Sacristan M. Transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder. *Cochrane Database of Systematic Reviews* 2003, Issue 2. Art. No.: CD003387. DOI: 10.1002/14651858.CD003387.
77. Rosa MA, Gattaz WF, Pascual-Leone A, Fregni F, Rosa MO, Rumi DO, 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 Dec;9(6):667-76.
78. Rossini D, Lucca A, Zanardi R, Magri L, Smeraldi E. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. *Psychiatry Res*. 2005 Nov 15;137(1-2):1-10. Epub 2005 Oct 12.
79. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one of several treatment steps: A STAR\*D report. *Am J Psych*, 2006 163, 1905-1917.
80. Rutherford BR, Roose SP. Mood disorders. In: Rakel RE, Bope ET, editors. *CONN's Current Therapy* 2009. 1st ed. Philadelphia, PA: W.B. Saunders Co.; 2009. Ch 282.
81. Schonfeldt-Lecuona C, Gron G, Walter H, Buchler N, Wunderlich A, Spitzer M et al. Stereotaxic rTMS for the treatment of auditory hallucinations in schizophrenia. *Neuro Report*. 2004 July 19; 15(10): 1669-73.
82. Schulze-Rauschenbach SC, Harms U, Schlaepfer TE, Maier W, Falkai P, Wagner M. Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression. *Br J Psychiatry*. 2005 May;186:410-6.
83. 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 Jan;39(1):65-75.
84. Schutter DJ, van Honk J. A framework for targeting alternative brain regions with repetitive transcranial magnetic stimulation in the treatment of depression. *J Psychiatry Neurosci*. 2005 Mar;30(2):91-7.
85. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. *J Clin Psychiatry*. 2010 Jul;71(7):873-84.
86. Sohn YH, Hallett M. Transcranial magnetic stimulation. In: Bradley WG, Fenichel GM, Jankovic J, editors. *Neurology in Clinical Practice*. 5<sup>th</sup> ed. Philadelphia, PA: Butterworth-Heinemann; 2008. Ch 35C.

87. The Royal Australian and New Zealand College of Psychiatrists. Transcranial Magnetic Stimulation (TMS). Clinical Memorandum #18. Adopted February 2008. Accessed December 7, 2010. Available at URL address: <http://www.ranzcp.org/>
88. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health (CDRH). Search Devices@FDA. NeuroStar® TMS System. Neuronetics. K061053. Date approved October 7, 2008. Accessed December 8, 2010. Available at: <http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/>
89. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health. Brief Summary from the Neurological Devices Panel Meeting - January 26, 2007. Updated February 5, 2007. Accessed December 8, 2010. Available at URL address: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm124779.htm>
90. U.S. National Institutes of Health (NIH). Transcranial magnetic stimulation: multiple clinical trials. Accessed December 8, 2010. Available at URL address: <http://www.clinicaltrials.gov/ct/search?term=transcranial+magnetic+stimulation>

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## Policy History

<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	7/15/2008	0383	Transcranial Magnetic Stimulation

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