Name of Policy:  
Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric Disorders

Policy #:  170       Latest Review Date:  July 2014  
Category: Medicine       Policy Grade:  A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Transcranial magnetic stimulation (TMS) is a non-invasive method of delivering electrical stimulation to the brain. A magnetic field is delivered through the skull, where it induces electric currents that affect neuronal function. Repetitive TMS (rTMS) is being evaluated as a treatment of depression and other psychiatric/neurologic brain disorders.

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

Interest in the use of transcranial magnetic stimulation as a treatment for depression was augmented by the development of a device that could deliver rapid, repetitive stimulation. Imaging studies had shown a decrease in activity of the left dorsolateral prefrontal cortex (DLPFC) in depressed patients, and early studies suggested that high frequency (e.g., 5–10 Hz) TMS of the left DLPFC had antidepressant effects. Low frequency (1–2 Hz) stimulation of the right DLPFC has also been investigated. The rationale for low frequency TMS is inhibition of right frontal cortical activity to correct the interhemispheric imbalance. A combination approach (bilateral stimulation), or deep stimulation with an H1 coil, is also being explored. In contrast to electroconvulsive therapy, transcranial magnetic stimulation does not require anesthesia and does not induce a convulsion. TMS is also being tested as a treatment for other disorders including alcohol dependence, Alzheimer’s disease, neuropathic pain, obsessive-compulsive disorder (OCD), post-partum depression, depression associated with Parkinson’s disease, stroke, post-traumatic stress disorder, panic disorder, epilepsy, dysphagia, Tourette’s syndrome, schizophrenia, migraine, spinal cord injury, tinnitus, and fibromyalgia. In addition to the potential for altering interhemispheric imbalance, it has been proposed that high frequency rTMS may facilitate neuroplasticity.

NeoPulse, now known as NeuroStar TMS Therapy®, is a non-systemic, non-invasive form of neuromodulation which stimulates nerve cells in an area of the brain that is linked to depression by delivering highly focused MRI-strength magnetic pulses. Patients do not require anesthesia or sedation and remain awake and alert. This is a 40-minute outpatient procedure that is prescribed by a psychiatrist and performed in a psychiatrist’s office and administered daily for four to six weeks.

In October, 2008, the U.S. Food and Drug Administration (FDA) approved NeuroStar TMS (Transcranial Magnetic Stimulation) Therapy System for the treatment of depression. It is specifically indicated for the treatment of major depressive disorder in adult patients who have failed to achieve satisfactory improvement from medication at or above the minimal effective dose and duration in the current episode.
Policy:

Effective for dates of service on or after July 1, 2014:

Repetitive transcranial magnetic stimulation (rTMS) of the brain meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as a treatment of major depressive disorder when ALL of the following conditions have been met:

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

   AND

2. Any one of the following (a, b, c, or d):
   a. Failure of 4 trials of psychopharmacologic agents including 2 different agent classes and 2 augmentation trials; OR
   b. Inability to tolerate a therapeutic dose of medications as evidenced by 4 trials of psychopharmacologic agents with distinct side effects; OR
   c. History of response to rTMS in a previous depressive episode (at least 3 months since the prior episode); OR
   d. Is a candidate for electroconvulsive therapy (ECT) and ECT would not be clinically superior to rTMS (e.g., in cases with psychosis, acute suicidal risk, catatonia or life-threatening inanition rTMS should NOT be utilized);

   AND

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

rTMS for major depressive disorder that does not meet the criteria listed above does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Continued treatment with rTMS of the brain as maintenance therapy does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Transcranial magnetic stimulation of the brain does not meet Blue Cross and Blue Shield of Alabama’s criteria for medical coverage and is considered investigational as a treatment of all other psychiatric/neurologic disorders, including but not limited to bipolar disorder, schizophrenia, obsessive-compulsive disorder, or migraine headaches.

Repetitive transcranial magnetic stimulation should be performed using an FDA-cleared device in appropriately selected patients, by physicians who are adequately trained and experienced in the specific techniques used. A treatment course should not exceed 5 days a
week for 6 weeks (total of 30 sessions), followed by a 3-week taper of 3 TMS treatments in week 1, 2 TMS treatments the next week, and 1 TMS treatment in the last week.

**Contraindications to rTMS include:**

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

**The following should be present for the administration of rTMS:**

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

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**Effective for dates of service prior to July 1, 2014:**

Transcranial magnetic stimulation of the brain does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as treatment of depression and/or other psychiatric disorders and is considered **investigational.**

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**

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

Martin et al (2003) conducted a systematic review of randomized controlled trials that compared rTMS with sham in patients with depression. 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. This is in accordance with the observations of Fitzgerald and colleagues (2002) who noted that TMS has a considerable role in neuropsychiatric research. It appears to have considerable potential as a therapeutic tool in depression, and perhaps a role in several other disorders, although widespread application requires larger trials and establishment of sustained response, as well as Gershon et al (2003) who stated that TMS shows promise as a novel antidepressant treatment. Systematic and large-scale studies are needed to identify patient populations most likely to benefit and treatment parameters most likely to produce success.

Pascual-Leone et al (1996) performed a sham controlled study that included a crossover design, enrolling 17 patients with medication-resistant depression of psychotic subtype. Nine of the patients had previously responded to electroconvulsive therapy (ECT). An attempt was made to withdraw medication before the TMS therapy but that was not possible in all patients, and some patients required reintroduction of medications during the trial. To create sham stimulation, the magnetic coil was held obliquely to the scalp surface, which mimicked the sensation of “real” TMS, but did not induce an intracerebral current. Each course of TMS consisted of five sessions over five consecutive days. The patients received five different courses of TMS, both real and sham, each applied at different scalp positions. The authors concluded that stimulation of the dorsal left prefrontal cortex and marked antidepressant effect, with 11 of 17 patients showing a decline in Hamilton Depression Rating Scale scores of 50%.

George et al (1997) reported the results of a placebo-crossover trial in 12 medication resistant depressed patients who sequentially underwent TMS of the left prefrontal cortex or sham treatment. Each treatment course consisted of ten sessions over a two-week period followed by crossover to the other study arm. There was a modest decline in Hamilton Depression Rating Scale scores when the subjects received active treatment.

Klein et al (1999) conducted a randomized placebo-controlled trial in 70 patients with depression who were assigned to receive active or sham TMS. The stimulation parameters used in this study, described as “slow” (<1 Hz) were different than the above studies, which used “fast” (>1 Hz) stimulation. In addition, sham TMS consisted of stimulation over the right (as opposed to left) prefrontal cortex using a differently designed coil. Treatment consisted of 10 daily sessions over a two-week period. At the end of the study, 41% of those in the treatment group reported at least a 50% reduction in Hamilton Depression Rating Scale scores compared to 17% of those in the sham-treated group.

Loo et al (2003) reported conflicting results from a double-blind study of 18 depressed adults who were randomly assigned to a two-week course of real or sham TMS, using the same stimulation parameters as Pascual-Leone, reviewed above. Both groups improved significantly during the two-week study period.

While these studies suggest the potential of TMS as a treatment of depression, larger placebo controlled trials of a homogeneous group of patients are needed to further define the optimal
stimulation parameters and validate a treatment effect. All of the above studies only examined the treatment effect immediately after the study ended, so durability of results is also unknown. The role of TMS in the overall treatment of depression requires further study. For example, it is not known whether TMS would be used as an alternative to electroconvulsive therapy or as an adjunct to partially effective pharmacologic therapy.

A Cochrane Review (2002) concluded in a review of 16 published trials that there is no strong evidence for benefit from using TMS for depression, finding no difference between TMS and sham TMS based on results of the Beck Depression Inventory or Hamilton Depression Rating Scale HAM-D. In addition, the Cochrane Review found electroconvulsive therapy was more effective than TMS. Studies and review of studies found no or even modest clinically significant difference between TMS and sham TMS treatment. Studies comparing ECT to TMS found that response rates and relapse rates for depression were comparable or that ECT is more effective. Several studies found no or minimal effect of TMS on other neuropsychiatric disorders such as other mood disorders, post-traumatic stress disorders, and schizophrenia.

Slotema et al (2010) examined if rTMS is effective for various psychiatric disorders. A literature search was performed from 1996 through October 2008. Data was obtained from randomized, sham-controlled studies of rTMS treatment for depression (34 studies), auditory verbal hallucinations (AVH, seven studies), negative symptoms in schizophrenia (seven studies), and obsessive-compulsive disorder (OCD, three studies). Studies of rTMS versus electro-convulsive therapy (ECT, six studies) for depression were meta-analyzed. 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. Monotherapy with rTMS was more effective than rTMS as an adjunctive to antidepressant medication. Electro-convulsive therapy was superior to rTMS in the treatment of depression (mean weighted effect size -0.47). In the treatment of AVH, rTMS was superior to sham treatment, with a mean weighted effect size of 0.54. The mean weighted effect size for rTMS versus sham in the treatment of negative symptoms in schizophrenia was 0.39 and for OCD, 0.15. Side effects were mild, yet more prevalent with high-frequency rTMS at frontal locations. While the authors concluded that it is time to provide rTMS as a clinical treatment method for depression, for auditory verbal hallucinations, and possibly for negative symptoms, they do not recommend rTMS for the treatment of OCD. Furthermore, the authors also 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. Future studies should assess symptom relief with longer follow-up periods to assess the cost-effectiveness of rTMS treatment, and to indicate its economic advantages and disadvantages. Although rTMS cannot replace ECT in depressive patients, there may be subgroups in which rTMS can replace antidepressant medication.

Triggs et al (2010) reported on a prospective, randomized, sham-controlled study of right or left pre-frontal rTMS in 48 patients with medication-resistant depression. Overall reductions in the HAM-D24 from baseline to three months were not different between rTMS and sham treatment groups. In this small study, right cranial stimulation was significantly more effective than left
cranial stimulation. This study does not add substantial new information to the existing body of evidence.

Janicak et al (2010) reported on the durability of antidepressant effect and the assessment of relapse after acute response to TMS in patients with major depressive disorder (MDD). In this study, patients who met criteria for partial response during either a sham-controlled or open-label phase of a prior study were tapered from rTMS and simultaneously started on maintenance antidepressant monotherapy. They were then followed for 24 weeks. Ten of 99 patients relapsed. Thirty-eight patients had symptom worsening and 32 of these (84%) had symptomatic benefit with adjunctive rTMS. Additional data are needed related to durability of effect and to maintenance phases.

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

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

Lam et al (2008) performed a systematic review and meta-analysis to examine the effectiveness of rTMS for treatment-resistant depression (TRD). They identified published randomized controlled trials of active rTMS, compared with a sham control condition in patients with defined TRD. The primary outcome was clinical response as determined from global ratings, or 50% or greater improvement on a rating scale. 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 six. The pooled response and remission rates were 25% and 17% respectively, for the sham conditions. The authors concluded that for patients with TRD, 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 suggested that further studies are needed before rTMS can be considered as a first-line monotherapy treatment for TRD. These conclusions are in agreement with the observations of two other researchers.

One double-blind multicenter study (23 study sites) by O’Reardon et al (2007) randomized 325 treatment-resistant depressed patients to daily sessions of high frequency active or sham rTMS (Monday to Friday for six weeks) of the left dorsolateral prefrontal cortex (left DLPCF). 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. Intent-to-treat analysis showed no significant difference between the active and sham groups in the primary outcome measure (two points on the Montgomery-Asberg Depression Rating Scale) and a modest (two-point) improvement over sham treatment on the Hamilton Rating Scale for Depression (HRSD). Following six weeks of treatment the patients in
the active rTMS group were more likely to have achieved remission (14% vs. 5%). Another multcenter double-blind trial randomized 130 patients with treatment-resistant depression to five sessions per week of either 1- or 2-Hz rTMS over the right DLPFC. Sixty-eight patients (52%) completed four weeks of treatment; there was an approximate 30% improvement in depression scales, with no differences between the 1- or 2-Hz groups. Due to large placebo effects for this type of intervention, the absence of a sham control group limits interpretation.

In 2010, George et al reported a randomized sham-controlled trial that involved 199 patients treated with left-prefrontal rTMS. This was a multcenter study involving patients with a moderate level of treatment resistance. The response rate using an ITT analysis was 14% for rTMS and 5% for sham (p=0.02). In this study, the site for stimulation was determined through pretreatment magnetic resonance imaging (MRI). Results from Phase 2 (open treatment of nonresponders) and Phase 3 (maintenance and follow-up) will be reported in the future. Another randomized sham-controlled double-blind trial was conducted in sixty-eight patients who had failed at least two courses of antidepressants. Three patients in each group did not complete the 15 treatment sessions or were excluded due to a change in medication during treatment, resulting in 91% follow-up. Independent raters found a clinical response in 31% (11 of 35) of the active rTMS patients and 6% (2 of 33) of the sham group. The average change in HAM-D was 7.8 for the active group and 3.7 for the control group. The Beck Depression Inventory (BDI) decreased by 11.3 points in the active rTMS group and 4.8 points in controls. Remission was observed in seven patients (20%) in the active rTMS group and one patient (3%) in the control group. Regarding effectiveness of blinding; 15% of subjects in each group guessed they were receiving active TMS after the first session. After the 15th session, 58% of the rTMS group and 43% of the sham group guessed they had received active TMS; responders were more likely than nonresponders (85% vs 42%, respectively) to think that they had received the active treatment. The 11 responders were treated with antidepressant medication and followed up for six months. Of these, one was lost to follow-up, five (45%) relapsed, and five (45%) did not relapse.

Rossini et al (2005) reported on a randomized, double-blind, placebo-controlled trial to investigate the efficacy and tolerability of high frequency rTMS to the left prefrontal cortex in drug-resistant depressed patients. There were 54 patients who had failed at least two adequate courses of antidepressants. Patients were randomly assigned to receive active rTMS or sham control at 80% or 100% of motor threshold (MT) for ten sessions over a two week period. Double-blind evaluation found an intensity-dependent response with 6% (1 of 16) of the sham, 28% (5 of 18) of the 80% MT, and 61% (11 of 18) of the 100% MT groups showing improvement of 50% or more over a five-week evaluation. All of the patients reported that they were unaware of the differences between sham and active stimulation.

McLoughlin et al (2007) reported on a United Kingdom National Institute for Health Research health technology assessment that compared efficacy and cost-effectiveness of rTMS and ECT. Forty-six patients who had been referred for ECT were randomized to either ECT (average of 6.3 sessions) or a 15-day course (five treatments per week) of rTMS of the left DLPFC. ECT resulted in a 14-point improvement in the HRSD and a 59% remission rate. rTMS was less effective than ECT (five-point improvement in HRSD and a 17% remission rate). Rosa et al (2006) published another study that reported no significant difference between ECT and rTMS in
42 patients with treatment-resistant depression; however, response rates for both groups were low. The number of remissions (score of seven or less on the HRSD) totaled three (20%) for ECT and two (10%) for rTMS. The evidence is insufficient to support efficacy of rTMS for depression and none of the devices have been FDA-approved for this indication.

Herwig et al (2007) reported on a randomized, double-blind, sham-controlled multicenter trial that included 127 patients with moderate to severe episodes and were randomly assigned to real or sham stimulation for three weeks in addition to simultaneously initiated antidepressant medication. There was no difference in the responder rates of the real and the sham treatment groups or in the decrease of the scores on the depression rating scales. The authors concluded that the data did not support previous reports from smaller samples indicating an augmenting or accelerating antidepressant effect of rTMS. Further exploration of the possible efficacy of other stimulation protocols or within selected sub-populations of patients is necessary. Mogg et al (2008) performed a randomized controlled trial comparing real and sham adjunctive rTMS with four-month follow-up. Fifty-nine patients with major depression were randomly assigned to a ten-day course of either real or sham rTMS of the left dorsolateral prefrontal cortex (DLPFC). From the results, the authors concluded that adjunctive rTMS of the left DLPFC could not be shown to be more effective than sham rTMS for treating depression. Demirtas-Tatlidede et al (2008) studied the impact and efficacy of rTMS in the treatment of major depressive disorder (MDD) and relapses. Sixteen medication-free patients with refractory MDD who had previously been treated for ten days with rTMS and had clinically significant antidepressant responses to the treatment were followed for four years. The cohort was studied during 64 episodes of relapse. The Hamilton Rating Scale for Depression (HAM-D) and the Beck Depression Inventory (BDI) were used for evaluation during and after each rTMS treatment. A clinically significant response was defined as a reduction in the HAM-D score of at least 50%. About half of the patients individually sustained a clinically significant response to the repeated courses of rTMS. The authors concluded that with repeated rTMS applications have demonstrated a reproducible antidepressant effect in patients with refractory depression who initially had a response to rTMS. The duration of effect varied across patients, but benefits were sustained for mean of nearly five months. More studies with larger cohorts will be useful in determining the long-term effectiveness of rTMS maintenance therapy.

Daskalis et al (2008) also reviewed recent meta-analyses and large multicenter studies which provided evidence that rTMS is a promising treatment for TRD, but has only modest therapeutic efficacy. They suggested that more studies are needed to address current limitations of rTMS and to optimize the effectiveness of this promising therapeutic option in TRD. They also suggested that research is needed to investigate the mechanisms of therapeutic efficacy of rTMS.

Loo, et al (2008) published a review of the safety of rTMS as a clinical treatment for depression. They reviewed all published, sham controlled, rTMS depression trials for reported side effects, outcomes of neuropsychological testing, reports of seizures. They noted that the long-term effects of repeated rTMS sessions are as yet unknown. When given within recommended guidelines, the overall safety profile of rTMS is good and supports its further development as a clinical treatment. Knapp et al (2008) reported that electroconvulsive therapy is more cost-effective than rTMS in the treatment of severe depression.
Demitrach and Thase (2009) studied the clinical significance of the treatment effects seen with TMS in pharmaco-resistant major depression in their recently completed studies by comparing those outcomes with the results reported in several large, comprehensive published reference data sets of antidepressant medications studied in both treatment-responsive and treatment-resistant patient populations. The efficacy of TMS reported in randomized controlled trials was comparable to that of antidepressants studied in similarly designed registration trials and to the adjunctive use of atypical antipsychotic medications in controlled trials of antidepressant non-responders. The authors noted that these data may be helpful in treatment-planning decisions when using TMS in clinical practice.

Fitzgerald et al (2009) reported on a small double-blind randomized trial that suggests that specific targeting of Brodman areas nine and 46 may enhance the anti-depressant response compared with the standard targeting procedure, i.e., measuring five cm anterior from the motor cortex. Fifty-one patients who had failed at least two six-week courses of antidepressant medication (average 5.7 failed courses) were randomized to a standard localization procedure or to structural MRI-aided localization for three weeks (with one-week extension if > 25% reduction on the MADRS). Six patients in the targeted group and ten in the standard group withdrew due to lack of response. A single patient in the targeted group and five in the standard group withdrew for other reasons, resulting in 17 patients in the targeted group and 12 in the standard group continuing for the full four weeks of treatment. To adjust for the imbalance in discontinuation rates, a mixed model statistical analysis was used. There was a significant difference between the groups in the overall mixed model analysis, and planned comparisons showed significant improvement in MADRS scores for the targeted group at four weeks. Response criteria were met by 42% of the targeted group and 18% of the standard group. Remission criteria were met by 30% of the targeted group and 11% of the standard group. Although encouraging, additional trials with a larger number of subjects are needed to evaluate this procedure.

**Deep TMS of the Left DLPFC for TRD**

The RCT leading to 510(k) clearance of the Brainsway deep TMS system was conducted at 20 centers in the U.S. (n=13), Israel (n=4), Germany (n=2), and Canada (n=1). The study included 229 patients with major depressive disorder who had not received benefit from one to four antidepressant trials or were intolerant to at least two antidepressant treatments. Per protocol analysis, which excluded 31 patients who did not receive adequate TMS treatment and 17 patients who did not meet the inclusion/exclusion criteria, showed a significant benefit for both response rate (38.4% vs 21.4%) and remission rate (32.6% vs 14.6%). Modified ITT analysis, which excluded the 17 patients who did not meet the inclusion/exclusion criteria, showed a significant benefit in both response rate (37% vs 22.8%) and remission rate (30.4% vs 15.8%). At the end of the maintenance period (16-week follow-up), the response rate remained significantly improved by deep TMS. Remission rates were not reported. ITT analysis found no significant benefit of treatment at four or 16 weeks.

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

Fitzgerald et al (2003) randomized 60 patients who had failed a minimum of at least two six-week courses of antidepressant medications into one of three groups; high frequency left rTMS,
low frequency right rTMS, or sham stimulation over ten sessions. All patients who entered the study completed the double-blind randomized phase, which showed no difference between the two active treatments (left: 13.5% reduction; right: 15% reduction) and greater improvements in the Montgomery-Asberg Depression Rating Scale (MADRS) scores compared to the sham group (0.76% reduction). Only one patient achieved 50% improvement during the initial two weeks. Then, only the subjects who showed at least 20% improvement at the end of the ten sessions (15 active and two sham) continued treatment. Patients who did not respond by at least 20% were switched to a different active treatment. From week two to week four there was greater improvement in the low frequency right rTMS group compared with the high frequency left rTMS group (39% vs. 14% improvement in MADRS). Seven patients (18% of 40) showed a clinical response of >50% by the end of the four weeks. In a subsequent study Fitzgerald and colleagues randomized 50 patients with treatment-resistant depression to sequential bilateral active or sham rTMS. After two weeks of treatment, three subjects had dropped out of the sham treatment group and there was a slight but non-significant improvement favoring the active group for the MADRS (26.2 vs. 30.9) and the BDI (18.3 vs. 21.6). At this time point, 60% of subjects receiving active rTMS and 50% of subjects receiving sham treatment guessed that they were in the active group. The clinical response was reported by subjects as the major reason for their guess, with 11 of 13 responders (nine active and two sham) guessing that they were in the active group. As in the earlier study, only the subjects who showed at least 20% improvement at the end of each week continued treatment. Treatment on week three was continued for 15 subjects in the active group and seven subjects in the sham group. By week six, 11 subjects in the active rTMS remained in the study, with no control subjects remaining. Final ratings for the 11 subjects who continued to respond through week six were 8.9 on the MADRS and 9.2 on the BDI.

Fitzgerald et al (2006) reported on another multicenter double-blind trial that randomized 130 patients with TRD to five sessions per week of either 1- or 2-Hz rTMS over the right dorsolateral prefrontal cortex. Sixty-eight patients (52%) completed four weeks of treatment; there was an approximate 30% improvement in depression scales, with no differences between the 1- or 2-Hz groups. Due to the potential for placebo effects for this type of intervention, the absence of a sham control group limits interpretation.

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

rTMS as an Adjunctive Treatment for Moderate to Severe Depression

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

A 2012 study examined the efficacy of ultra-high-frequency (30 Hz) rTMS over the left prefrontal cortex in moderate to severely depressed patients who were taking medication. Sham treatment consisted of low-frequency stimulation to the left prefrontal cortex. No benefit of rTMS for depressive symptoms was found when lithium was added as a covariate. Ultra-high-frequency rTMS was found to improve performance on the Trail-Making Test, which covaried with improvement of psychomotor retardation. Additional research on whether adjunctive rTMS can improve response to pharmacologic treatment as a first-line therapy is needed.

**Maintenance Therapy**

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

Fitzgerald et al reported a prospective open-label trial of clustered maintenance rTMS for patients with refractory depression. All patients had received a second successful course of rTMS following relapse, and were then treated with monthly maintenance therapy consisting of five rTMS treatments over a 2.5-day period (Friday evening, Saturday and Sunday). Patients were treated with maintenance therapy of the same type that they had initially received (fourteen high frequency to the left dorsolateral prefrontal cortex, twelve low frequency to the right dorsolateral prefrontal cortex, and nine bilateral). The primary outcome was the mean duration until clinical relapse, addition or change of antidepressant medication, or withdrawal from maintenance treatment to pursue other treatment options. Out of 35 patients, 25 (71%) relapsed at a mean of 10.2 months (range, 2 to 48 months), which was substantially shorter than the interval (< 3 months) for relapse from the initial treatment.

A variety of maintenance schedules are being studied. Richieri et al used propensity-adjusted analysis of observational data and found that the group of patients who had maintenance rTMS tapered over 20 weeks (from three times per week to once a month) had a significantly reduced relapse rate compared with patients who had no additional treatment (37.8% vs 81.8%). A retrospective study that included maintenance rTMS was reported by Connolly et al in 2012. Out of the first 100 cases treated at their institution, 42 received maintenance rTMS. Most of the patients had failed more than one adequate antidepressant trial and were treated with high frequency rTMS over the dorsolateral prefrontal cortex. Low frequency rTMS to the right dorsolateral prefrontal cortex was given in patients with a family or personal history of seizures and in some patients who were also receiving high frequency rTMS. The response rate was 50.6% of the first 100 cases and the remission rate was 24.7%. Maintenance treatment (42
patients) was tapered gradually from two sessions per week for the first three weeks to monthly. At six months after the initial rTMS treatment, 26 of the 42 patients (62%) maintained their response.

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

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

**Attention-Deficit/Hyperactivity Disorder**
In 2012, Weaver et al reported a randomized sham-controlled crossover study of rTMS in nine adolescents/young adults with attention-deficit/ hyperactivity disorder (ADHD). rTMS was administered in ten sessions over two weeks, with one week of no TMS between the active and sham phases. The clinical global impression and ADHD-IV scales improved in both conditions over the course of the study, with no significant differences between the active and sham phases.

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

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

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

**Epilepsy**

In 2012, Sun et al reported a randomized double-blind controlled trial of low frequency rTMS to the epileptogenic zone for refractory partial epilepsy. Sixty patients were randomized into two groups; one group received two weeks of rTMS at 90% of resting motor threshold and the other group received rTMS at 20% of resting motor threshold. Outcomes were measured for eight weeks after the end of treatment. With intent-to-treat analysis, high intensity rTMS resulted in a significant decrease in seizures when compared to baseline (from 8.9 per week at baseline to 1.8 per week at follow-up) and when compared to low intensity rTMS (from 8.6 at baseline to 8.4 per week at follow-up). High intensity rTMS also decreased interictal discharges (from 75.1 to 33.6 per hour) and improved ratings on the Symptom Checklist-90. These initial results are promising, but require substantiation in additional trials.

**Fibromyalgia**

In 2011, Short et al evaluated the efficacy of adjunctive rTMS as a treatment for fibromyalgia pain in a small randomized controlled pilot study. Twenty patients with fibromyalgia, defined by the American College of Rheumatology criteria, were randomized to ten sessions of left prefrontal rTMS or sham TMS along with their standard medications. At two weeks after treatment, there was a significant change from baseline in average visual analog scale (VAS) for pain in the rTMS group (from 5.60 to 4.41) but not in the sham-treated group (from 5.34 to 5.37). There was also a significant improvement in depression symptoms in the active group compared to baseline (from 21.8 to 14.10) but not in the sham group (from 17.6 to 16.4). There were no statistically significant differences between the groups in this small trial. Additional study with a larger number of subjects is needed.

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

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

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

**Migraine Headache**

A pivotal randomized, double-blind, multicenter, sham-controlled trial was performed with the Cerena™ TMS device to demonstrate safety and effectiveness for the de novo application. Enrolled in the study were 201 patients with a history of an aura preceding more than 30% of headaches with moderate or severe headache severity for approximately 90% of migraine attacks. Following a month baseline phase to establish the frequency and severity of migraine, patients were randomized to a treatment phase consisting of three treatments or three months, whichever occurred first. Patients were instructed to treat their migraine headache during the aura phase and to record their pain severity (0 to 3), severity of associated migraine symptoms (photophobia, phonophobia, nausea), presence of vomiting, and use of rescue medications at the time of treatment and at 1, 2, 24, 48 hours after treatment. The primary end point was the proportion of patients who were pain free two hours after treatment. Of the 201 patients enrolled, 164 recorded at least one treatment and 113 recorded at least one treatment when there was pain. Post hoc analysis of these 113 patients showed a benefit of the device for the primary end point (37.74% pain free after two hours for Cerena™ and 16.67% for sham, p=0.018) and for the proportion of subjects who were pain free after 24 hours (33.96% for Cerena™ and 10% for sham, p=0.002). Active treatment was not inferior to sham for the proportion of subjects free of photophobia, suggesting that the device does not worsen photophobia. However, the device was not non-inferior to sham for the proportion of subjects free of nausea and phonophobia.

These results are limited by the 46% drop-out rate and post hoc analysis. According to the FDA labeling, the device has not been demonstrated as safe or effective when treating cluster headache, chronic migraine headache, or when treating migraine headache during the aura phase. The device has not been demonstrated as effective in relieving the associated symptoms of migraine (photophobia, phonophobia, nausea).

**Obsessive-Compulsive Disorder**

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

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

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

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

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

A 2013 exploratory multicenter double-blind trial randomized 106 patients to eight weeks of 1-Hz rTMS, 10 Hz rTMS, or sham stimulation over the supplementary motor area. At nine weeks, all groups showed a similar amount of improvement. At the 20-week follow-up, only the 1 Hz group showed a significant improvement (6.84 points) in the primary outcome measure, the UPDRS part III. There was no significant improvement in other outcome measures.
Additional study with a larger number of subjects and longer follow-up is needed to determine if rTMS improves motor symptoms in patients with Parkinson disease.

**Postpartum Depression**

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

**Post-traumatic Stress Disorder**

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

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

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

In another double-blind trial, 30 patients with PTSD were randomized to deep, high frequency rTMS after brief exposure to a script of the traumatic event, rTMS after a script of a non-traumatic event, or sham stimulation after a brief script of the traumatic event. Patients received three treatment sessions per week for four weeks, and response was defined as a 50% or greater improvement in CAPS score. Intent-to-treat analysis showed a significant improvement in the total CAPS score in the exposure + stimulation group (24.3) compared to rTMS alone (7.9) or traumatic exposure with sham rTMS (9.1). The greatest improvement was in the intrusive component of the CAPS scale. Heart rate responses to the traumatic script were also reduced over the four weeks of treatment. The proportion of patients who showed a response to treatment was not reported and the durability of the response was not assessed.
Several small randomized controlled trials have reported improvement of PTSD with rTMS over the right dorsolateral cortex. Results of high frequency versus low frequency stimulation are conflicting, and durability of the response has not been assessed. Additional study is needed.

**Schizophrenia**
The largest area of TMS research outside of depressive disorders appears to be treatment of auditory hallucinations in schizophrenia resistant to pharmacotherapy. Tranulis et al (2008) published a meta-analysis that included six double-blind sham-controlled and four crossover controlled trials, reporting encouraging results. Two small (n = 14 and 18) randomized sham-controlled trials found no evidence of efficacy for treatment of bulimia nervosa or obsessive compulsive disorder (OCD), although another small sham-controlled trial (n=21) reported promising results with bilateral stimulation of the supplementary motor area in patients with medication-resistant OCD. Initial results from another small randomized controlled trial suggest that TMS may be able to abort migraine with aura. These results will need to be confirmed in larger randomized studies.

In 2011, TEC published an Assessment of TMS as an adjunct treatment for schizophrenia. Five meta-analyses were reviewed, along with randomized controlled trials (RCTs) in which measurements were carried out beyond the treatment period. A meta-analysis of the effect of TMS on positive symptoms of schizophrenia (hallucinations, delusions, and disorganized speech and behavior) did not find a significant effect of TMS. Four meta-analyses that looked specifically at auditory hallucinations showed a significant effect of TMS. It was noted that outcomes were evaluated at the end of treatment, and the durability of the effect is unknown. The Assessment concluded that the available evidence is insufficient to demonstrate that TMS is effective in the treatment of schizophrenia.

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

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

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

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

A 2013 Cochrane review included 19 trials with a total of 588 participants on the effect of TMS for improving function after stroke. The two largest trials showed that rTMS was not associated with a significant improvement in function. The review concluded that current evidence does not support the routine use of rTMS for the treatment of stroke.

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

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

Evidence consists of a number of randomized controlled trials and a meta-analysis of the effect of rTMS on recovery from stroke. Results are conflicting, and efficacy may depend on the location of the stroke and frequency of the rTMS. Additional study is needed to determine whether rTMS facilitates standard physiotherapy in patients with stroke.

**Summary**

The literature on rTMS for treatment-resistant depression (variably defined) includes a number of double-blind randomized sham-controlled short-term trials. Results of these trials show mean improvements of uncertain clinical significance across groups as a whole. The percentage of subjects who show a clinically significant response is reported at about two to three times that of sham controls, with around 15% to 25% of patients responding. The treatment protocols are time intensive, and the patients most likely to benefit from treatment are not currently known. Based on the short-term benefit observed in randomized controlled trials, clinical input, and the lack of alternative treatments aside from electroconvulsive therapy (ECT) in patients with TRD, rTMS may be considered medically necessary in patients with TRD who meet specific criteria.

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

**Technology Assessments, Guidelines and Position Statements**

The national Institute for Health and Clinical Excellence published an interventional procedure overview of TMS for severe depression (2007) and concluded that current evidence suggests there are no major safety concerns associated with TMS for severe depression, but there is no evidence that the procedure has clinically useful efficacy. Thus, TMS should be performed only in the context of research studies. Any future research should focus on factors including dose intensity, frequency and duration. Furthermore, the Institute for Clinical Systems Improvement published a guideline on major depression in adults in primary care (2008) and stated that results of research studies to date on rTMS for the treatment of MDD have been inconsistent and inconclusive.

**A 2009 TEC Assessment** evaluated rTMS for depression. The Assessment concluded that the available evidence does not permit conclusions regarding the effect of TMS on health outcomes. Limitations of the evidence included:

- Equivocal efficacy in the largest sham-controlled trial of TMS,
- Uncertain clinical significance of the short-term anti-depressant effects found in meta-analyses,
- A lack of information beyond the acute period of treatment, and
- Lack of comparison with standard therapy (a second course of antidepressant therapy) in the population for whom TMS is indicated (patients who have failed one six-week course of antidepressant medication).

**A 2011 TEC Updated Assessment** of TMS for depression. Included were six recent meta-analyses, the largest of which evaluated 30 double-blind sham-controlled trials with a total of 1,383 patients. Recent clinical trials were also reviewed. The 2011 TEC Assessment reached the following conclusions:

“The meta-analyses and recent clinical trials of TMS generally show statistically significant effects on depression outcomes at the end of the TMS treatment period. However, the clinical significance and durability of the effect are not well-characterized.”

The largest randomized clinical trial showed a greater effect in patients with only one prior treatment failure, with possibly minimal or no effect in patients with greater than one prior treatment failure. Based on current evidence, it cannot be determined whether TMS after one treatment failure would be as effective as the current standard of a second course of antidepressant therapy.

Also identified as gaps in current knowledge are whether TMS is effective as an adjunctive treatment and whether retreatment is effective.

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

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

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

Direct Evidence
The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions for Tier one TRD was limited to two fair trials (both in major depressive disorder-only populations). One compared electroconvulsive therapy (ECT) and rTMS, and the other compared ECT and ECT plus rTMS. They showed, with low strength of evidence, no differences between treatment options for depressive severity, response rates, and remission rates. No trial involved a direct comparison of psychotherapy with another nonpharmacologic intervention.

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

rTMS was beneficial relative to controls receiving a sham procedure for all three outcomes (severity of depressive symptoms, response rate, remission rate). rTMS produced a greater decrease in depressive severity (high strength of evidence). Specifically, rTMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than five points relative to sham control, and this change meets the minimum threshold of the three-point HAM-D difference that is considered clinically meaningful. Response rates were greater with rTMS than sham (also high strength of evidence); those receiving rTMS were more than three times as likely to achieve a depressive response as patients receiving a sham procedure. Finally, rTMS was also more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving rTMS were more than six times as likely to achieve remission as those receiving the sham.
Efficacy of Nonpharmacologic Interventions Compared With Antidepressant Pharmacotherapies (KQ 1b)

Direct Evidence
No direct evidence was identified for rTMS.

Maintenance of Remission or Prevention of Relapse (KQ 2)

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

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

AHRQ Authors’ Conclusions
The evidence review suggests that comparative clinical research on nonpharmacologic interventions in a TRD population is early in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data is substantially hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence is for ECT and rTMS. However, even for the few comparisons of treatments that are supported by some evidence, the strength of evidence is low for benefits, reflecting low confidence that the evidence reflects the true effect and indicating that further research is likely to change our confidence in these findings. This finding of low strength is most notable in two cases: ECT and rTMS did not produce different clinical outcomes in TRD, and ECT produced better outcomes than pharmacotherapy. No trials directly compared the likelihood of maintaining remission for nonpharmacologic interventions. The few trials addressing adverse events, subpopulations, subtypes, and health-related outcomes provided low or insufficient evidence of differences between nonpharmacologic interventions. The most urgent next steps for research are to apply a consistent definition of TRD, to conduct more head-to-head clinical trials comparing nonpharmacologic interventions with themselves and with pharmacologic treatments, and to delineate carefully the number of treatment failures following a treatment attempt of adequate dose and duration in the current episode.

In June 2012, the New England Comparative Effectiveness Public Advisory Council (CEPAC), an AHRQ funded, independent body composed of public representatives and clinicians and led by a research team at the Institute for Clinical and Economic Review (ICER) at the Massachusetts General Hospital, published a coverage policy analysis addressing repetitive transcranial magnetic stimulation (rTMS). In December 2011, CEPAC reviewed the 2011 AHRQ evidence review on rTMS along with supplementary information. The authors reported that the supplementary analysis is not meant to revisit the core scientific findings and conclusions of the AHRQ review on “Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults” but is intended to supplement those findings with updated information on the patient management options for treatment-resistant depression. CEPAC members voted on
questions concerning the comparative clinical effectiveness of the treatment options discussed: 1) repetitive transcranial magnetic stimulation (rTMS) and 2) electroconvulsive therapy (ECT).

- Comparative clinical effectiveness of rTMS versus usual care (i.e., general supportive psychotherapy with or without continued use of antidepressant medication). A majority of CEPAC voted (ten to five) that for patients with TRD, the evidence is adequate to demonstrate that rTMS provides a net health benefit equivalent or superior to usual care. CEPAC members split (five to five) on whether rTMS has a net health benefit that is superior or equivalent to usual care.

- Comparative clinical effectiveness of rTMS versus electroconvulsive therapy (ECT). A majority of CEPAC members voted (nine to six) that for patients with TRD, the evidence is adequate to demonstrate that rTMS provides a net health benefit equivalent to ECT.

The questions and discussions section of the coverage policy analysis lists the following comments:

- “CEPAC desired greater clarity on the ideal number of treatment failures required before rTMS is used, since standard practice differs from the FDA label (one failed trial of antidepressants).
- Although the majority of CEPAC voted that the evidence is adequate to suggest that rTMS is more effective than usual care, comments from some CEPAC members noted the need for more data on which patients are ideal candidates for rTMS.
- Some members expressed concern about the potential for overutilization of rTMS without a standard definition of the ideal patient population.
- Many CEPAC members who voted that the evidence was inadequate to determine if rTMS is as effective as or better than usual care cited the dearth of evidence on the benefits of rTMS beyond the initial four to six week treatment phase.”

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

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

2006 Practice Guidelines on the evaluation and treatment of depression, psychosis, and dementia in Parkinson disease from the American Academy of Neurology concluded that there is insufficient evidence to support or refute the efficacy of TMS or ECT in the treatment of
depression associated with Parkinson disease (Level U; Data inadequate or conflicting given current knowledge, treatment is unproven).

The American Psychiatric Association 2010 practice guidelines for the treatment of patients with major depressive disorder states that treatment in the acute phase should be aimed at inducing remission of the major depressive episode and achieving a full return to the patient’s baseline level of functioning [I, Recommended with substantial clinical confidence]. Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as ECT, TMS, or light therapy. A number of strategies are available when a change in the treatment plan seems necessary. Transdermal selegiline, a relatively selective MAO B inhibitor with fewer dietary and medication restrictions, or transcranial magnetic stimulation could also be considered [II, Recommended with moderate clinical confidence].

**Key Words:**
Transcranial magnetic stimulation (TMS), depression, NeoPulse®, repetitive transcranial magnetic stimulation (rTMS), NeuroStar TMS®, Therapy System

**Approved by Governing Bodies:**
Devices for transcranial stimulation have received approval by the U.S. Food and Drug Administration (FDA) for diagnostic uses. One device, NeoPulse (Neuronetics, Atlanta, GA), received approval in Canada, Israel, and the United States as a therapy for depression. Initially examined by the FDA under a traditional 510(k) application, the NeoPulse, now known as NeuroStar® TMS, received clearance for marketing as a “De Novo” device in 2008. NeuroStar® TMS is indicated for the treatment of patients with depression who have failed one six-week course of antidepressant medication. The Brainsway™ H-Coil Deep TMS device (Brainsway Ltd.) received FDA clearance in 2013. This device is indicated for the treatment of depression in patients who have failed to respond to antidepressant medications in their current episode of depression and is a broader indication than that of the NeuroStar® TMS, which specifies the failure of 1 course of antidepressant medication (FDA product code: OBP).

In March, 2011, the FDA classified the NeuroStar® TMS System, and substantially equivalent devices of this generic type into class II under the generic name, Repetitive Transcranial Magnetic Stimulation (rTMS) System.

FDA identifies this generic type of device as:
A repetitive transcranial magnetic stimulation (rTMS) system is an external device that delivers transcranial repetitive pulsed magnetic fields of sufficient magnitude to induce neural action potentials in the prefrontal cortex to treat the symptoms of major depressive disorder (MDD) without inducing seizure in patients who have failed at least one antidepressant medication and are currently not on any antidepressant therapy.

The FDA determined that the NeuroStar® TMS System is indicated for the treatment of Major Depressive Disorder 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.

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

Warnings, precautions, and contraindications include the following:

- The device is only intended for use by patients experiencing the onset of pain associated
  with a migraine headache with aura.
- The device should not be used on headaches due to underlying pathology or trauma.
- The device should not be used for medication overuse headaches.
- The device has not been demonstrated as safe or effective when treating cluster
  headache or chronic migraine headache.
- The device has not been shown to be effective when treating during the aura phase.
- The device has not been demonstrated as effective in relieving the associated symptoms
  of migraine (photophobia, phonophobia, and nausea).
- Safety and effectiveness have not been established in pregnant women, children under
  the age of 18, and adults over the age of 65.

The de novo 510(k) review process allows novel products with moderate or low-risk profiles
and without predicates which would ordinarily require premarket approval as a class III device
to be down-classified in an expedited manner and brought to market with a special control as a
class II device.

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this
policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: FEP does not consider investigational if FDA approved. Will be reviewed for
medical necessity

Current Coding:
CPT codes:

90867 Therapeutic repetitive transcranial magnetic stimulation (TMS)
treatment; including cortical mapping, motor threshold
determination, delivery and management. (Effective 01/01/2011)

90868 Therapeutic repetitive transcranial magnetic stimulation (TMS)
treatment; subsequent delivery and management, per session.
(Effective 01/01/2011)

90869 Therapeutic repetitive transcranial magnetic stimulation (TMS)
treatment; subsequent motor threshold re-determination with
delivery and management. (Effective 01/01/2012)
Previous Coding:
CPT codes:

0160T  Therapeutic repetitive transcranial magnetic stimulation treatment planning (Pre-treatment determination of optimal magnetic field strength via titration, treatment location determination and stimulation parameter and protocol programming in the therapeutic use of high power, focal magnetic pulses for the direct, non-invasive modulation of cortical neurons) (Deleted 01/01/2011)

0161T  Therapeutic repetitive transcranial magnetic stimulation treatment delivery and management, per session (Treatment session using high power, focal magnetic pulses for the direct, non-invasive modulation of cortical neurons. Clinical evaluation, safety monitoring and treatment parameter review in the therapeutic use of high power, focal magnetic pulses for the direct, non-invasive modulation of cortical neurons) (Deleted 01/01/2011).

0018T  Delivery of high power, focal magnetic pulses for direct stimulation to cortical neurons (Deleted 07/01/2006)

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7. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transcranial magnetic stimulation for depression. TEC Assessments 2011; Volume 26, Tab 3.


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Policy History:
Medical Policy Group, June 2004 (4)
Medical Policy Administration Committee, July 2004
Available for comment July 12-August 25, 2004
Medical Policy Group, June 2006 (1)
Medical Policy Group, June 2008 (1)
Medical Policy Group, November 2008 (1)
Medical Policy Group, January 2010 (1)
Medical Policy Group, December 2010: Key Points, References, 2011 Code updates
Medical Policy Group, January 2011: Description, Key Points, References
Medical Policy Group, November 2011 (3): Added new CPT Code 90869 and updated verbiage on 90867 and 90868 effective 1/1/12
Medical Policy Group, January 2012 (1): Update to Key Points and References related to MPP update; no change in policy statement
Medical Policy Group, July 2013 (2): 2013 Updates to Key Points and References.
Medical Policy Panel, June 2014.
Medical Policy Group, July 2014 (5): 2014 update to Policy Statement to provide coverage for severe major depressive disorder (single or recurrent) when certain criteria is met; Updates: Description, Key Points, Governing Bodies, and References to support policy statement.
Available for comment July 17 through September 1, 2014

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.