Health Net

National Medical Policy

Subject: **Transcranial Magnetic Stimulation**

Policy Number: **NMP508**

Effective Date*: **March 2012**

Update: **July 2016**

This National Medical Policy is subject to the terms in the IMPORTANT NOTICE at the end of this document

The Centers for Medicare & Medicaid Services (CMS)

For Medicare Advantage members please refer to the following for coverage guidelines first:

Use	Source	Reference/Website Link
	National Coverage Determination (NCD)	
	National Coverage Manual Citation	
X	Local Coverage Determination (LCD)	http://www.cms.gov/medicare-coverage-database/ AZ, WA and OR: **L34641** CA: **L36219**
	Article (Local)	
	Other	
	None	Use Health Net Policy

Instructions

- Medicare NCDs and National Coverage Manuals apply to ALL Medicare members in ALL regions.
- Medicare LCDs and Articles apply to members in specific regions. To access your specific region, select the link provided under "Reference/Website" and follow the search instructions. Enter the topic and your specific state to find the coverage determinations for your region *Note: Health Net must follow local coverage determinations (LCDs) of Medicare Administration Contractors (MACs) located outside their service area when those MACs have exclusive coverage of an item or service. (CMS Manual Chapter 4 Section 90.2)
- If more than one source is checked, you need to access all sources as, on occasion, an LCD or article contains additional coverage information than contained in the NCD or National Coverage Manual.
- If there is no NCD, National Coverage Manual or region specific LCD/Article, follow the Health Net Hierarchy of Medical Resources for guidance.

Policy Statement

Health Net considers transcranial magnetic stimulation medically necessary for the treatment of adults with the diagnosis of Major Depressive Disorder without psychosis, when all the following are met:

1) Treatment is provided by a licensed psychiatrist, and

2) The patient has demonstrated a failure to respond to a combination of multiple trials of medication and evidence based psychotherapy treatment during the current episode of illness, with the Physician's Health Questionaire-9 (PHQ-9) score of > 15 throughout the current course of treatment, and

3) The Major Depressive Disorder diagnosis is not part of a presentation with multiple psychiatric comorbidities that could potentially clinically masquerade as Major Depression symptoms, and,

4) The patient has demonstrated treatment resistance or intolerance with psychopharmacologic agents as evidenced by a lack of clinically significant response to up to four trials of such agents, in the current depressive episode, from at least two different agent classes. At least two of the treatment trials must have been administered at an adequate course of mono- or poly-drug therapy with antidepressants involving standard therapeutic doses of at least 6 weeks duration.

   Note: This requirement is not necessary if the patient is unable to take anti-depressants due to drug interactions with medically necessary medications or the patient has demonstrated an inability to tolerate psychopharmacologic agents as evidenced by trials of four such agents with distinct side effects in the current episode.

   and

5) The patient has not responded to a properly conducted episode of treatment with evidence based psychotherapy such as a formal trial of Cognitive Behavioral Therapy and/or Interpersonal Therapy, and

6) The patient has failed an adequate trial of Electroconvulsive Therapy (ECT) unless its use is contraindicated or the documented side effects were intolerable.

Treatment Course
An acute treatment course consists of no less than thirty, 30 min to 60 min sessions or treatments, usually delivered as daily 5 days a week (with some recent studies advocating even longer TMS exposure for better results). Each session consists of rTMS to the left prefrontal dorso-lateral cortex area at around 120% motor threshold (10Hz, 4-second train duration, 26 second inter-train interval, between 3000 and 5000 pulses per session), using a figure-eight solid core coil.

Treatment response is usually defined as at least a 50% drop from the baseline depression scores. The definition for remission is generally accepted as a PHQ-9 score of $\leq$9.

Contraindications:
- History of seizures
- Ferromagnetic material anywhere in the head other than the mouth (e.g. cochlear implants, brain stimulators or electrodes, aneurysm clips, plates, metallic dyes in tattoos)
- Cardiac pacemaker
- Implanted defibrillator
- Implanted medical pump, or
- Severe cardiovascular disease

- History of failure to respond to an episode of 30 TMS treatments without a 50% reduction in baseline PHQ-9 scores

Codes Related To This Policy

ICD-9 Codes

296.2x* - 296.3x	Major depressive disorder, single episode Major depressive disorder, recurrent, moderate to severe

NOTE:
The codes listed in this policy are for reference purposes only. Listing of a code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit documents and medical necessity criteria. This list of codes may not be all inclusive.

On October 1, 2015, the ICD-9 code sets used to report medical diagnoses and inpatient procedures will be replaced by ICD-10 code sets. Health Net National Medical Policies will now include the preliminary ICD-10 codes in preparation for this transition. Please note that these may not be the final versions of the codes and that will not be accepted for billing or payment purposes until the October 1, 2015 implementation date.

ICD- 10 Codes

F32.x* - Depressive episode
F33.x* - Recurrent depressive disorder

CPT Codes

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

Scientific Rationale – Update June 2016

Fitzgerald P.B. et al. (2016), have completed a meta-analysis with data from 11 clinical trials, with an eye for establishing a rate of response and remission as well as demographic and clinical predictors of response to rTMS. The study reported a remission rate of 31%, and response rate of 46%. Again, as reported by other studies before, response was seen more in patients with less severe depression at baseline, shorter duration of the current episode, and recurrent rather than single type of Depression. Higher stimulation intensity seemed to be correlated with higher response rates.

Lan M.J. et al. (2016), have described brain structural changes (grey matter volume increased by 3.5-11.2%) occurring in patients with Major Depression during rTMS treatment. The four regions where these changes were seen were: left anterior cingulate cortex, left insula, left superior temporal gyrus and the right angular gyrus. The increase in the left anterior cingulate volume correlated with improvement in severity of depression.

Tor P.C. et al. (2016) reported on a pilot study of accelerated low frequency right sided rTMS for treatment resistant Depression, which consisted of 16200 pulses delivered across 18 sessions over 10 consecutive weekdays. They found it safe, possibly efficacious, but results were clouded by the selection process (7 patients, 4 unipolar, 3 bipolar). There was no clear clinical response, but the protocol was well tolerated. Also the literature is mixed on use of rTMS in Bipolar Depression, so they may have chosen the wrong sample to test this idea on.

Scientific Rationale – Update June 2015

Liu et al. (2014) completed a meta-analysis with seven RCTs that were included, to demonstrate the efficacy demonstrated the efficacy of repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder (MDD) treatment. The total sample size was 279, with 171 in the rTMS group and 108 in the sham group. The pooled response and remission rate for the repetitive transcranial magnetic stimulation (rTMS) and sham group was 46.6% and 22.1%, respectively; the pooled odds ratio (OR) was 5.12 [95% confidence interval (CI) 2.11-12.45, z=3.60, p=0.0003, and the associated number needed to treat (NNT) was 3.4. rTMS group achieved a significant reduction of HAMD score than the sham group, the pooled SMD of change from baseline was 0.86 [95% confidence interval (CI) 0.57-1.15, z=5.75, p<0.00001]. Because of the small number of included RCTs, the preplanned sensitivity and subgroup analyses were finally abandoned. The dropouts in both groups were relatively low, indicating the high acceptability of rTMS. For treatment resistant depression (TRD) patients, augmentative rTMS after the failure of medications significantly increases the effect of antidepressants, and rTMS was a safe strategy with relatively low adverse events and low dropout rate, suggesting that augmentative rTMS is an effective intervention for TRD.

Brunelin et al. (2014) completed a large multicenter study to evaluate the efficacy and safety of low frequency repetitive transcranial magnetic stimulation for treatment-resistant depression. The aim of this study was to assess whether the combination of low frequency repetitive transcranial magnetic stimulation (rTMS) and venlafaxine (150-225 mg/day) is effective and safe for treatment-resistant unipolar depression (TRD). 18 centers were involved in a randomized double blind controlled trial with three arms. 170 patients were allocated to receive active rTMS combined with active venlafaxine (n = 55), active rTMS combined with placebo venlafaxine (n =60) or sham rTMS combined with active venlafaxine (n = 55). The patients received once daily sessions of active or sham 1 Hz rTMS applied over the right dorsolateral prefrontal cortex (360 pulses/day delivered at 120% of the resting motor threshold) for two to six weeks; rTMS was combined with active or sham

venlafaxine (mean dose: 179.0 ± 36.6 mg/day). The primary outcome was the number of patients who achieved remission, which was defined as an HDRS17 score <8. The authors reported a similar significant antidepressant effect in the 3 groups (P < 10(-6)), with a comparable delay of action and a comparable number of remitters at the endpoint (28% in the combination group, 41% in the rTMS group and 43% in the venlafaxine group; P = .59). Low frequency rTMS appears to be as effective as venlafaxine and as effective as the combination of both treatments for TRD. Because of its short session duration (the duration of one session was 8.5 min) and its safety, slow rTMS might be a useful alternative treatment for patients with TRD.

Scientific Rationale – Update June 2014

HAYES (Mar 2014) evaluated 16 peer-reviewed, generally double-blind, randomized controlled (or comparator) trials (RCTs) comparing TMS with sham stimulation, published from 2003 through 2013. These trials included 1426 adult patients with moderate to severe major depressive disorders and treatment refractory depression. Most studies required patients to have undergone ≥ 1, and most typically ≥ 2, previous failed trials of AD medication. The post treatment differences between unilateral TMS and sham stimulation "consistently favored TMS" (14 studies; 1156 patients); most differences were reported to be statistically significant but the magnitude was generally small as measured by the MADRS scale and the various HAMD scales. No standard definition of clinically relevant improvement or a clinically relevant effect was identified in the literature. There is evidence of a strong placebo effect and, from a patient's perspective, response or remission is beneficial, whether due to a placebo effect or a true treatment effect.

Berlim et al (2013) searched the literature for randomized, double-blind and sham-controlled trials (RCTs) on bilateral rTMS for treating MD from 1995 to July 2012 to evaluate the overall efficacy of fTMS with respect to response, remission and dropout rates. Data were obtained from seven RCTs, totaling 279 subjects with MD. After an average of 12.9 (s.d. = 2.7) sessions, 24.7% (40/162) and 6.8% (8/117) of subjects receiving active bilateral rTMS and sham rTMS were classified as responders [OR 4.3, 95% confidence interval (CI) 1.95-9.52, p < 0.0001]. Also, 19% (23/121) and 2.6% (2/77) of subjects were remitters following active bilateral rTMS and sham rTMS, respectively (OR 6.0, 95% CI 1.65-21.8, p = 0.006). No difference between baseline mean depression scores for the bilateral and sham rTMS groups was found, and the former was comparable with the latter in terms of drop-out rates at study end. The authors did not find significant differences efficacy- and acceptability-wise between active bilateral and unilateral rTMS at study end and concluded that bilateral rTMS is a promising treatment for MD as it provides clinically meaningful benefits that are comparable with those of standard antidepressants and unilateral rTMS. Furthermore, bilateral rTMS seems to be an acceptable treatment for depressed subjects.

Scientific Rationale: Initial

In the United States in a given year, major depression affects 14 to 15 million adults, or approximately 5% to 8% of the adult population. Major depression, also known as major depressive disorder (MDD), unipolar depression, or clinical depression, is a severe illness that results in significant disability and morbidity, and is the leading cause of disability in many developed countries. More than 60% of the individuals experiencing a major depressive episode (MDE) will have additional MDEs as often as once or twice a year. If untreated, the frequency and severity of depressive illness increase, often leading to suicide.

Antidepressant medications are the standard medical somatic therapy for Major Depression. Antidepressant drugs and/or evidence based psychotherapy are successful in producing remission in up to 65% of the treated patients with MDD. Each of the numerous antidepressant drugs available is categorized by class according to the neurotransmitter system with which it mostly interacts (noradrenalin, serotonin, dopamine, etc). If an antidepressant drug in one class does not relieve symptoms or causes intolerable side effects, an antidepressant drug in another class may be prescribed. The rate of remission, or complete symptom relief, is only 33% for monotherapy with the first antidepressant drug tried and diminishes with each successive antidepressant drug tried. After failing = 2 antidepressant drug classes trials, plus augmentation techniques, patients are then considered drug-resistant and remission rates drop to = 20%. These data and the increasing prevalence of MDD and drug-resistant MDD suggest a need for alternative treatments for depression.

Psychotherapy is the standard non-medication treatment for Major Depression. Cognitive-Behavioral Therapy and Interpersonal Therapy have both been found to be effective in the treatment of this disorder.

ECT is the standard non-drug somatic therapy for depression. Other non-medication somatic therapies include vagus nerve stimulation (VNS), deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS). All rely on electrical stimulation of neurons in regions of the brain responsible for mood. Theoretically, electrical stimulation alters mood by altering brain chemistry or metabolism and/or neurotransmitter release. VNS has not lived up to its original promise and the trials of DBS are not yet conclusive enough for wide use of this invasive procedure.

ECT delivers electrical pulses to the brain via electrode pads positioned on the scalp above mood centers. As currently practiced, ECT triggers brief 'controlled' seizures, requires general anesthesia and a muscle relaxant to prevent severe body convulsions, raises heart rate and blood pressure during treatment, and leads to transient confusion and anterograde memory loss after treatment. ECT induces rapid improvement in symptoms but must be repeated over several sessions (usually 6-10) to prevent relapse.

Transcranial Magnetic Stimulation consists of brief repetitive pulses of magnetic energy applied to the scalp via a large electromagnetic coil positioned on the scalp over the right or left dorsolateral prefrontal cortex (DLPFC), the mood center considered as directly associated with depression. The magnetic pulses generate low levels of electrical current in underlying brain tissue, which is postulated to 'entrain' local neuronal activity back to euthymia. TMS does not require anesthesia or surgery and may be performed on an out-patient basis but typically is repeated 5 times per week over the course of = 4-6 weeks to achieve maximum response. TMS may be used alone or as an adjunct to antidepressant medication.

Repeated daily left prefrontal transcranial magnetic stimulation (rTMS or TMS) was first proposed as a potential treatment for depression in 1993. Multiple studies from researchers around the world since then have repeatedly demonstrated that TMS has antidepressant effects greater than sham treatment, and that these effects are clinically meaningful. A large industry-sponsored trial, published in 2007, resulted in US FDA approval in October 2008 for the treatment of adult patients with Major Depression without psychosis (MDD) who "have not adequately responded to appropriate pharmacological treatment intervention." There are now two FDA approved TMS treatment devices producing TMS, one produced by Neuronetics and one by Brainsway marketed by Nvation. At this time there are over 500 TMS treatment centers spread throughout the country.

The TMS Therapy system is a computerized electromechanical instrument that delivers non-invasive magnetic stimulation to the brain in the form of brief duration, rapidly alternating, or pulsed, magnetic fields, which induce small electric fields in the cortex directly below the area where the transducer is placed on the patient's head. These electric fields are sufficient to produce an action potential across the membranes of the neurons in the targeted region of the left prefrontal cortex. This induced electric field, which is internal to the cortex, is the intended substrate for stimulation. The magnetic pulse is simply a conduit to transfer the electrical energy within the system to the cortex. This energy transfer system brings the unique ability to stimulate selected spatially discrete regions of the cortex, using non-invasive direct electrical stimulation. Once action potentials are created, these neurons fire, releasing naturally produced neurotransmitters. This release starts a cascade of neurochemical events typical of normal neuro-network function.

Literature Review:
O'Reardon (2007) conducted a study under an Investigational Device Exemption (IDE) from the U.S. Food and Drug Administration (FDA) to determine whether repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) was effective and safe.

Three hundred and one (301) patients with major depressive disorder (MDD) were enrolled at 23 study sites and randomized to either active or sham rTMS. Treatment and rating personnel were blinded to patient assignments. Eligible patients were antidepressant medication-free, aged 18-70, with a single or recurrent MDD episode and a current MDD episode duration of three (3) years or less. Treatments occurred daily five days a week for six (6) weeks followed by a tapering period of three additional weeks during which time patients were begun on an antidepressant. Subjects achieving less than a 25% reduction on the Hamilton Depression Rating Scale-17 (HAMD-17) at four weeks could crossover to an open-label, acute treatment extension study. The primary outcome was the difference between active and sham TMS using the last visit Montgomery-Asberg Depression Rating Scale (MADRS). Secondary outcomes included changes on the 17- and 24-item Hamilton Depression Rating Scale and response and remission rates using the MADRS and HAMD.

At the primary efficacy point of four weeks, the baseline to endpoint change on both the HAMD-17 and the HAMD-24 but not the MADRS showed a significant improvement for the active rTMS group. The result was sustained at six weeks. Significant response rates (> 50% improvement from baseline) were present at four and six weeks for the active treatment group using each of the three scales (HAMD-17, HAMD-24, and MARDS). A significant difference in remission rates did not occur at four weeks but was higher for the active group at six weeks for the MARDS and HAMD-24.

Limitations of the study included the period of randomization lasting only through the first four weeks of the study with 74 (47.7%) in the active group and 92 (63.0%) in the sham group electing to enter the open-label extension study; no follow-up after the study; and the study was supported by the manufacturer

Avery (2008) reported on the results of the open-label study summarized immediately above [O'Reardon (2007)]. Non-responders at four weeks could enroll in a second six-week extension trial of open-label rTMS at each of the 23 treatment sites. The first six-week phase of the study was anti-depressant free followed by a three-week rTMS taper phase with initiation of one of 15 different antidepressants. During the taper phase rTMS was delivered three, two and one time in the first, second and third weeks, respectively. As noted above, 166 patients entered the study but only 158 were present for at least one

post-baseline observation, 73 of whom had been in the active arm and 85 in the sham. The primary efficacy outcome was the change in total score on the MADRS from the start of the open-label phase to six weeks or study endpoint. Secondary outcome measures included the HAMD-17 and HAMD-24. Remission was defined as a score <10 on the MARDS, <8 on the HAMD-17, or <11 on the HAMD-24. Improvement was noted in both groups over the six-week active and the three-week taper periods. Response was defined as > 50% reduction from baseline. Remission at the end of the taper phase was achieved by 30.6% using MARDS and 36.7% using the HADM-24. Study limitations included its open-label design and a probabilistic surface anatomy approach for magnet positioning.

George et al (2010) conducted a National Institutes of Health–sponsored, industry-independent sham controlled randomized trial using TMS therapy for major depressive disorder.The major goal of this study was to assess whether active, compared with sham, rTMS increased the remission rate during the initial phase of the study. The trial took place from 2004 – 2009 at 4 university hospital clinics with 199 study participants. The study inclusion criteria included 18 – 70 year olds with the DSM-IV diagnosis of major depressive disorder (single episode or recurrent with less than 5 year from onset) with a Hamilton Scale for depression score of 20. The study participants needed to be stable during a 2-wk medication-free lead-in period and have a moderate level of treatment resistance defined as: insufficient clinical benefit to 1- 4 adequate medication trials or intolerant to 3 trials of medications. Participants were excluded if they had a history of seizure or neurologic disorder, previous treatment with TMS or vagus nerve stimulation, failure to respond to electroconvulsive treatment or currently taking medication that could lower the seizure threshold.

Patients were randomized 1:1 to either active or sham repetitive transcranial magnetic stimulation (rTMS). There was a 2-week lead-in phase, a 3 week fixed-treatment phase and a variable 3 week extension phase of clinical improvers. During the 3-week fixed treatment phase, rTMS sessions were scheduled daily in a 5 day sequence for a total of 15 sessions. Each treatment lasted about 50 minutes, including 40 minutes of the actual delivery of rTMS or the sham treatment. A certified masked clinical rate who was not involved in administering the TMS assessed patients weekly.

The primary efficacy outcome measure was the dichotomous variable of remission, defined as a Hamilton Scale for Depression (HAM-D) score of 3 or less or 2 consecutive HAM-D scores less than 10 during phase 1. Secondary outcome measures included the dichotomous variable of the responses defined as a 50% decrease in the HAM-D score from baseline at the final phase 1 visit, Montgomery-Asperg Depression Rating Scale scores, Clinical Global Impression Severity of Illness Scale scores, and patient-reported reported Inventory of Depressive Symptoms–Self-report scores

Results
Primary (Remitters)
For the primary analysis of remission in the intention to treat (ITT) sample (=190), there was a significant effect of the treatment (odds ratio, 4.2; 95% confidence interval, 1.32-13.24; P=.02). There were 18 remitters (9.5% [14.1% in the active arm and 5.1% in the sham arm]).

Secondary (Responders)
The responder analysis had similar results. All remitters were also responders, but not all responders were remitters. There were 19 responders (10.0%) (15% active and 5% sham in the ITT sample, 14 (9.1%) (14% active and 5% sham) in the complete sample and 7

(5.8%) in the fully adherent sample. Similar to the remission analyses, logistic regression detected a main effect of treatment condition for the ITT (P=.009) and completer (P=.02)

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 and 5.1% sham) (P=.02). The odds of attaining remission were 4.2 times greater with active rTMS than with sham (95% confidence interval, 1.32 – 13.24). The number needed to treat was 12; most remitters had low antidepressant treatment resistance. Almost 30% if the patients remitted in the open-label follow-up (30.2% originally active and 29.6% sham.)

Study limitations included failure to enroll the projected 240 suggested by the initial power analysis. It was also unclear how long patients needed to be treated. Patients who met the 30% improvement criteria continued randomized treatment for an additional 3 weeks or until the patient stopped showing meaningful response to treatment. With this rule, no one received treatment for a full 6 weeks. Despite more rigorous requirements for progression (30% improvement at 3 weeks vs 25% improvement at 4 weeks), this study showed a significant improvement in remission at 3 to 5 weeks.

The authors concluded that the treatment was relatively well tolerated, with no difference in the adverse events between the sham and the active TMS treatment arms. Adverse events included headache (active 29% vs sham 23%), discomfort at the stimulation site (active 17% vs sham 10%), Insomnia (active 10% vs sham 7%) and worsening of depression or anxiety (active 6% vs sham 8%). There were no seizures,
and the retention rate was high at 88%. They also concluded that the high- intensity rTMS for at least 3 weeks is significantly more likely than sham rTMS to induce remission in antidepressant free patients with moderately treatment resistant unipolar MDD. The treatment effect seen in the primary analysis was also reflected in the secondary analyses in the remitted completer samples and in analyzing the number of responders. Similar treatment differences were found with continuous measures of symptom change, such as the Montgomery- Asberg Depression Rating Scale, the Clinical Global Impression Severity of Illness Scale, and the patient rated inventory of Depressive Symptoms self-report. Daily left prefrontal rTMS as monotherapy produced statistically significant and clinically meaningful antidepressant therapeutic effects greater than sham. The odds of attaining remission were 4.2 times greater with active rTMS than with sham (95% confidence interval, 1.21-13.24).

Janicak et al (2010) noted that transcranial magnetic stimulation (TMS) can be an effective acute antidepressant treatment, but few studies systematically examine persistence of benefit. They 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 3 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 re-administered if patients met pre-specified criteria for symptom worsening (i.e., a change of at least one point on the CGI-S scale for 2 consecutive weeks). Relapse was the primary outcome measure. The reported results stated that 10 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. They concluded that the initial data suggested that the therapeutic effects of TMS are durable and that TMS may be successfully used as an intermittent rescue strategy to preclude impending relapse.

Holtzheimer et al (2010) reported that repetitive transcranial magnetic stimulation (rTMS) has shown safety and efficacy for treatment-resistant depression, but requires daily treatment for 4-6 weeks. Accelerated TMS, with all treatments delivered over a few days, would have significant advantages in terms of access and patient acceptance. They administered open-label accelerated TMS (aTMS), consisting of 15 rTMS sessions administered over 2 days, was tested in 14 depressed patients not responding to at least one antidepressant medication. Effects on depression, anxiety, and cognition were assessed the day following treatment, then after 3 and 6 weeks. No seizure activity was observed and only one patient had a serious adverse event (increased suicidal ideation). Two patients failed to complete a full course of aTMS treatments, and 36% did not complete all study visits. Depression and anxiety significantly decreased following aTMS treatments and improvements persisted 3 and 6 weeks later. Response rates immediately following treatment and at 3 and 6 weeks were 43, 36, and 36%, respectively. Remission rates at the same timepoints were 29, 36, and 29%. The authors concluded that accelerated TMS demonstrated an excellent safety profile with efficacy comparable to that achieved in daily rTMS in other trials. Limitations primarily include open-label treatment and a small sample size.

Triggs et al (2010) conducted a prospective, randomized, sham-controlled, double blind, parallel group study of right or left pre-frontal rTMS in 48 subjects with medication-resistant depression. Two thousand (50x8-s trains of 5Hz) stimuli at MEP threshold were delivered each weekday for 2weeks. They employed a sham coil and simultaneous electrical stimulation of the scalp to simulate rTMS. Mean (+/-S.D.) reductions in the HAMD-24 from baseline to 3-months were not significantly different between rTMS and sham treatment groups. However, right cranial stimulation (sham or rTMS) was significantly more effective than left cranial stimulation (sham or rTMS) (P=0.012). Mean (+/-S.D.) reductions in the HAMD from baseline to 3 months were: left: 28.1 (+/-5.36) to 19.2 (+/-11.2); and right 27.2 (+/-4.2) to 11.5 (+/-9.4). Left rTMS achieved a reduction in HAMD 9.5 points greater than that achieved by left sham, a benefit greater than that reported in a recent multi-center Phase III trial of rTMS (O'Reardon et al., 2007), albeit not statistically significant. These results suggest that somatosensory stimuli that repeatedly engage the left hemisphere may be important to the achievement of therapeutic effect.

The Agency for Healthcare Research and Quality published a comparative effectiveness review entitled, "Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults" (Gaynes et al., 2011). Modalities reviewed included ECT, rTMS, vagal nerve stimulation and psychotherapy. Conclusions were as follows:
Our 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.

The Institute for Clinical Systems (ICSI) published a heath care guideline: Major Depression in Adults in Primary Care in 2010. They concluded, based on the review of the medical literature, that in spite of the ongoing lack of clarity about the patients population who should be targeted for rTMS, there is enough evidence to consider rTMS using a 6 week protocol as an evidence based treatment for treatment-resistance in adults, but not a first line treatment.

The American Psychiatric Association's workgroup on the treatment for major depression published a practice guideline in October 2010 stating that for patients whose symptoms have not responded adequately to medications, ECT remains the most effective form of therapy and should be considered as well as TMS when ECT is not effective or tolerated. They site a number of meta-analyses in the recent literature finding that individuals with treatment-resistant depression were more likely to respond to TMS than sham treatments (25% with TMS vs 17% with sham.)

Summary

In general, studies of rTMS in the medical literature show a short-term benefit for patients with a treatment resistant major depressive disorder who received active versus sham rTMS. Treatment benefit has been defined by response or remission rates using measurements made with validated depression rating scales. Most studies have short treatment periods, varying from one to six weeks and few studies have included long term outcomes. Questions remain about stimulation parameters and the length of optimal treatment but treatment is well-tolerated without significant adverse events and clinically significant results. Additional questions are raised about the comparative effectiveness of the devices used, and their use for "maintenance" or prevention of post-treatment relapse as well as the durability of the clinical effect after end of treatment.

Review History

March 2012	Medical Advisory Council initial approval
April 2013	Removed requirement for Anti-depression Treatment History Form, revised trial of psychopharmacologic agents, added that if further treatment may not be indicated if no response within in 30 treatments
June 2014	A second device was FDA approved for treatment with TMS. Updated criteria to require two trials of mono- or poly-drug therapy etc… rather than one
June/July 2015	Strengthened evidence-based guidelines, revised criteria by removing that the patient had a good response to previous TMS treatment
October 2015	Added Medicare LCDs
April 2016	Added New Medicare LCDs for coverage reference
July 2016	Added new Medicare LCDs for coverage reference, revised policy statement and removed pregnancy as a contraindication

Patient Education Websites

English
http://www.nimh.nih.gov/health/topics/depression/index.shtml

http://www.nimh.nih.gov/health/topics/brain-stimulation-therapies/brain-stimulation-therapies.shtml

http://www.effectivehealthcare.ahrq.gov/ehc/index.cfm/search-for-guides-reviews-and-reports/?pageAction=displayProduct&productID=1011

Spanish
http://www.nimh.nih.gov/health/publications/espanol/index.shtml

This policy is based on the following evidence-based guidelines:

1. The Institute for Clinical Systems Improvement 2011 *Major Depression in Adults in Primary Care*
   https://www.icsi.org/guidelines__more/catalog_guidelines_and_more/catalog_guidelines/catalog_behavioral_health_guidelines/depression/

   Gelenberg, A et al *Practice Guideline for the Treatment of Patients with Major Depressive Disorder* Third Edition American Psychiatric Association
   http://www.psychiatry.org/mental-health/depression
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Important Notice

General Purpose.
Health Net's National Medical Policies (the "Policies") are developed to assist Health Net in administering plan benefits and determining whether a particular procedure, drug, service or supply is medically necessary. The Policies are based upon a review of the available clinical information including clinical outcome studies in the peer-reviewed published medical literature, regulatory status of the drug or device, evidence-based guidelines of governmental bodies, and evidence-based guidelines and positions of select national health professional organizations. Coverage determinations are made on a case-by-case basis and are subject to all of the terms, conditions, limitations, and exclusions of the member's contract, including medical necessity requirements. Health Net may use the Policies to determine whether under the facts and circumstances of a particular case, the proposed procedure, drug, service or supply is medically necessary. The conclusion that a procedure, drug, service or supply is medically necessary does not constitute coverage. The member's contract defines which procedure, drug, service or supply is covered, excluded, limited, or subject to dollar caps. The policy provides for clearly written, reasonable and current criteria that have been approved by Health Net's National Medical Advisory Council (MAC). The clinical criteria and medical policies provide guidelines for determining the medical necessity criteria for specific procedures, equipment, and services. In order to be eligible, all services must be medically necessary and otherwise defined in the member's benefits contract as described this "Important Notice" disclaimer. In all cases, final benefit determinations are based on the applicable contract language. To the extent there are any conflicts between medical policy guidelines and applicable contract language, the contract language prevails. Medical policy is not intended to override the policy that defines the member's benefits, nor is it intended to dictate to providers how to practice medicine.

Policy Effective Date and Defined Terms.
The date of posting is not the effective date of the Policy. The Policy is effective as of the date determined by Health Net. All policies are subject to applicable legal and regulatory mandates and requirements for prior notification. If there is a discrepancy between the policy effective date and legal mandates and regulatory requirements, the requirements of law and regulation shall govern. * In some states, prior notice or posting on the website is required before a policy is deemed effective. For information regarding the effective dates of Policies, contact your provider representative. The Policies do not include definitions. All terms are defined by Health Net. For information regarding the definitions of terms used in the Policies, contact your provider representative.

Policy Amendment without Notice.

Health Net reserves the right to amend the Policies without notice to providers or Members. In some states, prior notice or website posting is required before an amendment is deemed effective.

No Medical Advice.
The Policies do not constitute medical advice. Health Net does not provide or recommend treatment to members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

No Authorization or Guarantee of Coverage.
The Policies do not constitute authorization or guarantee of coverage of particular procedure, drug, service or supply. Members and providers should refer to the Member contract to determine if exclusions, limitations, and dollar caps apply to a particular procedure, drug, service or supply.

Policy Limitation: Member's Contract Controls Coverage Determinations.
Statutory Notice to Members: The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illnesses or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. The determination of coverage for a particular procedure, drug, service or supply is not based upon the Policies, but rather is subject to the facts of the individual clinical case, terms and conditions of the member's contract, and requirements of applicable laws and regulations. The contract language contains specific terms and conditions, including pre-existing conditions, limitations, exclusions, benefit maximums, eligibility, and other relevant terms and conditions of coverage. In the event the Member's contract (also known as the benefit contract, coverage document, or evidence of coverage) conflicts with the Policies, the Member's contract shall govern. The Policies do not replace or amend the Member's contract.

Policy Limitation: Legal and Regulatory Mandates and Requirements
The determinations of coverage for a particular procedure, drug, service or supply is subject to applicable legal and regulatory mandates and requirements. If there is a discrepancy between the Policies and legal mandates and regulatory requirements, the requirements of law and regulation shall govern.

Reconstructive Surgery
CA Health and Safety Code 1367.63 requires health care service plans to cover reconstructive surgery. "Reconstructive surgery" means surgery performed to correct or repair abnormal structures of the body caused by congenital defects, developmental abnormalities, trauma, infection, tumors, or disease to do either of the following:

(1) To improve function or
(2) To create a normal appearance, to the extent possible.

Reconstructive surgery does not mean "cosmetic surgery," which is surgery performed to alter or reshape normal structures of the body in order to improve appearance.

Requests for reconstructive surgery may be denied, if the proposed procedure offers only a minimal improvement in the appearance of the enrollee, in accordance with the standard of care as practiced by physicians specializing in reconstructive surgery.

Reconstructive Surgery after Mastectomy
California Health and Safety Code 1367.6 requires treatment for breast cancer to cover prosthetic devices or reconstructive surgery to restore and achieve symmetry for the patient incident to a mastectomy. Coverage for prosthetic devices and reconstructive surgery shall be subject to the co-payment, or deductible and coinsurance conditions, that are applicable to the mastectomy and all other terms and conditions applicable to other benefits. "Mastectomy" means the removal of all or part of the breast for medically necessary reasons, as determined by a licensed physician and surgeon.

Policy Limitations: Medicare and Medicaid
Policies specifically developed to assist Health Net in administering Medicare or Medicaid plan benefits and determining coverage for a particular procedure, drug, service or supply for Medicare or Medicaid members shall not be construed to apply to any other Health Net plans and members. The Policies shall not be interpreted to limit the benefits afforded Medicare and Medicaid members by law and regulation.