Clinical Policy: Transcranial Magnetic Stimulation

Description
Transcranial magnetic stimulation (TMS) is a noninvasive technique approved as a modality for treatment resistant major depression (TRD). Brief repetitive pulses of magnetic energy are applied to the scalp via a large electromagnetic coil to generate low levels of electrical current in the underlying brain tissue. The intent is to stimulate areas of the brain involved in mood regulation to lessen the duration or severity of depressive episodes.

Policy/Criteria
I. It is the policy of Pennsylvania Health and Wellness® (PHW), that transcranial magnetic stimulation is medically necessary when all of the following are met:
   A. Age ≥ 18 years with a diagnosis of major depressive disorder without psychosis;
   B. Treatment is provided by a licensed psychiatrist;
   C. 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;
   D. The major depressive disorder diagnosis is not part of a presentation with multiple psychiatric comorbidities that could masquerade as major depression symptoms;
   E. Failure of or intolerance to psychopharmacologic agents, choose one:
      1. Failure of psychopharmacologic agents, both of the following:
         a. Lack of clinically significant response in the current depressive episode to four trials of agents from at least two different agent classes;
         b. At least two of the treatment trials were administered as an adequate course of mono- or poly-drug therapy with antidepressants, involving standard therapeutic doses of at least 6 weeks duration;
      2. The patient is unable to take anti-depressants due to one of the following:
         a. Drug interactions with medically necessary medications;
         b. Inability to tolerate psychopharmacologic agents, as evidenced by trials of four such agents with distinct side effects in the current episode;
   F. Failure of an evidence based psychotherapy such as a formal trial of cognitive behavioral therapy and/or interpersonal therapy;
   G. Failure of an adequate trial of electroconvulsive therapy (ECT) unless its use is contraindicated or physician documentation states why TMS is clinically preferable;
   H. Does not have any of the following contraindications:
      1. History of seizures
      2. Conductive or ferromagnetic or other magnetic-sensitive metals implanted or embedded in head or neck within 30 cm of TMS coil placement other than dental fillings (e.g. cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, metallic dyes in tattoos)
      3. Vagus nerve stimulator leads in the carotid sheath
      4. Other implanted stimulators controlled by or that use electrical or magnetic signals, (eg. deep brain stimulation, cardiac pacemaker, cardioverter defibrillator, intracardiac lines and medication pumps)
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5. Substance abuse at time of treatment
6. Severe dementia
7. Severe cardiovascular disease
8. Known non-adherence with previous treatment for depression.

A course of thirty sessions, followed by an additional 6 sessions for tapering, over 2 months is considered medically necessary.

II. It is the policy of PHW that maintenance treatment of TMS is considered **not medically necessary**, as there is insufficient evidence to support this at this time.

III. It is the policy of PHW that retreatment with TMS is **medically necessary** when meeting both of following:
   A. Current major depressive symptoms have worsened by 50% from the prior best response of the PHQ-9 score; and
   B. Prior treatment response was at least a 50% drop from the baseline depression scores.

Background

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 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, 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, 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.”

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.

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 health 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 in those 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.)

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 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 $\leq 3$ or 2 consecutive HAM-D scores $< 10$ 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 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 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 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. 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 time points were 29, 36, and 29%. The authors concluded that aTMS demonstrated an excellent safety profile with efficacy comparable
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), ALTHOUGH NOT STATISTICALLY SIGNIFICANT. THESE RESULTS SUGGEST THAT SOMATOSENSORY STIMULI THAT REPEATEDLY ENGAGE THE LEFT HEMISPHERE MAY BE IMPORTANT TO THE ACHIEVEMENT OF THERAPEUTIC EFFECT.

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.

A 2018 HAYES REVIEW FINDS EVIDENCE SUGGESTING THERE MAY BE A POTENTIAL BUT UNPROVEN BENEFIT FOR THE USE OF TMS AS AUGMENTATION FOR PHARMACOTHERAPY FOR DEPRESSION. NEW FORMS OF TMS ARE UNDER INVESTIGATION IN GENERAL MDD POPULATIONS. TWO EXAMPLES ARE PAIRED PULSE TMS AND THETA BURST STIMULATION (TBS). STANDARD TMS DELIVERS SINGLE PULSES OF MAGNETIC ENERGY REPETITIVELY, WHEREAS PAIRED PULSE TMS DELIVERS 2 PULSES OF MAGNETIC ENERGY SIMULTANEOUSLY. FOR PAIRED PULSE TMS, PULSES MAY BE DELIVERED AT THE SAME OR DIFFERENT INTENSITY. AS WITH STANDARD TMS, STIMULATION PARAMETERS VARY AND MAY INVOLVE LOW-FREQUENCY PULSES, WHICH INHIBIT CORTICAL ACTIVITY, OR HIGH-FREQUENCY PULSES, WHICH STIMULATE CORTICAL ACTIVITY. TBS INVOLVES SHORT BURSTS OF 3 LOW-INTENSITY PULSES WITH INNER HIGH-FREQUENCY (WITHIN THE GAMMA RANGE) PULSES THAT ARE DELIVERED AT 5 Hertz (WITHIN THE THETA RANGE). APPLYING TBS CONTINUOUSLY FOR 40 SECONDS HAS STIMULATORY EFFECTS, WHILE APPLYING TBS INTERMITTENTLY (E.G., 2-SECOND PULSES EVERY 10 SECONDS) HAS HIBITORY EFFECTS.

SOME INVESTIGATORS HAVE CONSIDERED WHETHER NEURONAVIGATION (E.G., WITH MAGNETIC RESONANCE IMAGING GUIDANCE) WOULD IMPROVE THE EFFECTIVENESS OF TMS FOR TREATMENT-RESISTANT DEPRESSION (FITZGERALD ET AL., 2009). IT IS POSSIBLE THAT EITHER OF THESE TECHNIQUES MAY IMPROVE THE RESULTS OBTAINED WITH STANDARD TMS, BUT EXTENSIVE STUDY WILL BE REQUIRED TO DETERMINE THIS.
Coding Implications
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ICD-10-CM Diagnosis Codes that Support Coverage Criteria

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Reviews, Revisions, and Approvals

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Restructured (with no wording changes) section regarding failure of or intolerance to psychopharmacologic agents.

References
2. Berlim M, Van den Eynde F, Daskalakis Z. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary
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