

Subject: Transcranial Magnetic Stimulation for the Treatment of Major Depression		Original Effective Date: 8/28/2013
Molina Clinical Policy: MCP-104	Revision Date(s):	
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PREFACE

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members. 1Molina Clinical Policy

FDA INDICATIONS

The only magnetic stimulator system approved by the FDA for treating depression is the NeuroStar® TMS Therapy System (Neuronetics Inc.). This system (product code, OBP) was approved in 2008 for treating adult patients with major depressive disorder (MDD) only when the affected patient has failed to attain satisfactory improvement from at least one antidepressant medication administered in the current depressive episode at or above the minimal effective dose for at least the minimal effective duration and only when TMS is prescribed by and performed under the supervision of a licensed psychiatrist. ⁴

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.

CMS does not have a NCD for transcranial magnetic stimulation (TMS) used to treat major depression. There are various LCD's that have outlined both coverage and non coverage of TMS for patients diagnosed with severe Major Depression (single or recurrent episode). ^{2 14}

INITIAL COVERAGE CRITERIA

Transcranial magnetic stimulation (TMS) for the treatment of major depression or any other diagnosis is considered investigational as there is insufficient evidence in the peer reviewed scientific literature on whether the effect of TMS improves health outcomes as compared with alternatives.

CONTINUATION OF THERAPY

N/A

COVERAGE EXCLUSIONS

Transcranial magnetic stimulation (TMS) for the treatment of major depression or any other diagnosis is considered investigational as there is insufficient evidence in the peer reviewed scientific literature on whether the effect of TMS improves health outcomes as compared with alternatives.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Transcranial magnetic stimulation (TMS) is a noninvasive technique that may be used as a treatment for major depression. TMS is described as brief repetitive pulses of magnetic energy that are applied to the scalp via a large electromagnetic coil that generates low levels of electrical current in the underlying brain tissue. The goal of TMS is to stimulate areas of the brain involved in mood regulation to lessen the duration or severity of depressive episodes.¹

TMS does not require anesthesia and can be performed on an outpatient basis. The patient usually wears ear plugs to diminish the noise from the discharging coil. Magnetic resonance imaging can be used to facilitate precise targeting of selected brain regions, which can be unilateral or bilateral. For treatment of depression, a variant of TMS called repetitive TMS (rTMS) is used. This delivers rhythmic pulses of electromagnetism, rather than a single pulse, using a cut-off of 1 Hz; high or low frequency can be used. The intensity of rTMS is usually set as a percentage of the patient's motor threshold (MT), defined as the minimum stimulus strength required to evoke involuntary muscle movements (usually in the hand) five times out of ten. Depending on intensity parameters, the patient may experience involuntary spasms of scalp muscles. Treatment with rTMS usually involves daily sessions lasting about 30 minutes for 2–4 weeks and possibly longer.⁷

GENERAL INFORMATION

Summary of Medical Evidence

Randomized, Double-Blind, Sham-Controlled Studies Evaluating TMS

A recently available study (George et al., 2010) compared active and sham HFL-TMS at 10 Hz and 120% MT in 199 patients with MDD who were antidepressant medication-free. In a 2-week lead in phase, no treatment or drugs were allowed other than minimal use of sedatives, hypnotics, or anxiolytics. In phase 1, active or sham

TMS was delivered daily for three weeks, and patients achieving a reduction of $\geq 30\%$ in the HAMD-24 score could continue assigned treatment for an additional three weeks. The study applied the standard definition for response for the HAMD-21 but defined remission as a HAMD-24 score of ≤ 3 on two consecutive evaluations. Compared with patients receiving sham TMS, patients receiving active TMS demonstrating significantly greater improvement in mean scores for the MADRS, CGI-S, and IDS-SR but not the HAMD-24. Despite this, active TMS led to higher rates of response (15% versus 5%) and remission (14% versus 5%) than sham TMS. Logistic regression analysis revealed that the treatment approach was the only variable with a significant effect on response or remission, whether analyzing data for the ITT sample ($P=0.009$ for response; $P=0.02$ for remission) or analyzing data for the so-called completer sample, 154 patients with ≥ 4 rescheduled, missed, or partially completed TMS sessions ($P=0.02$ for response; $P=0.02$ for remission). There was no significant treatment effect in the fully adherent sample, 120 patients with < 2 rescheduled, missed, or partially completed TMS sessions.⁸

Slotema et al. (2010) performed a meta-analysis of the efficacy of rTMS in psychiatric disorders. Data were obtained from randomized, sham-controlled studies of rTMS treatment for depression (34 studies), auditory verbal hallucinations (AVH, 7 studies), negative symptoms in schizophrenia (7 studies), and obsessive-compulsive disorder (OCD, 3 studies). Studies of rTMS versus electroconvulsive treatment (ECT, 6 studies) for depression were meta-analyzed. The mean weighted effect size of rTMS versus sham for depression was 0.55 ($P<.001$). Monotherapy with rTMS was more effective than rTMS as adjunctive to antidepressant medication. ECT was superior to rTMS in the treatment of depression (mean weighted effect size -0.47, $P = .004$). In the treatment of AVH, rTMS was superior to sham treatment, with a mean weighted effect size of 0.54 ($P<.001$). The mean weighted effect size for rTMS versus sham in the treatment of negative symptoms in schizophrenia was 0.39 ($P = .11$) and for OCD, 0.15 ($P = .52$). Side effects were mild, yet more prevalent with high-frequency rTMS at frontal locations. The authors concluded that rTMS may be used as a clinical treatment method for depression, for auditory verbal hallucinations, and possibly for negative symptoms. rTMS is not recommended for the treatment of OCD.²⁰

Schutter (2009) conducted another large meta-analysis that included 30 double-blind sham-controlled trials with 1,164 patients. Studies enrolling patients with major depression, employing high frequency (>5 Hz) TMS over the left DLPFC, a minimum of 5 treatment sessions, and measuring pretreatment and post-treatment depression scores using either the HAMD or MADRS were selected. In addition to calculating an overall treatment effect, they performed additional analyses comparing effects between studies that treated patients with medication-resistant depression only ($n=17$) and patients with non-medication resistant depression ($n=8$), and studies that used lower-intensity MT intensity ($<100\%$ MT, $n=14$) versus studies that used higher intensity (100–120% MT, $n=16$). The overall weighted mean effect size for treatment was 0.39 (95% CI: 0.25–0.54, $p<0.0001$). An analysis comparing studies with patients with treatment-resistant depression versus nontreatment-resistant depression found no difference in effect size. Treatment intensity, comparing studies using high versus low MT intensity, also did not show a difference in effect size.¹⁵

The next largest meta-analysis by Lam et al. (2008) examined only studies with patients with treatment-resistant depression. They identified 24 trials enrolling 1,092 patients. It was noted that the studies used various criteria for the definition of treatment resistant depression. Nine studies used the criteria of failing one or more trials of antidepressants. The rest of the studies used a definition of failing 2 or more trials of antidepressants. This meta-analysis synthesized the reported response and remission rates of the studies and calculated a summary risk difference. The summary risk difference for clinical response was 17% (95% CI: 10–23%, n=22 studies) and the summary risk difference for clinical remission was 14% (95% CI: 6–21%, n=16 studies). The weighted standardized mean effect size was 0.48 (95% CI: 0.28–0.69, n=21 studies). The pooled response rates were 25% for TMS versus 9% for sham, and the pooled remission rates were 17% for TMS versus 6% for sham.¹⁶

Jorge et al. (2008) examined two different HFL-TMS protocols in a cohort of 92 patients with MDE. Patients received active or sham HFL-TMS at 10 Hz and 110% MT once daily for a total of 10 sessions over two weeks (TMS1 and Sham1 groups) or twice daily for the first week and once daily for the second week for a total of 15 sessions over two weeks (TMS2 and Sham2 groups). Antidepressant medications were discontinued prior to TMS treatment and not permitted during the 2-week TMS program. Response was defined typically for HAMD-17 but remission was defined as a HAMD-17 score of < 8 *and* no longer meeting DSM-IV criteria for MDE. At the end of treatment, mean HAMD-17 score improved to a significantly greater degree in the TMS1 group than in the Sham1 group (decrease of 33.1% versus 13.6%) and in the TMS2 group than in the Sham2 group (decrease of 42.4% versus 17.5%). While the TMS1 group also demonstrated substantially greater response and remission rates than the Sham1 group (33.3% and 13.3% versus 6.7% and 6.7%), the differences were not significant, perhaps due to the small number of patients in these groups (15 in each group). In contrast, the TMS2 group demonstrated significantly greater rates of response (39.4% versus 6.9%) and remission (27.3% versus 3.5%) than the Sham2 group.⁹

Mogg et al. (2008) performed a randomized controlled trial comparing real and sham adjunctive rTMS with 4-month follow-up to determine the effectiveness of repetitive transcranial magnetic stimulation (rTMS) for major depression. Fifty-nine patients with major depression were randomly assigned to a 10-day course of either real (n=29) or sham (n=30) rTMS of the left dorsolateral prefrontal cortex (DLPFC). Primary outcome measures were the 17-item Hamilton Depression Rating Scale (HAMD) and proportions of patients meeting criteria for response (50% reduction in HAMD) and remission (HAMD8) after treatment. Secondary outcomes included mood self-ratings on Beck Depression Inventory-II and visual analogue mood scales, Brief Psychiatric Rating Scale (BPRS) score, and both self-reported and observer-rated cognitive changes. Patients had 6-week and 4-month follow-ups. Overall, Hamilton Depression Rating Scale (HAMD) scores were modestly reduced in both groups but with no significant group time interaction (p=0.09) or group main effect (p=0.85); the mean difference in HAMD change scores was -0.3 (95% CI -3.4 to 2.8). At end-of-treatment time-point, 32% of the real group were responders compared with 10% of the sham group (p=0.06); 25% of the real group met the remission criterion compared with 10% of the sham group (p=0.2); the mean difference in HAMD change scores was 2.9 (95% CI -0.7 to 6.5). The authors concluded that there were no significant differences between the two groups on any secondary outcome measures. Blinding was difficult to maintain for both patients and

raters. Adjunctive rTMS of the left DLPFC could not be shown to be more effective than sham rTMS for treating depression.¹⁹

Randomized Controlled Trials Comparing TMS and Other Treatments for Depression

Keshtkar et al. (2011) compared the efficacy of rTMS and ECT in adult patients with refractory major depressive disorder (MDD). 73 patients with MDD were randomized to ECT-controlled or parallel-group clinical trial to analyze the antidepressant effects of ECT and rTMS. The Beck Depression Inventory and Hamilton Depression Rating Scale were used to measure depression. The results showed that both ECT and rTMS significantly improved depression and suicidal behavior scores. However, ECT reduced depression and suicidal behavior scores more than rTMS. There were no significant adverse effects in the rTMS group. The investigators concluded that both ECT and rTMS improved MDD in the short term, but the antidepressant efficacy of ECT was greater than rTMS. Additionally, ECT led to greater reductions in suicidal behavior than rTMS. Until strong evidence for the safety and efficacy of rTMS is available, further studies are needed to compare ECT and rTMS in terms of the long-term relapse rate and quality of life.¹⁸

Bares et al. (2009) randomized 60 patients with major depression to active LFR-TMS at 1 Hz and 100% MT + placebo drug (TMS group) or sham TMS + venlafaxine (Drug group). Active and sham TMS were delivered for 20 sessions over four weeks, and placebo and active medication were administered daily during that time. Other antidepressant drugs were withdrawn during a drug wash-out phase 5 to 9 days before beginning study treatment. The study was double-blind, defined response as a decrease of 50% in the MADRS score, and defined remission as a MADRS score of 10. At the end of treatment, mean scores for the three depression measures used (MADRS, CGI, BDI) were similar between groups. There also were no significant differences between groups in the rates of response or the rates of remission, whether analyzed for all patients (ITT, sample) or only patients completing treatment (completer sample). In the ITT sample and the completer sample, respectively, the rate of response was 33.3% and 34.6% in the TMS group and 38.7% and 42.3% in the Drug group, and the rate of remission was 18.5% and 19.2% in the TMS group and 22.6% and 26.9% in the Drug group.¹²

The study by O'Reardon et al. (2007) is the largest clinical trial of TMS, and was the clinical trial on which the FDA decision to clear TMS for marketing was based. The study was a multicenter study conducted at 23 sites. Patients were enrolled who had uncomplicated major depression meeting severity criteria. They were required to have failed at least one but no more than four adequate antidepressant treatments in the current or most recent episode of depression. After a 1-week washout, patients were scheduled to have 6 weeks of TMS, 5 sessions per week. Characteristics of the treatment given were left DLPFC treatment location, 120% motor threshold field intensity, 10 Hz pulse frequency, and 3000 pulses per treatment. Patients were not given antidepressant medication during the treatment period. Three-hundred twenty-five patients were randomized, and the analysis presented in the published study is based on 301 patients who had at least one post-baseline assessment. The

results of the trial's 4-week outcomes reported that the mean difference in 4-week change MADRS was declared a priori to be the primary outcome of the study. The TMS patients improved 5.6 points on the MADRS, and the sham group improved 3.5 points, leading to a mean difference of 2.1 points which was not statistically significant ($p=0.057$). On other outcomes measured by mean changes from baseline, the HAMD 24 had a mean difference 2.4 ($p=0.012$), the HAMD 17 had a mean difference of 1.9 ($p=0.006$) and the CGI-S had a mean difference of 0.4 ($p=0.009$). Results were also presented in terms of response and remission rates. Response rates were generally low, but depending on the scale used, the differences in response rates ranged from 7.1 to 9%, and were statistically significant. The remission rates were even lower, between 7.1% and 9.0%, and were not significant when compared to sham treated patients.¹⁷

The study conducted by Eranti et al. (2007) involved 46 patients with MDE who were randomized to HFL-TMS or ECT. HFL-TMS was delivered at 10 Hz and 110% MT for 15 sessions over three weeks. ECT was delivered bilaterally or unilaterally for 2 sessions a week for a duration that depended on response. While the study was single-blind, blinding was compromised in 70% of the cohort. Patients were followed for 6 months, but many (19%) dropped out prior to that, with higher drop-out rates in the ECT group than the TMS group (27.2% versus 12.5%). The study defined response as a decrease of 50% in the HAMD-17 score and defined remission as a HAMD-17 score of 8. Compared with the ECT group, the TMS group demonstrated significantly higher (worse) mean scores on all depression measures used (HAMD-17, BDI, BPRS, VAS for mood) and significantly lower rates of response (59.1% versus 16.7%) and remission (59.1% and 16.7%). At the 6-month follow-up, mean scores on the HAMD-17 decreased (improved) to an equal value in both groups, but mean scores on the other three depression measures remained relatively constant and still were significantly lower in the TMS group than in the ECT group. Additionally, the rate of remission decreased to 9.5% in the TMS group and 25% in the ECT group, indicating relapse in both groups, but the significance of the difference in remission rate was not reported.¹⁰

In a study by Rosa et al. (2006), 42 patients with major depression received HFL-TMS at 10 Hz and 100% MT for 20 sessions over four weeks or unilateral ECT over 12 sessions for four weeks. If patients showed deterioration or no improvement in depression symptoms after two weeks of treatment, those in the TMS group crossed over to ECT and those in the ECT group received bilateral ECT. The study was single-blind and involved no follow-up after the immediate post-treatment evaluation. Response was defined as a decrease of 50% in the HAMD-17 score, and remission was defined as a HAMD-17 score of 7. There were no significant differences between groups in mean scores on the HAMD-17, CGI, VAS for depression, or cognitive measures at any evaluation point. Whether analyzing data for all patients (ITT sample) or only patients completing treatment, there also were no significant differences between the TMS group and the ECT group in response rates (45.5% and 50% versus 30% and 40%, respectively) or remission rates (9.1% and 10% versus 15% and 20%, respectively).¹¹

Hayes, Cochrane, UpToDate, MD Consult etc.

Hayes: There is Medical Technology Directory report called transcranial magnetic stimulation for major depression (updated June 2013). This report describes that there is some evidence from a number of randomized, sham-controlled trials that TMS may have some short term antidepressive effect in adult patients with drug-resistant depression, with average response and remission rates of 36% and 24%. However, improvement was generally seen in some but not all outcome measures and assessment time points, and not all of the studies demonstrated a clear treatment effect. In addition, these studies were relatively small, may not have had adequate blinding, varied with respect to type of TMS and treatment protocol, and did not provide extended follow up after treatment. Results of three randomized comparative studies suggested that TMS may be comparable to antidepressant drug therapy in relieving depression symptoms. Another 4 randomized trials compared HFL-TMS and ECT and reported inconsistent findings, precluding clear conclusions regarding the superiority of one approach over the other. TMS rarely caused serious side effects in the reviewed studies and is considered a safe procedure. The report summarizes that additional research is needed to define optimal treatment protocols, identify definitive patient selection criteria, and establish the magnitude and durability of treatment effect of TMS. ¹

UpToDate:

In a report called Unipolar Depression in Adults: Treatment with Transcranial Magnetic Stimulation ³ the following treatment recommendations are outlined:

Indications:

- Patients with major depression who do not respond to standard treatment with pharmacotherapy and psychotherapy are candidates for noninvasive neuromodulation procedures, including repetitive transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT).
- Repetitive TMS is indicated for patients with unipolar major depression who have failed at least one antidepressant medication; in many studies, patients have failed multiple courses of pharmacotherapy and psychotherapy as well as a trial of ECT.
- The stimulation parameters, number of treatments, and position of the magnetic coil required to optimize efficacy for major depression are not known and administration is thus not standardized.
- Investigational techniques of administering repetitive TMS include an accelerated schedule as well as high dose, theta burst, deep, and bilateral stimulation.
- Prior to repetitive TMS treatment, the patient should be evaluated to confirm the primary diagnosis of treatment resistant depression and whether the intervention can be used safely. The assessment includes a psychiatric history and mental status examination, with emphasis upon depressive symptoms length of the current depressive episode, types and number of failed treatments during the present episode, as well as the number, length, and treatment history of prior depressive episodes.

Contraindications:

Repetitive TMS is contraindicated in patients with any of the following:

- Increased risks for seizures

- Implanted metallic hardware (eg, aneurysm clips or bullet fragments)
- Cochlear implants
- Implanted electrical devices (eg, pacemakers, intracardiac lines, and medication pumps)
- Unstable general medical disorders

Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center (TEC):

A recent TEC report (2009) evaluated transcranial magnetic stimulation for the treatment of depression and summarized that the randomized clinical trial of TMS does not show definitive evidence of efficacy for its primary endpoint at 4 weeks. Not all outcomes show efficacy, and the analysis is sensitive to alternative methods of analysis. Another limitation of this and other studies of TMS is lack of rigorous evaluation beyond the period of treatment. Although short-term studies are consistent with changes in depression scores due to TMS, the clinical significance and durability of the effect are not well characterized. One metaanalysis indicated no difference in effect between patients with treatment-resistant and nontreatment-resistant depression. The 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. The TEC report indicated that the available evidence does not permit conclusions regarding the effect of TMS on health outcomes or compared with alternatives and it has not yet been demonstrated whether TMS improves health outcomes in the investigational setting.¹³

Professional Organizations

American Psychiatric Association (APA):

In the Practice Guideline for the Treatment of Major Depressive Disorder published 2010, transcranial magnetic stimulation is mentioned as a treatment option for patients who do not respond to pharmacotherapy. The guidelines outline the following key points⁶:

- In comparisons of actual TMS versus sham TMS, recent meta-analyses have found relatively small to moderate benefits of TMS in terms of clinical response. These meta-analyses also support the use of high-frequency TMS over the left dorsolateral prefrontal cortex.
- In comparison with ECT, TMS has been found in randomized studies to be either less effective than ECT or comparable in efficacy to ECT.
- Across all studies, TMS was well tolerated and was associated with low rates of treatment dropout
- Transient scalp discomfort and headaches were the most commonly reported side effects
- In clinical practice, the need for daily TMS could produce logistical barriers for some patients

Canadian Network for Mood and Anxiety Treatments (CANMAT):

The CANMAT recently updated its 2001 evidence-based clinical practice guidelines for treating depressive disorders. A section of the updated guidelines (Section IV) relates to neurostimulation therapies, including

TMS, electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), and deep brain stimulation (DBS), for treating MDD in adults. The subsection for TMS notes that in 2002, Canada approved the use of TMS for treating depressed adults who fail to respond to at least one antidepressant drug. Most available evidence pertains to the use of high-frequency left-sided TMS (HFL-TMS) for this indication. However, direct comparisons among the many open-label studies and randomized controlled studies are hampered by variations in study design and stimulation parameters. Based on available data, the CANMAT recommended that, when using TMS for treatment-resistant MDD, the first TMS approach should be HFL-TMS and the treatment duration should be 30 sessions (3 weeks) instead of 20 sessions (2 weeks). The CANMAT noted that there was minimal evidence regarding the use of TMS for maintaining response/preventing relapse and drew no conclusions regarding TMS for this indication. ⁵

National Institute for Health and Clinical Excellence (NICE) ⁷:

The NICE Guidance (2007) for Transcranial Magnetic Stimulation for Severe Depression indicates that current evidence suggests that there are no major safety concerns associated with transcranial magnetic stimulation (TMS) for severe depression. However, there is uncertainty about the procedure’s clinical efficacy, which may depend on higher intensity, greater frequency, bilateral application and/or longer treatment durations than have appeared in the evidence to date. The guidance recommends that TMS should therefore be performed only in research studies designed to investigate these factors.

CODING INFORMATION

CPT	Description
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

ICD-9	Description
296.23	Major depressive disorder, single episode, severe, without mention of psychotic behavior
296.33	Major depressive disorder, recurrent episode, severe, without mention of psychotic behavior

ICD-10	Description
F32.2	Major depressive disorder, single episode, severe, without psychotic features
F33.2	Major depressive disorder, recurrent, severe, without psychotic features

RESOURCE REFERENCES

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