Transcranial Magnetic Stimulation

Policy Number: BH803TMS102022
Effective Date: October 18, 2022

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Introduction & Instructions for Use

Introduction

Behavioral Clinical Policies are a set of objective and evidence-based behavioral health criteria used by medical necessity plans to standardize coverage determinations, promote evidence-based practices, and support members' recovery, resiliency, and wellbeing for behavioral health benefit plans that are managed by Optum®.

Instructions for Use

This guideline is used to make coverage determinations as well as to inform discussions about evidence-based practices and discharge planning for behavioral health benefit plans managed by Optum. When deciding coverage, the member's specific benefits must be referenced.

All reviewers must first identify member eligibility, the member-specific benefit plan coverage, and any federal or state regulatory requirements that supersede the member's benefits prior to using this guideline. In the event that the requested service or procedure is limited or excluded from the benefit, is defined differently or there is otherwise a conflict between this guideline and the member's specific benefit, the member's specific benefit supersedes this guideline. Other clinical criteria may

apply. Optum reserves the right, in its sole discretion, to modify its clinical criteria as necessary using the process described in Clinical Criteria.

This guideline is provided for informational purposes. It does not constitute medical advice.

Optum may also use tools developed by third parties that are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.
Optum may develop clinical criteria or adopt externally-developed clinical criteria that supersede this guideline when required to do so by contract or regulation.

Benefit Considerations

Before using this policy, please check the member-specific benefit plan document and any federal or state mandates, if applicable.

Description of Service

Transcranial Magnetic Stimulation (TMS) is a non-invasive technique using a device that has been approved by the Food and Drug Administration (FDA) to apply brief magnetic pulses to the brain for the treatment of major depressive disorder. The pulses are administered by passing currents through an electromagnetic coil placed adjacent to the individual's scalp. The pulses induce an electrical field in the brain tissue, activating neurons in the targeted brain structure. By stimulating areas of the brain, the goal is to lessen the duration or severity of depressive episodes. TMS is typically applied daily in subjects with major depressive disorder who have failed previous antidepressant trials in the current depressive episode. Published evidence shows that a standard acute phase of treatment, 6 weeks in duration is most likely required to achieve improvement (McClintock et al., 2018).

Accelerated and/or Theta burst stimulation is currently unproven and being investigated as a newer type of TMS in which the magnetic pulses are applied in a certain pattern, called bursts. Conventional TMS sessions typically last up to 40 minutes whereas TBS sessions are shorter, with an average session length of a few minutes (Fitzgerald et al., 2019).

Navigated transcranial magnetic stimulation is currently unproven and being studied as a tool which allows for stimulation of the specific area of the brain associated with the treatment of depression. The navigation system can locate a specific anatomical site based on MRI data of the brain to administer treatment; the three-dimensional head image is considered more precise (Zhang et al., 2021).

Coverage Rationale

Transcranial magnetic stimulation (see below for theta burst stimulation) is proven and medically necessary for the treatment of individuals 18 years of age or older with a confirmed diagnosis of major depressive disorder (MDD) when all of the following conditions are met:

- One of the following scenarios applies:
  - Resistance to treatment with psychopharmacologic agents (evidence-based depression treatment regimen) as evidenced by a lack of a clinically significant response to four trials of psychopharmacologic agents (evidence-based depression treatment regimen) in the current depressive episode from at least two different agent classes (CMS L36469, 2022; L34522, 2019). The individual's medication dose during the failed trials should have been above the minimal effective dose and duration in the current episode.
  - Inability to tolerate psychopharmacologic agents (evidence-based depression treatment regimen) as evidenced by four trials of psychopharmacologic agents (evidence-based depression treatment regimen) from at least two different agent classes, with distinct side effects (CMS L36469, 2022; L34522, 2019). Psychopharmacologic agent (evidence-based depression treatment regimen) side effects will be considered intolerable, when those side effects are of a nature where they are not expected to diminish or resolve with continued administration of the drug (CMS L36469, 2022; L34998, L37086, L37088, 2019).
  - The individual has a documented history of response to transcranial magnetic stimulation (TMS) in a previous depressive episode, as evidenced by a greater than 50% improvement on a standardized rating scale for depression symptoms (CMS L36469, 2022; L34522, L37086, L37088, 2019).
- A trial of an evidence-based psychotherapy known to be effective in the treatment of MDD of an adequate frequency and duration has been attempted without significant improvement in depressive symptoms as documented on a standardized

rating scale for depression symptoms (CMS L34869, L36469, 2022; L33398, L34641, 2020; L34522, L34998, L37086, L37088, 2019).
- The individual's current baseline depression measurement score has been documented using an evidence-based validated rating scale (e.g., BDI; HAM-D; MADRS).
- TMS treatment is provided using a device that is approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder (CMS L34869, L36469, 2022; L33398, L34641, 2020; L34522, L34998, L37086, L37088, 2019).
- The TMS treatment order is written by a psychiatrist (MD or DO) who has examined the individual and reviewed the record. The psychiatrist must have experience in administering rTMS therapy and the treatment must be given under direct supervision of this psychiatrist, i.e., he or she must be in the area and be immediately available (CMS L34869, L36469, 2022; L34641, 2020; L34998, L37086, L37088, 2019). The treatment is administered under direct supervision of this psychiatrist and present in the area and immediately available but does not necessarily personally provide the treatment) (CMS L34869, L36469, 2022; L34641, 2020; L34998, L37086, L37088, 2019).
- TMS is considered reasonable and necessary for up to 30 treatment sessions, followed by 6 tapered treatments (CMS L34522, L34998, L37086, L37088, 2019).

The following are unproven and not medically necessary due to insufficient evidence of efficacy:
- TMS for individuals not meeting the above evidence-based coverage criteria
- TMS for individuals who are pregnant or nursing
- TMS for individuals with acute suicidality, acute psychosis or with psychiatric emergencies where a rapid clinical response is needed, such as marked physical deterioration, catatonia, or immediate suicide risk
- TMS maintenance therapy and/or booster treatments
- Accelerated TMS protocols and/or Theta burst stimulation protocols
- Navigated transcranial magnetic stimulation (nTMS) for treatment planning
- Use of TMS for treating behavioral disorders in which the current focus of treatment is a diagnosis other than major depressive disorder. These disorders include but are not limited to:
  - Alzheimer's disease and other dementia
  - Autism spectrum disorder
  - Bipolar disorder
  - Obsessive-compulsive disorder (OCD)
  - Post-traumatic stress disorder (PTSD)
  - Psychotic disorder (including schizoaffective disorder and major depression with psychotic features)
  - Individuals with a primary substance abuse, eating disorder, or post-traumatic stress disorder diagnosis whose symptoms are the primary contributors to the clinical presentation.

Contraindications
- Individuals who have conductive, ferromagnetic, or other magnetic-sensitive metals implanted in their head within 30 cm of the treatment coil. Examples include metal plates, aneurysm coils, cochlear implants, ocular implants, deep brain stimulation devices, and stents.
- Individuals who have active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators.
- Individuals with a poor response or serious adverse effects to TMS therapy.
- Individuals with a history of or risk factors for seizures during TMS therapy.

Utilization Management Criteria

Transcranial Magnetic Stimulation Admission Criteria
- The criteria from the coverage rationale section of this document are met
- AND
  - Suicide risk should be evaluated. Assessment of suicide risk should include the following:
  - The member's most current diagnoses;
  - Current suicidal ideation, plan, and means;
  - The history of suicidal behavior;

- The nature of the current crisis or other unique issues that may have precipitated suicidal behavior;
- Relevant familial factors, such as history of attempts, completion of suicide, and mental illness; if there is active suicidality, additional review may be warranted to evaluate whether TMS is the most appropriate treatment, or whether a more intensive treatment is indicated.

- AND
- Prior to initiating treatment, the member's motor threshold (MT) is determined in order to provide an estimate of the magnetic field intensity, and to provide a head surface landmark to permit navigation to the treatment location.

Transcranial Magnetic Stimulation Continued Service Criteria

- Motor Threshold (MT) should be initially established to ensure the most accurate treatment location.
- Treatment consists of a maximum of 30 sessions plus 6 tapering sessions.

Clinical Evidence

Summary of Clinical Evidence

The results from a majority of studies, including multicenter randomized controlled trials, support the hypothesis that treatment with TMS is superior to sham TMS for the treatment of major depressive disorder. There is also growing research as to the durability of TMS treatment for this population, though the possible influence of concurrent antidepressant use in many study designs continues to pose a methodological limitation. FDA-approved TMS devices can be administered safely when treatment is provided under proper supervision and with adherence to the appropriate therapy manual. There is a need for conclusive evidence from controlled trials on the benefit of maintenance TMS therapy, such as when compared to maintenance antidepressant use. TMS has not been demonstrated to be equivalent in efficacy when compared to ECT for the treatment of major depressive disorder. Individuals who are candidates for ECT and instead receive TMS likely do so because TMS is regarded as less invasive.

Systematic Reviews and Meta-Analyses

Valiengo and colleagues (2022) systematically reviewed 14 RCTs for meta-analysis and 26 studies for meta-regression analysis. Study participants were receiving rTMS for MDD treatment and older than 50. A total of 1,028 participants received active (n=728) or sham (n=300) TMS at baseline. The primary outcome was outlined as reduction in depression severity scores after rTMS or sham treatment, while secondary outcomes were defined as treatment response or remission rates. The Hamilton Depression Rating Scale (HDRS) was utilized as the scoring tool when possible. The meta-analysis of the primary outcome produced a medium effect size of 0.36 (95% CI = 0.13–0.6) across the 10 studies reporting these data, representing a statistically significant improvement in HDRS with active rTMS in comparison to sham. Significant results for secondary outcomes of treatment response were (OR = 3.26; 95% CI = 2.11–5.04) and remission rates (OR = 4.63; 95% CI = 2.24–9.55). The meta-regression analysis assessed the association of variables with the primary outcome; the results found that mean age (p = .02) and total number of sessions (p = .003), but not any of the remaining variables, were significantly associated with improvement in depression severity scores. The authors rated the reviewed studies as moderate to high quality. Limitations acknowledged by the authors include a low number of RCTs (n=14), methodological heterogeneity among the studies, and the average age was younger than 75 years in all studies, therefore, limiting the generalizability to those older than 75 years. The authors recommend future large, multi-site designs with a focus on the geriatric population to determine treatment protocols and durability data.

Chen et al. (2020) conducted a systematic review of 12 clinical studies published between 2001 and 2018, regarding the efficacy and safety of high-frequency (HF) repetitive transcranial magnetic stimulation applied more than once a day in depression. There were 5 randomized, sham -controlled studies and 3 open label trials. All rTMS courses ranged 15 to 30 sessions. The most commonly used depression severity rating scale used across the studies was the Hamilton Depression Rating Scale (HDRS). The results showed that accelerated HF rTMS appears similarly effective as once daily rTMS. It is noted, however, there is a small number of trials this conclusion is drawn from. Overall, the small number of studies suitable for quantitative analysis led to pooled effect sizes that did not achieve statistical significance. Future studies with homogeneous study designs, rTMS protocols, and treatment outcome measures are needed to validate accelerated rTMS utility and guide clinical treatment plans.

Lefaucheur et al. (2019) examined 10 clinical studies with various study designs for the efficacy of rTMS in major depressive disorder with techniques to the left and right hemispheres, high frequency and/or deep high frequency. The first 4 studies (n=237) assessed the efficacy of high frequency, left dorsolateral prefrontal cortex (DLFPC) in major depressive disorder; 3 studies (n=156) revealed significant decreases of 40-58% in depression scores. The next group of 3 studies (n=276), examined deep high frequency, left DLFPC in major depressive disorder; 2 studies (n=224) showed reduction of depression scores of 50% > and higher rates of remission, with 1 study (n=52) that did not report reduced depression scores, but high rates of remission. The last group of 3 studies (n=148) performed both left and right stimulation; 2 studies (n=92) discovered reduction in depression scores of 50%>, while 1 study (n=56) showed a trend toward higher response rate at follow-up. In conclusion, the authors report definite antidepressant properties for left and right hemisphere rTMS. The authors recommend the focus of future research needs to be regarding management of the maintenance phase for long-term effectiveness of rTMS.

Miljevic et al. (2019) performed a systematic review regarding research on variables relating to relapse following rTMS and the long-term durability of the antidepressant effect of rTMS. Inclusion criteria involved either prospective or retrospective studies, treating individuals officially diagnosed with MDD (unipolar or bipolar), and treated with repetitive and/or deep TMS. Peer-reviewed journal articles published in English from 2000 to October 2018 were considered; 18 studies met inclusion criteria. Sample sizes ranged from 10-300 participants across the 18 included studies. Length of follow-up across the 18 studies ranged from 3-27 months. The results showed that the risks and predictors of relapse following rTMS treatment for depression have been examined to limited capacity. There is some evidence that variables including comorbid anxiety, acute response, and enduring symptomatology may have the potential for prediction, the data relevant to this issue remains insufficient. This issue is due to few studies, great inconsistencies, and the minimal number of RCTs on this topic. The authors conclude that only half of the studies examining the effect of rTMS maintenance treatment on relapse prevention have shown positive effects, the recommendation of maintenance rTMS is not supported by the current literature. The authors encourage future large scale RCTs along with research on brain-based biomarkers.

Somani and colleagues (2019) completed a meta-analysis regarding the efficacy of TMS treatment with individuals diagnosed with depression. A total of 7 systematic reviews that included 186 clinical studies from 1996-2018 were examined. The results indicated that overall TMS showed improvement in depressive symptoms with positive cognitive effects in executive function. Evidence in one study regarding deep TMS for treatment of depression was inadequate. The authors state that there is increasing evidence for rTMS as monotherapy or as adjunct therapy to antidepressants. In conclusion, the authors recommend further research into standard protocols for rTMS delivery, the maintenance protocol, and concomitant use with antidepressants.

Senova et al. (2019) performed a systematic review of studies reporting antidepressant outcome measures collected three or more months after the end of an induction course of rTMS for depression. Among responders to the induction course, the authors used a meta-analytic approach to assess response rates at 3 (m3), 6 (m6) or 12 (m12) months after induction and studied predictors of responder rates using meta-regression. Nineteen studies published between 2002 and 2018 were included in the review. Eighteen were eligible for analysis at m3 (732 patients) and m6 (695 patients) and 9 at m12 (247 patients). Among initial responders, 66.5% sustained response at m3, 52.9% at m6, and 46.3% at m12, in the absence of any major bias. Random-effects meta-regressions further demonstrated that a higher proportion of women, as well as receipt of maintenance treatment, predicted higher responder rates at specific time-points. The authors concluded that rTMS is a durable treatment for depression, with sustained responder rates of 50% up to 1 year after a successful induction course of treatment. Maintenance treatment may enhance the durability of the antidepressant effects of rTMS, and should be considered in clinical practice, as well as systematically explored in future clinical trials.

Voight et al. (2019) conducted a systematic review of studies from the year 2000-2019 to determine the clinical efficacy of repetitive transcranial magnetic stimulation (rTMS) in participants after ≤1 medication trials. Twenty- two articles were assessed for eligibility with 10 articles included in the systematic review and graded. The risk of bias in each study was not assessed. However, CEBM and GRADE assessments were evaluated. Six articles were graded high quality (CEBM/GRADE: 1c/B) demonstrating that the use of rTMS was clinically efficacious in patients after ≤1 medication trial. Four additional trials demonstrated a positive effect of rTMS in patients after ≤1 medication trial but were of a lower quality. Four of the studies identified were randomized controlled trials. In each of these trials it was identified that the GRADE quality of evidence was moderate (level B). The literature shows high quality evidence regarding the effectiveness of rTMS in individuals who have not experienced success with medication treatment. The authors concluded that the use of rTMS in participants after ≤1 medication trial should be considered.

Rachid (2018) described and discussed studies that evaluated the safety and efficacy of maintenance repetitive transcranial magnetic stimulation in the long-term treatment and relapse prevention of depression. The electronic literature on maintenance repetitive transcranial magnetic stimulation for depression was reviewed. A limited number of controlled, open-label studies as well as case series have been published on maintenance rTMS after successful response to acute rTMS. In the majority of these studies, most patients with treatment-resistant unipolar or bipolar depression with or without medications experienced either moderate or marked benefit with maintenance rTMS, sometimes remission for three months and up to eight years. Many of the reviewed studies have shown promising results, however, future well-designed sham-controlled studies are needed to confirm the long-term safety and efficacy of maintenance rTMS in the relapse prevention of depression.

Guo et al. (2017) conducted a meta-analysis regarding the antidepressant effect of rTMS that included 16 double-blind, parallel-design RCTs examined the stability of the antidepressant effect of high frequency (HF) rTMS on the left dorsolateral prefrontal cortex (DLPFC) in the absence of active maintenance treatment. In this meta-analysis, the results showed that HF rTMS displayed a small antidepressant effect during follow-up, with yet a lower efficacy in RCTs with longer (8–16 weeks) compared to shorter (1–4 weeks) follow-up periods. In addition, the post-treatment antidepressant effect was higher in those who were less severely ill, unipolar, nonpsychotic, treatment-resistant, and currently on antidepressants.

Clinical Trials & Studies

Johansson and associates (2021) examined the optimal rTMS dose and antidepressant correlation. The study was a double-blind, three-arm parallel-group, randomized, pilot trial. There were 29 adult participants diagnosed with MDD, randomized to 3 different doses of 1000, 2000, or 4000 pulses of rTMS for 20 sessions in 4 weeks. The primary outcome was measured at baseline, weekly, and the last visit utilizing the Montgomery Asberg Depression Rating Scale (MADRS). Results revealed upon session completion of 4 weeks, the 3 treatment groups decreased the mean MADRS (95% CI) by 11.6 (4.0–19.2), 9.1 (5.0–13.3), and 11.3 (4.1– 18.5) points respectively. Eleven of the 29 participants met criteria for treatment response and 10 for remission with the mean reduction in Clinical Global Impression-Severity scale (CGI-S) of (95% CI) 1.1 (0.6 to 1.6). Additional results showed that the higher dose of 4000 pulses showed the largest treatment effect during the first two treatment weeks. There were no serious adverse events reported. Limitations of the study include small sample size, unclear if participants may have known their treatment group, possible placebo effect of 4000 pulses cannot be ruled out, and no durability data. According to these results the researchers suggest future well-designed, double-blinded RCTs to assess optimal rTMS dosing to relieve symptoms quicker and possibly shorten hospital stays.

In a randomized, double-blind controlled study, Benadhira et al. (2017), assessed the benefits of maintenance repetitive transcranial magnetic stimulation (rTMS) for participants diagnosed with unipolar or bipolar treatment-resistant depression (TRD). Participants scored at least 18 points on the Hamilton Depression Rating Scale (HDRS-17), plus, taking a stable dose of antidepressants for 6 weeks or more. Fifty-eight TRD patients received rTMS over one month in an open-labeled design study (phase I). Responder participants were then randomized into active and sham high-frequency rTMS groups for the subsequent eleven months (phase II). The regularity of sessions was gradually reduced. Intention-to-treat analysis was performed to assess the effectiveness of maintenance sessions. Of the 58 patients included, 35 participants were responders after one month of active rTMS (phase I), and 17 patients were randomized for the maintenance sessions (phase II). The HDRS scores revealed a significant improvement between the first month and the fourth month in active group in comparison with sham group (phase II). There was no significant difference between these two groups for other periods of time. According to the authors, repetitive TMS could denote an innovative approach for preventing relapse in TRD patients who respond to rTMS treatment. The authors conclude that these results should be confirmed in a larger sample.

Other Reports

Consensus recommendations for the application of repetitive transcranial magnetic stimulation (rTMS) were published in 2018 by the National Network of Depression Centers rTMS Task Group and the American Psychiatric Association Council on Research Task Force on Novel Biomarkers and Treatments (McClintock et al., 2018). A total of 118 publications (including 3 RCTs) from 1990 through 2016 were included in the consensus statement and were supplemented with expert opinion to achieve consensus recommendations on key issues surrounding the administration of rTMS for major depressive disorder (MDD) in clinical practice settings.

- This consensus recommendation document indicates the following:
    - The expert opinion is that rTMS is an applicable treatment in individuals with MDD even when there is medication resistance or has significant comorbid anxiety.

- There is no solely recommended maintenance antidepressant strategy for individuals after a successful rTMS acute course. Rather, it is recommended that the following available evidence-based antidepressant approaches be used after successful acute rTMS treatment: repeat rTMS, pharmacotherapy, manualized psychotherapy, exercise and a combination of those treatments. Additional future research is needed to develop evidenced-based antidepressant maintenance strategies following acute clinical benefits with rTMS.
- Regarding allowable psychoactive medications during TMS treatment the consensus statement indicates that the safety guidelines for rTMS were determined in study participants who were largely antidepressant-free. While it is plausible that psychotropic medication can affect the motor threshold, there are no known absolute contraindications to psychotropic medication usage during rTMS.
- FDA approval of rTMS is limited to adults with MDD. However, there is evidence of safe effective use and clinical benefit of rTMS in adolescents with mood disorders, women with perinatal depression and other neuropsychiatric disorders including bipolar disorder, panic disorder, obsessive-compulsive disorder, depersonalization disorder, posttraumatic stress disorder and schizophrenia. However, at this time, there is insufficient evidence to support routine clinical rTMS use with these diagnoses.

TMS and Obsessive-Compulsive Disorder (OCD)

Emergency Care Research Institute (ECRI, 2022), completed a clinical evidence assessment stating that the evidence for TMS in treating adults with OCD remains inconclusive. The clinical literature included 2 systematic reviews published in 2021, 5 RCTs published in 2021, 1 RCT published in 2020, and 1 cost-effectiveness study published in 2022. The meta-analysis of the 2 SRs revealed a modest improvement in OCD symptoms at the end of 2-10 weeks of treatment. Limitations noted in the individual studies were the different TMS protocols utilized such as target, frequency, and stimulation type, in addition to the brief follow-up periods. Additional limitations across the RCTs were small sample sizes which creates a high risk of sampling and operator bias. Due to these limitations, clinical benefits and clinical durability beyond the brief follow-up times is unclear. The authors recommend larger, multi-site, double-blind RCTs with greater than 6 month follow-up to determine the optimal TMS protocol for treating OCD.

Fitzsimmons and colleagues (2022) completed a systematic review and meta-analysis of 21 randomized controlled studies, n=662 with 368 receiving active rTMS and 294 receiving sham rTMS. Only treatment resistant participants were included in 18 of the 21 studies. In terms of efficacy, rTMS for OCD was found more effective than sham rTMS. In the analysis, the stimulation protocols of low frequency (LF) right dorsolateral prefrontal cortex (dlPFC), high frequency (HF) bilateral dlPFC and low frequency (LF) pre-supplementary motor area (preSMA) were 3 highly ranked protocols. Each of these protocols are described as efficacious with significant and comparable clinical improvements as evidenced by a 4- point reduction on the Yale-Brown Obsessive Compulsive Scale (YBOCS) score. Limitations amid the studies are moderate heterogeneous rTMS methods and protocols, lack of generalizability due to most studies including only treatment resistant participants, and unclear primary outcomes for 3 studies. The authors assigned a GRADE certainty rating for all studies of low or unknown risk of bias score, a rating of moderate for rTMS as a whole, and moderate to high for the different stimulation protocols. The authors suggest there is a need for future studies with a focus on direct comparisons of the different protocols in multi-arm clinical trials. In addition, the authors recommend that future studies assess the benefit of adjunctive CBT and medication, and use of biomarkers to identify possible rTMS responders.

Emergency Care Research Institute (ECRI, 2021), completed a clinical evidence assessment stating that the evidence for TMS in treating adults with OCD is inconclusive. The evidence assessed was from a systematic review with meta-analysis of 26 randomized controlled trials; 3 additional RCTs were included with different protocols, frequencies, and brain targets. The assessment reports improvement in OCD symptoms in the short term (up to 4-weeks post-treatment) more than sham stimulation for some patients with OCD whose symptoms have not responded to drug therapies, however, the studies assess too few patients to determine whether benefits are maintained after 6 weeks or greater of treatment. The studies in the systematic review assess too few patients per stimulation frequency and intensity in relation to brain target location to be conclusive on optimal treatment regimens. Future, large, multicenter RCTs with at least 6-month follow-up are required to confirm efficacy and to determine the optimal TMS protocol, frequency, and brain location-target for treating OCD.

Liang et al. (2021) conducted a systematic review and meta-analysis regarding the efficacy and tolerability of repetitive transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder in adults. Twenty-two randomized controlled trials were included, n=698 with 365 assigned to active rTMS and 333 assigned to sham rTMS. The results indicated that efficacy, low-frequency (LF) rTMS over the dorsolateral prefrontal cortex (DLPFC; mean difference (MD) 6.34, 95% credible interval (CrI) 2.12–10.42) and supplementary motor area (MD 4.18, 95% CrI 0.83–7.62), and high-frequency rTMS over the

DLPFC (MD 3.75, 95% CrI 1.04–6.81) were more effective than sham rTMS. Regarding tolerability, all rTMS treatment strategies were similar to the sham rTMS. The results show that LF-rTMS over the DLPFC might be the most effective intervention among all rTMS strategies. The authors conclude that although the FDA has approved the application of rTMS for treatment of OCD, this approach continues to lack robust evidence. The authors evaluation of the quality of evidence was described as very low. Recent studies have suggested that rTMS efficacy in neuropsychiatric disorders still needs future well-designed RCTs to establish efficacy along with exact strategies and protocols.

Hayes, Inc. (2019) completed an evidence evaluation report of 14 peer-reviewed randomized controlled trials that examine TMS as an add-on therapy or as monotherapy for the treatment of obsessive-compulsive disorder in adults. The evaluation states that the current body of evidence for the use of repetitive transcranial magnetic stimulation (rTMS) as an add-on therapy in adults with failure of ≥ 1 prior treatments is rated as low quality. The efficacy, durability, optimal course of treatment, and outcomes remain uncertain and unproven at this time. Evaluation results also showed that there is insufficient clinical evidence to support the use of rTMS as monotherapy for OCD in adults with inadequate responses to ≥ 1 prior treatments and no contraindications to rTMS.

Lusicic et al. (2018) performed a systematic review on the effect of rTMS and dTMS on different brain targets in OCD. Twenty studies met inclusion criteria with 19 using rTMS and one dTMS. Treatment duration varied from 2 to 6 weeks with follow-up ranging from none to 14 weeks. Nine had Y-BOCS score reductions with rTMS versus sham; eight showed no significant difference. The authors concluded treatment of OCD with neurostimulation shows promise, however, a barrier is determining which brain areas are responsible for mediating various OCD symptoms. The authors report that future research with larger well-designed studies is needed to assess clinically relevant results.

TMS and other conditions

The use of TMS has been investigated for other conditions including the following:

- Alzheimer's disease, dementia and cognitive impairment (Chang et al., 2018; Dong et al., 2018)
- Anxiety, panic disorder and generalized anxiety disorder (Parikh et al., 2022; Rodrigues et al., 2019)
- Autism spectrum disorder (Barahona-Corrêa et al., 2018)
- Bipolar disorders (Nguyen et al., 2021)
- Borderline personality disorder (Konstantinou et al., 2021)
- Posttraumatic stress disorder (Belsher et al., 2021; McGirr et al., 2021)
- Schizophrenia (Guttesen et al., 2021; Marzouk et al., 2018)
- Substance use disorders (Bolloni et al., 2018)

Due to limited studies, small sample sizes, and weak study designs, there is insufficient data to conclude that TMS is safe and/or effective for treating behavioral conditions other than major depressive disorder.

Accelerated and/or Theta Burst Transcranial Magnetic Stimulation

Voight et al. (2021) conducted a systematic review and meta-analysis of 10 RCTs addressing the theta burst stimulation (TBS) method with a total of 667 participants. Selected RCT criteria specified participants 18 years of age or older, a primary diagnosis of MDD, and treatment with any form of TBS. The primary outcome was defined as a >50% reduction in depression severity scores, per the Hamilton Rating Scale for Depression (HRSD) at treatment conclusion. Eight of the RCTs compared TBS to sham treatment and 1 compared TBS to standard rTMS (i.e., high frequency stimulation over left dorsolateral prefrontal cortex). The results indicated that TBS was superior to sham on response measured by the HRSD (RR = 2.4; 95% CI: 1.27 to 4.55; P = 0.007). The HRSD response rates for TBS when compared to rTMS yielded no statistically significant difference (RR = 1.02; 95% CI: 0.85 to 1.23; P = 0.80). Adverse events were reported such as suicide, hospitalization, headache, dizziness, nausea, pain, however, no significant difference was found between the TBS and sham groups when calculating all adverse events: (RR = 1.95; 95% CI: 0.96–3.96; P = 0.06). The authors rated the quality of evidence for the primary outcome as high. Limitations among the studies include heterogeneity between treatment protocols and insufficient durability data with only 2 studies providing follow-up at 8-12 weeks. The authors conclude that future TBS studies center around optimization of the TBS technique in treating MDD.

Chen and associates (2021) completed a three-arm, single blind, randomized, controlled, multi-site trial exploring accelerated theta burst stimulation for treatment-resistant depression (TRD). The study comprised 252 adult participants over the age of 18, with confirmed diagnoses of MDD or bipolar disorder (major depressive episode (MDE)), a score of > 10 (moderate depression) on the Quick Inventory of Depressive Symptomatology – Clinician Rated Version (QIDS-C), and a minimum Stage II TRD

defined by the Thase and Rush classification. All participants were on consistent antidepressant regimens or no antidepressant therapy for at least 4 weeks. Participants were randomized to 1 of 3 groups: 1) Daily 10 Hz rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) over 4 weeks to serve as an active control group 2) Low intensity sequential continuous TBS (cTBS) and intermittent TBS (iTBS) applied to the right then left DLPFC in a 10-day accelerated schedule, or 3) High intensity sequential cTBS and iTBS applied to the right then left DLPFC in the same 10-day accelerated schedule. Clinical assessments were conducted at 1,2,4 and 8 weeks after treatment completion. Results for the primary outcome showed the overall treatment response rate was 43.7 % and the remission rate was 28.2 %. There were no significant differences for response (p = 0.180) or remission (p = 0.316) throughout the three groups. No significant difference was found when comparing low intensity versus high intensity, response (p=0.319) or remission (p=0.673). Limitations noted are heterogeneity in the interventions applied, lack of blinding for participant treatment groups, no detailed data regarding if participants were taking mood stabilizers or benzodiazepines in combination with antidepressants, and brief follow-up data. The authors recommend future large, double-blind, sham-controlled robust study designs to determine the role of accelerated TBS for treatment-resistant depression.

Fitzgerald and colleagues (2019) investigated the efficacy of accelerated or intensive forms of repetitive TMS (rTMS), a novel form of theta burst stimulation (TBS) treatment as compared to standard rTMS treatment in a randomized controlled trial. There were 74 participants, ages 18-70 years, and diagnosed with major depressive disorder or bipolar disorder (depressive episode). The Montgomery Asberg Depression Rating Scale was used for measurement of depressive symptoms and participants had a score of >19. Participants received either intensive TBS (3 intermittent TBS treatments per day for 3 days in week 1, 3 treatments a day for 2 days in week 2, and 3 treatments in 1 day in week 3 and in week 4, or standard rTMS (5 daily sessions per week for 4 weeks). At the end of 4 and 8 weeks, outcomes showed there was no significant difference in MADRS response rates or remission rates between the groups in any of the analyses. The overall results revealed that intensively applied TBS appears to have similar efficacy to standard rTMS when applied in this study but does not produce more rapid clinical results. The authors note that there are a currently a limited number of randomized trials that confirm the efficacy of accelerated TMS or intensive TBS. Further research is needed from a large multisite trial to demonstrate the clinical benefits of intensive TBS.

Rachid (2019) described and discussed studies evaluating the safety and efficacy of accelerated transcranial magnetic stimulation (aTMS) in the acute treatment of depression. The electronic literature (NCBI Pubmed; Science Direct) on aTMS for the treatment of depression was reviewed. A limited number of controlled and open-label studies have been published on the subject. The majority of these studies have shown promising results with aTMS, this protocol probably being at least as safe and as efficacious as conventional rTMS (five sessions per week) in the treatment of treatment-resistant depression (TRD) with a trend for faster response rates when more intensive protocols are used (15 sessions over two days). The author found that since there were a limited number of randomized controlled studies with heterogeneous stimulus parameters, it was impossible to perform a systematic review or a meta-analysis. According to the authors, future sham-controlled studies with increased statistical power, rigorous standards of randomization, blinding procedures, optimal stimulus parameters, more limited number of days of treatment with a higher number of sessions while monitoring for safety, and better clinical outcome as well as global functioning measures are needed to confirm the short and long-term safety and efficacy of aTMS in the treatment of depression.

In a systematic review and meta-analysis, Sonmez et al. (2019) examined accelerated TMS (aTMS) studies for depressive disorders. Inclusion criteria consisted of studies with full text publications available in English describing more than one session of TMS (repetitive or theta burst stimulation) per day. Eighteen articles describing eleven distinct studies (seven publications described overlapping samples) met eligibility criteria. Randomized controlled trials (RCTs) included a total of 301 unique patients. Among these, 197 were allocated to aTMS protocols. The five open-label studies involved a total of 65 unique patients. A Hedges' g effect size and confidence intervals were calculated. The summary analysis of three suitable randomized control trials revealed a cumulative effect size of 0.39 (95% CI 0.005–0.779). A separate analysis including open-label trials and active arms of suitable RCTs revealed a g effect size of 1.27 (95% CI 0.902–1.637). The authors stated that existing preliminary work suggests that these compact treatment schedules are safe, tolerable, and feasible. Larger, systematic trials with enhanced blinding and sham delivery are needed to demonstrate safety, feasibility, and tolerability of accelerated TMS.

In a randomized, multisite clinical trial, Blumberger et al. (2018) assessed the clinical effectiveness, safety, and tolerability of intermittent theta burst stimulation (iTBS) compared with standard 10 Hz repetitive transcranial magnetic stimulation (rTMS) in adults with treatment-resistant depression. The primary outcome measure was change in 17-item Hamilton Rating Scale for Depression (HRSD-17) score, with a non-inferiority margin of 2·25 points. A total of 414 patients with treatment-resistant major depressive disorder were enrolled and randomized to 4 to 6 weeks of rTMS (n=205) or iTBS (n=209). One hundred ninety-two (94%) participants in the 10 Hz rTMS group and 193 (92%) in the iTBS group were assessed for the primary outcome after 4-6

weeks of treatment. HRSD-17 scores improved from 23·5 (SD 4·4) to 13·4 (7·8) in the 10 Hz rTMS group and from 23·6 (4·3) to 13·4 (7·9) in the iTBS group which indicated non-inferiority of iTBS. Self-rated intensity of pain associated with treatment was greater in the iTBS group than in the 10 Hz rTMS group, this did not result in higher dropout rates; rates did not differ between groups (10 Hz rTMS: 13 [6%] of 205 participants; iTBS: 16 [8%] of 209 participants). The most common treatment-related adverse effect was headache in both groups (10 Hz rTMS: 131 [64%] of 204; iTBS: 136 [65%] of 208). The authors report that in participants with treatment-resistant depression, iTBS was non-inferior to 10 Hz rTMS for the treatment of depression. Both treatments had low numbers of dropouts and similar side-effects, safety, and tolerability profiles. This trial was limited by a lack of a treatment group with placebo. The authors state that iTBS has the potential of reducing healthcare costs and improving access for individual's treatment-resistant depression.

Brunoni et al. (2017) performed a meta-analysis to evaluate the relative efficacy and acceptability of the different modalities of repetitive transcranial magnetic stimulation (rTMS) used for major depressive disorder (MDD). The review included randomized clinical trials that compared any rTMS intervention with sham or another rTMS intervention. Eighty-one studies with a total sample size of 4233 patients were included. The interventions more effective than sham were priming low-frequency (OR, 4.66; 95% CI, 1.70-12.77), bilateral (OR, 3.96; 95% CI, 2.37-6.60), high-frequency (OR, 3.07; 95% CI, 2.24-4.21), theta burst stimulation (TBS) (OR, 2.54; 95% CI, 1.07-6.05), and low-frequency (OR, 2.37; 95% CI, 1.52-3.68) rTMS. Novel rTMS interventions (accelerated, synchronized, and deep rTMS) were not more effective than sham. Except for theta burst stimulation vs sham, similar results were obtained for remission. All interventions were at least as satisfactory as sham. The estimated relative ranking of treatments suggested that priming low-frequency and bilateral rTMS might be the most efficacious and viable interventions among all rTMS strategies. However, results were vague and relatively few trials were available for interventions other than low-frequency, high-frequency, and bilateral rTMS. The authors note that most studies presented an unclear risk of bias, mainly owing to blinding inadequacy. The authors concluded that few differences were found in clinical efficacy and acceptability between the different rTMS modalities, favoring to some extent bilateral rTMS and priming low-frequency rTMS. These findings warrant the design of larger RCTs investigating the potential of these approaches in the short-term treatment of MDD. Current evidence cannot support novel rTMS interventions as a treatment for MDD.

Navigated Transcranial Magnetic Stimulation (nTMS)

In a randomized controlled trial, Blumberger et al. (2016) evaluated MRI-targeted repetitive transcranial magnetic stimulation for treatment resistant depression (TRD). A total of 121 patients between the ages of 18 and 85 years were included in the study. Participants were randomized to receive sequential bilateral rTMS (600 pulses at 1 Hz followed by 1500 pulses at 10 Hz), unilateral high-frequency left (HFL)-rTMS (2100 pulses at 10 Hz) or sham rTMS for 3 or 6 weeks depending on treatment response. Stimulation was targeted with MRI localization over the junction of the middle and anterior thirds of the middle frontal gyrus, using 120% of the coil-to-cortex adjusted motor threshold. The primary outcome of interest was the remission rate. The remission rate was significantly higher in the bilateral group than the sham group. The remission rate in the HFL-rTMS group was intermediate and did not vary statistically from the rate in the 2 other groups. There were no significant differences in decreased depression scores among the 3 groups. The authors concluded that these findings suggest that sequential bilateral rTMS is superior to sham rTMS; however, adjusting for coil-to-cortex distance did not yield enhanced efficacy rates. According to the authors, study limitations include the following: the number of pulses used per session in the unilateral group was somewhat lower in this trial than in more recent trials, and the sham condition did not involve active stimulation.

Guidelines & Consensus Statements

- *Canadian Network for Mood and Anxiety Treatments*
  - According to the Canadian Network for Mood and Anxiety Treatments (CANMET), rTMS is considered the first line treatment approach in those individuals who have failed at least 1 antidepressant trial. The CANMAT rationale explains that over 30 systematic reviews and meta-analyses have been completed and examined regarding rTMS in depression. A majority of those studies have been in individuals with some degree of treatment resistance such as treatment failure of 1-2 antidepressants. Overall, CANMAT rates the strength of evidence as level 1 (strong) for rTMS efficacy and safety for treatment resistant depression management (Milev et al., 2016).

- *Clinical TMS Society*
  - In their 2016 consensus review and treatment recommendations for TMS therapy for major depressive disorder, the Clinical TMS Society systematically reviewed the peer-reviewed literature on TMS therapy. In total, over 100 publications were identified, reviewed, and graded on their strength of evidence. When the current published evidence was seen as incomplete or insufficient, expert opinion was included where available. The results of the review

recommend that left prefrontal rTMS repeated daily for 4-6 weeks is an effective and safe treatment for depression in patients who are treatment resistant or intolerant (Perera et al., 2016).
    - In 2021, the Clinical TMS Society published coverage guidance for TMS in the treatment of obsessive- compulsive disorder (OCD). The coverage guidance is based on 28 publications from 1997-2020. The guidance includes indications for coverage, initial treatment criteria, coverage limitations, and utilization guidelines that include retreatment recommendations. After initial treatment criteria are met, treatment recommendations are performing TMS 5 days per week for 6 weeks, for a total of 29 sessions, and prescribed by a licensed psychiatrist who is trained in TMS administration.

- *Department of Veterans Affairs and Department of Defense (VA/DoD)*
    - The VA/DoD Clinical Practice Guidelines for the Management of Major Depressive Disorder (2022) suggests offering treatment with repetitive transcranial magnetic stimulation (rTMS) for treatment during a major depressive episode in patients with treatment-resistant major depressive disorder.

- *The Royal Australian and New Zealand College of Psychiatrists (RANZCP)*
    - According to the RANZCP Clinical Practice Guidelines for Mood Disorders (2021), TMS is considered a depression treatment option with consensus-based criteria. Before considering rTMS, the consensus recommendation is failure to respond to a reasonable and sufficient number of pharmacotherapy trials and psychological treatments. In addition, patient expectations should be thoroughly discussed during the consenting process, due to the moderate response and remission rates, and the effect size of rTMS when compared to sham.

- *World Federation of Societies of Biological Psychiatry (WFSBP)*
    - In their 2015 guidelines for biological treatment of unipolar depressive disorders, the WFSBP notes that antidepressant effects [of rTMS] “have now been confirmed in several large-scale clinical trials and a number of meta-analyses” (Bauer et al., 2015, p.88).

U.S. Food and Drug Administration

Transcranial Magnetic Stimulation must be administered by an FDA-cleared device and utilized in accordance with the FDA-labeled indications. See the following for more information:

- U.S. Food and Drug Administration. (2022). 510(K) Summary: ALTMS Magnetic Stimulation Therapy System, Blossom TMS Therapy System. 510(K) Number K220625. FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K220625.
- U.S. Food and Drug Administration. 510(K) Summary: Apollo TMS Therapy System. (2018). 510(K) Number K180313. FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K180313.
- U.S. Food and Drug Administration. 510(K) Summary: Axilum Robotics TMS-Cobot TS MV. (2019). 510(K) Number K182768. FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm.
- U.S. Food and Drug Administration. 510(K) Summary: Brainsway Deep TMS System. (2013, 2018, 2019, 2020, 2021). 510(K) Number K122288, K173540, K183303, K200957, K203735, K203616, K210201. FDA Website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm.
- U.S. Food and Drug Administration. (2022). 510(K) Summary: BTL-995-rTMS. 510(K) Number K212723. FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K212723.
- U.S. Food and Drug Administration. 510(K) Summary: Horizon TMS Therapy System. (2017, 2018, 2019). 510(K) Number K180907, K182853, K183376. FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.
- U.S. Food and Drug Administration. 510(K) Summary: Magstim Rapid2 Therapy System. (2015, 2017, 2021). 510(K) Number K143531, K162935, K211389. FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.
- U.S. Food and Drug Administration. (2020). 510(K) Summary: Magventure TMS Therapy System – For treatment of OCD. 510(K) Number K193006: FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K193006.
- U.S. Food and Drug Administration. 510(K) Summary: MagVita TMS Therapy System. (2015, 2017, 2018). 510(K) Number K150641, K170114 (MagproR20), K171481, K171967, K172667, K173620. FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm.

- U.S. Food and Drug Administration. 510(K) Summary: NexStim Navigated Brain Therapy. (2017, 2019). 510(K) Number K171902, K182700. FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.
- U.S. Food and Drug Administration. 510(K) Summary: Neurosoft TMS by TeleEMG (also CloudTMS). (2016, 2017). 510(K) Number K160309, K173441. FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm.
- U.S. Food and Drug Administration. 510(K) Summary: NeuroStar TMS Therapy System, Neurostar Advanced Therapy System. (2008, 2013, 2014, 2016, 2021, 2022). 510(K) Number K083538, K130233, K133408, K160703, K161519, K213543, K212289 (for OCD), K220127, K222230. FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm.

On August 17, 2018, the FDA granted a de novo marketing classification for the Brainsway Deep Transcranial Magnetic Stimulation (TMS) System for treatment of obsessive-compulsive disorder (OCD). See the following for more information: https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-transcranial-magnetic-stimulation-treatment-obsessive-compulsive-disorder; https://www.clinicaltmssociety.org/tms/devices.

For information about medical conditions and TMS approved devices, please see the UnitedHealthcare Medical Policy: Transcranial Magnetic Stimulation

Centers for Medicare and Medicaid Services

Medicare does not have a National Coverage Determination (NCD). Local Coverage Determinations (LCDs) and Local Coverage Articles (LCAs) exist; see the LCDs and/or LCAs for Repetitive Transcranial Magnetic Stimulation (rTMS) in Adults with Treatment Resistant Major Depressive Disorder, Repetitive Transcranial Magnetic Stimulation (rTMS) in Adults, and Transcranial Magnetic Stimulation for Major Depressive Disorder.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member-specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other clinical criteria may apply.

Procedure Codes	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 and management

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Diagnosis Codes	Description
F32.2	Major depressive disorder, single episode, severe without psychotic features
F32.3	Major depressive disorder, single episode, severe with psychotic features
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms

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Revision History

Date	Summary of Changes
06/13/2017	Version 1
11/16/2017	Policy revision: Added language to indicate that treatment is for patients 18 years of age and older, updated language surrounding provider supervision, changed Utilization Management to 30 sessions plus 6 taper, updates to template.
06/17/2019	Version 2
08/24/2020	Version 3: Updated the following: language in coverage rationale section, link to medical policy, sourcing, references, and appendix.
09/21/2020	Updated coverage rationale section with CMS sourcing.

Date	Summary of Changes
03/15/2021	Updated language regarding antidepressants, psychiatrist, and CMS sourcing regarding TMS administration and number of sessions.
10/19/2021	Annual Review and Update: Updated Coverage Rationale section regarding antidepressants, updated references/sources.
06/21/2022	Interim Update: removed L34869, L36469 from Coverage Rationale section, updates references/sources.
10/18/2022	Annual Review

Appendix

Additional resources considered in support of this policy:

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