

Level of Care Guidelines: UnitedHealthcare Transcranial Magnetic Stimulation

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INTRODUCTION

Level of Care Guidelines 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.

INSTRUCTIONS FOR USE

This guideline is used to make coverage determinations as well as to inform discussions about evidence-based practices and discharge planning. 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.

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

BENEFIT CONSIDERATIONS

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

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, 2021; L34869, 2020; 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

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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, 2021; L34869, 2020; 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, 2021; 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, 2021; L34522; L37086; L37088, 2019).
- If the individual is currently receiving electro-convulsive therapy, rTMS may be considered reasonable and necessary as a less invasive treatment option (CMS L36469, 2021; L34641; L34869, 2020).
- 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 L36469, 2021; L33398; L34641; L34869, 2020; L34522; L34998; L37086; L37088, 2019; Gaynes et al., 2011).
- 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 L36469, 2021; L33398; L34641; L34869, 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 L36469, 2021; L33398; L34641; L34869, 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 L36469, 2021; L34641; L34869, 2020; L34998; L37086; L37088, 2019).
- TMS is considered reasonable and necessary for up to 30 treatment sessions, followed by 6 tapered treatments (CMS L36469, 2021; L34869, 2020; 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.

DESCRIPTION OF SERVICES

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 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. This is achieved by visualizing the electrical field generated by the system in a three-dimensional image generated from a magnetic resonance image scan. Stimulation intensity is then calculated and delivered (Blumberger et al., 2016).

CLINICAL EVIDENCE

Transcranial Magnetic Stimulation for Major Depressive Disorder

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/Meta-Analyses

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.

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.

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 trial. 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.

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.

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% \geq 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% \geq , 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.

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

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

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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.

Philip and colleagues (2016) conducted a pilot feasibility study investigating 12-month outcomes of two maintenance TMS approaches. Participants were individuals not currently taking antidepressants with unipolar, non-psychotic, treatment-resistant depression. After an acute treatment phase consisting of 30 sessions of TMS (5 days per week for 6 weeks plus a three-week taper), individuals who met study-defined response criteria (HAM-D17 total score < 15 and more than 25% improvement in total score HAM-D17 compared with baseline) were randomized into a maintenance phase. Individuals were randomized to either (1) a single TMS session once every four weeks; or (2) observation only at each follow-up visit. All maintenance treatments were delivered open-label. Symptoms were assessed at monthly follow-up visits, and any patient meeting criteria for symptom recurrence (HAM-D17 > 16 and > 25% worsening from HAM-D17 score at entry into maintenance phase) received reintroduction TMS. All participants were antidepressant-free throughout the maintenance phase. A total of 67 individuals were enrolled, with 49 (73%) completing acute treatment and randomized for the maintenance phase (23 into the TMS sessions and 26 into the observation only groups, respectively). The odds of achieving remission in the acute phase did not differ between groups; of the 49 randomized patients, sixteen (33%) completed all 53 weeks of the study. The group randomized to TMS sessions had non-significantly longer time to first TMS reintroduction (91 vs. 77 days). The authors conclude that maintaining treatment-resistant depressed individuals off medications with periodic TMS appears feasible in some cases. The authors note that interpretations should be tempered by attention to the population studied, the relatively limited sample size, attrition rate, and open-label design. They further note that the results indicate a maintenance TMS schedule of only one treatment per month is not sufficient to prevent return of depressive symptoms within the year.

Levkovitz and colleagues (2015) conducted a multi-center, double blind, controlled study evaluating clinical outcomes of deep TMS (dTMS) for up to 4 months. At 20 sites, a total of 212 outpatients were antidepressant-free, who had failed 1-4 antidepressant treatments within the current depressive episode were enrolled. Eligible subjects were aged 22-68 and diagnosed with major depressive disorder, with duration of current episode at least one month but no more than 7 years. Subjects were required to have a HDRS-21 score of at least 20 at screening visit. Participants were randomly assigned to undergo dTMS using either H-coil or sham TMS, applied as a monotherapy after patients had tapered off antidepressant medications. Participants received daily weekday treatments at motor threshold (MT) 120% for 4 weeks acutely, then biweekly for an additional 12 weeks. Response was defined as a reduction of at least 50% in the total HDRS-21 score at week 5 compared to baseline, and remission was defined by a total HDRS-21 score < 10 at week 5. Response rates were 38.4% for dTMS vs. 21.4% for sham TMS. Remission rates were 32.6% and 14.6% for dTMS and sham TMS, respectively. The majority of participants achieving remission at the primary endpoint did not relapse until the end of the study. A total of 8 serious adverse events were reported in 7 subjects. One of the events, a seizure, was considered to be device-related and was reported to the FDA. Differences between active and sham treatment were stable during the 12-week maintenance treatment phase and were also observed in patients with higher degrees of treatment-resistance. In conclusion, the results demonstrate that dTMS is an effective and tolerable treatment for individuals diagnosed with MDD, and who have not positively responded to treatment with antidepressant medications in the current episode. The results appear durable, with maintenance of efficacy up to 16 weeks. A clinically noteworthy improvement was seen in even the higher treatment-resistant individuals. The authors also highlight the importance of adequate intensity (MT 120%) when training operators to use this system for antidepressant treatment.

Dunner and colleagues (2014) assessed a subset (n = 257) of patients from a previous acute efficacy

TMS treatment outcomes study (Carpenter, et al 2012). This subset of patients completed their acute treatment and then, regardless of outcome, agreed to enroll in a 12-month long-term follow-up phase. Efficacy measures included the CGI-S, the IDS-SR, and the PHQ-9. A total of 205 patients completed outcome evaluations through 12 months. Of the 120 patients who were responders or remitters after acute treatment, seventy-five (62.5%) continued to meet response criteria at all measured time points (3 mo, 6 mo, 9 mo, and 12 mo). Approximately one-third of patients received TMS reintroduction. Patients who received clinical benefit from TMS were significantly more likely to receive TMS reintroduction and were also significantly more likely to experience subsequent clinical benefit from reintroduction treatment. TMS reintroduction was seen in 15/77 (19.5%), 19/59 (32.2%), 27/44 (61.4%), and 32/76 (42.1%) of IDS-SR nonresponders, partial responders, responders, and remitters, respectively. The authors note limitations of no concurrent control population, and a lack of exploration on the influence of concomitant treatments, including the role of TMS reintroduction.

Carpenter and colleagues (2012) conducted a multisite, observational study to assess the efficacy of TMS in real-world practice. Outcomes experienced by a large population of depressed patients treated with TMS therapy in 42 clinical practice settings were measured. A total of 339 patients were screened, leading to a final study population of 307. The study design permitted patients to continue concurrent psychiatric medications during TMS treatment. Outcome assessments were obtained at baseline, week 2, and week 6 in cases where the acute course of TMS extended beyond 6 weeks. Efficacy measures included the CGI-S, IDS-SR and the PHQ-9. For the CGI-S (primary outcome measure), response was defined as achieving an endpoint rating of 3 or less, while remission was defined as achieving an endpoint of 2 or 1. The average number of overall antidepressant treatment attempts in the current episode was 3.6, with a range of 0-21. The average number of adequate antidepressant treatments in the current episode was 2.5, with a range of 0-14. The average number of TMS sessions across the acute phase was 28.3 (range: 2-94). A significant change in CGI-S from baseline to end of treatment was found. Clinician-assessed response rate was 58% and remission rate was 37.1%. Patients who had failed a minimum of one adequate antidepressant trial were as likely to be TMS responders as those who had failed two or more trials in the current episode. One case of seizure induction was reported. The authors conclude that observed clinical response and adherence rates in this naturalistic study were similar to those reported in open-label clinical trials in research study populations.

Janicak and colleagues (2010) assessed the durability of antidepressant effect after acute response to TMS in patients with MDD using protocol-specified maintenance antidepressant monotherapy. Participants were randomly assigned to active or sham TMS in a 6-week controlled trial. Using the randomized trial examining the acute efficacy and safety of TMS and a 6-week open trial of TMS, patients who met criteria for partial response (i.e., > 25% decrease from baseline on the HAM-D17) were followed for 24 weeks in a naturalistic follow-up study examining the long-term durability of TMS. During this durability study, TMS was readministered if patients met 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. A total of 142 patients achieved at least partial response from either of the prior two trials, and a total of 99 patients who successfully transitioned from active TMS to maintenance antidepressant monotherapy agreed to follow-up for the additional 24 weeks. Thirty-eight patients (38.4%) had symptom worsening and received reintroduction TMS. Ten of the 99 patients relapsed. Safety and tolerability were similar to acute TMS monotherapy. The authors suggest that the therapeutic effects of TMS are durable and that TMS may be successfully used as an intermittent rescue strategy to preclude impending relapse. They note that limitations include a lack of a controlled comparison.

George and colleagues (2010) conducted a sham-controlled, randomized trial to test whether daily left prefrontal rTMS safely and effectively treats major depressive disorder. The study was conducted at 4 U.S. sites, and included a 2-week no-treatment lead-in phase, a 3-week fixed-treatment phase (delivered daily on weekdays), and a variable 3- week extension for clinical improvers. Randomization of 199 patients to active and sham conditions was based on randomized permuted blocks stratified by site and higher or lower treatment resistance. Patients not showing sufficient improvement (< 30% drop from baseline in HAM-D score) at the end of the fixed 3-week period were discontinued from phase 1 and crossed over to open treatment (phase 2) without unmasking original assignment. If patients improved sufficiently (i.e., > 30% reduction in HAM-D score), treatment was continued for up to 3 additional weeks, with HAM-D assessments performed twice weekly. Antidepressant medication was started after the 3-week taper period. A total of 190 patients composed the intention-to-treat sample, with current average treatment resistance of 1.5 failed research-quality adequate treatment trials, and a range of 0-6

failed trials. There was a significant effect of treatment in the 190 patients, with 18 remitters (14.1% in the active arm and 5.1% in the sham arm). Five patients discontinued study participation because of adverse events, all of whom were receiving active TMS. No seizures or suicides occurred. In the open-label follow-up, 30.2% of originally active and 29.6% of sham patients remitted. The authors conclude that high-intensity rTMS for at least 3 weeks was significantly more likely than sham rTMS to induce remission in antidepressant medication-free patients with moderately treatment-resistant unipolar major depression. The authors do note several limitations to the study, including failure to enroll the projected 240 individuals suggested by the initial power analysis. Treaters were also able to guess randomization assignment better than chance. Although the treatment effect was statistically significant on a clinically meaningful variable (remission), the authors point out that the overall number of remitters and responders was less than one would like with a treatment requiring daily intervention for 3 weeks or more. The authors anticipate greater rates of overall response and remission if the TMS were delivered in combination with pharmacotherapy.

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.

The Agency for Healthcare Research and Quality (AHRQ) (Gaynes et al., 2011) conducted a Comparative Effectiveness Review of Nonpharmacologic Interventions for Treatment Resistant Depression, focused primarily on Tier 1 studies - defined as those studies of patients that have two or more antidepressant medication (ADM) failures. In addition, the review looked at lower tier studies (defined as one or more ADM failures or that didn't include number of failures as a variable in analyses). The report concluded that there was limited direct evidence for rTMS (where rTMS was compared head-to-head to other available treatments). Among Tier 1 studies, two "fair" trials were identified, one that compared ECT and rTMS, and one that compared ECT and ECT plus rTMS. The conclusion was that studies had "low strength of evidence". No differences between treatment conditions were found for depressive severity, response rates, and remission rates between ECT and rTMS. There was no evidence of comparative effectiveness compared to any other treatments. When combining Tier 1 studies with lower tier studies, evidence for rTMS efficacy compared to ECT was mixed. The studies had differential intervention methodologies and possible overlap in populations across studies, making comparisons across the various tiers difficult. The strength of the indirect evidence for rTMS (examining comparisons between treatment and sham) concluded that there was evidence for greater effectiveness of rTMS versus sham in Tier 1 studies. rTMS was beneficial relative to controls receiving a sham procedure on severity of depressive symptoms, response rate, and remission rate outcomes. rTMS produced a greater decrease in depressive severity; response rates were greater with rTMS than sham - those receiving rTMS were more than three times as

likely to achieve a depressive response as patients receiving a sham procedure.

As part of a previously published comparative effectiveness review on nonpharmacologic interventions for patients with treatment-resistant depression (Gaynes et al., 2011), the AHRQ (Gaynes et al., 2014) reviewed and published evidence addressing the efficacy of rTMS compared with sham control. The authors selected randomized controlled trials comparing rTMS with sham. The core patient population of interest was patients with major depressive disorder (MDD) who met the defined criteria of treatment-resistant depression as 2 or more treatment failures, though many trials did not use this definition when formulating their inclusion criteria. In total, 35 published articles reporting on 27 trials were included. Of the trials, 18 were labeled as “Tier 1 evidence” (evaluation of outcomes in a treatment-resistant population), with sample sizes ranging from 12 to 74 subjects and study duration ranging from 1 week to 6 weeks. Seven of the trials reported the mean number of antidepressant treatment failures (with a range of 3.2 - 6.5 failures). Results found rTMS to be beneficial compared to sham treatment, averaging a clinically meaningful decrease on the HDRS of more than 4 points when compared to sham. Limited evidence and variable treatment parameters prevented conclusions about which specific treatment options are more effective than others. How long these benefits persist also remained unclear. The authors conclude that for MDD patients with antidepressant treatment failure, rTMS is a reasonable, effective consideration.

TMS and Obsessive-Compulsive Disorder

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. 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 verify efficacy and exact strategy.

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.

In a randomized, controlled, partial crossover trial, D’Urso and colleagues (2016) assessed the efficacy of anodal or cathodal transcranial direct current stimulation (tDCS) regarding individuals diagnosed with OCD. Participants were ages 18-65, diagnosed with treatment resistant OCD and a Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score of ≥ 16 . A total of 10 participants completed the study. At post-treatment of 10 sessions, a statistically significant decrease was observed in the mean Y-BOCS scores of those participants (n=6) who underwent cathodal tDCS. There was not a pre-post difference in the Y-BOCS

scores of participants (n=4) following anodal tDCS. The authors conclude tDCS may have a future role in OCD treatment. Lastly, the authors acknowledge that the small sample of the study is a limitation and that additional studies are needed.

Hawken and colleagues (2016) examined six weeks of low frequency rTMS, applied bilaterally and simultaneously over the sensory motor area, in OCD individuals in a randomized, double-blind placebo-controlled multi-site clinical trial. Twenty-two participants were randomly enrolled into the treatment (active = 10) or placebo (sham = 12) groups. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was administered to determine baseline and post-treatment symptoms. At the conclusion of six weeks of rTMS, participants in the active group showed a clinically significant reduction in Y-BOCS scores compared to both the baseline and the sham group. In addition, this effect was maintained six weeks following the end of rTMS treatment. The authors report that further studies are needed to confirm the generalizability of these findings and to define the duration of rTMS clinical effect on the individuals with the diagnosis of OCD.

Trevizol et al. (2016) conducted a systematic review to assess the efficacy of TMS for OCD in randomized clinical trials (RCTs). Fifteen RCTs (n = 483) were included in the review. Most of the trials had small-to-modest sample sizes. Comparing active versus sham TMS, active stimulation was significantly superior for OCD symptoms. The funnel plot showed that the risk of publication bias was low and between-study heterogeneity was low. Meta-regression showed no particular influence of any variable on the results. The authors report that active transcranial magnetic stimulation was superior to sham stimulation for the alleviation of OCD symptoms. Trials had moderate heterogeneity results, despite different protocols of stimulation used. According to the authors, further RCTs with larger sample sizes are needed to clarify the precise impact of TMS in OCD symptoms.

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 treatment 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 treatment and no contraindications to rTMS.

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 (Rodrigues et al., 2019)
- Autism spectrum disorder (Barahona-Corrêa et al., 2018)
- Bipolar disorders (Tavares et al., 2017)
- Borderline personality disorder (De Vidovich et al., 2016)
- Posttraumatic stress disorder (Yan et al., 2017; Belsher et al., 2021)
- Schizophrenia (Dougall et al., 2015; 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

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.

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.

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.

Oberman et al. (2011) conducted a meta-analysis to evaluate the safety of theta burst stimulation (TBS). The adverse events were documented, and crude risk was calculated. The majority of adverse events attributed to TBS were mild and occurred in 5% of subjects. The authors indicated that based on this review, TBS seems to be a safe and efficacious technique. However, given its novelty, it should be applied with caution. Additionally, this review highlights the need for rigorous documentation of adverse events associated with TBS and intensity dosing studies to assess the seizure risk associated with various stimulation parameters (e.g., frequency, intensity, and location).

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 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.

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.

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.

Professional Societies

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 (2016) 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. 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. 510(K) Summary: Horizon TMS Therapy System. (2017, 2018, 2019). 510(K) Number ~~K171051~~, 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). 510(K) Number K143531, K162935. FDA website: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>.
- U.S. Food and Drug Administration. 510(K) Summary: MagVita TMS Therapy System. (2015, 2017, 2018). 510(K) Number K150641, K170114, 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. (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. (2008, 2013, 2014, 2016). 510(K) Number K083538, K130233, K133408, K160703, K161519. 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>.

In 2018, the FDA cleared theta burst stimulation using the MagVita TMS Therapy System. See the following for more information: <https://www.clinicaltmssociety.org/tms/devices>.

On November 11, 2017, the FDA cleared Nexstim’s NBT® system for marketing and commercial distribution in the US for the treatment of major depressive disorder (MDD). The NBT system stimulates the brain using navigated transcranial magnetic stimulation (nTMS), which is achieved by visualizing the electrical field generated by the system in a three-dimensional image generated from a magnetic resonance image scan. Stimulation intensity is then calculated and delivered. See the following for more information: <https://www.nexstim.com/news-and-events/news/press-release/news/nexstim-gains-fda-clearance-to-commercialise-its-nbtr-system-in-the-us-for-the-treatment-of-depressi/>; <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 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

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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APPENDIX

Additional resources considered in support of this guideline:

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