United Behavioral Health

Behavioral Clinical Policy: Transcranial Magnetic Stimulation

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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®[1].

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.

[1] Optum is a brand used by United Behavioral Health and its affiliates.

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:
  - The individual's depression has not responded to at least four (4) prior antidepressant medication trials at or above the minimal effective dose and duration in the current episode.
  - The individual has a documented inability to tolerate psychopharmacologic agents as evidenced by trials of four such agents, from at least two different agent classes, with distinct side effects
  - 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
- 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
- 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.
- TMS treatment is prescribed by a psychiatrist trained in the use of the specific device. The procedure is provided by or is under the direct supervision of a psychiatrist trained in the use of the specific device The TMS operator should be trained and certified to deliver repetitive transcranial magnetic stimulation (rTMS) including device operation, TMS coil targeting, and recognition and management of side effects. He or she should be trained as a first responder to a seizure and have basic life support training certification. (McClintock 2018).

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 maintenance therapy
- Theta burst stimulation (a type of TMS)
- Navigated transcranial magnetic stimulation (nTMS) for treatment planning
- Use of TMS for treating behavioral disorders other than major depressive disorder. These disorders include but are not limited to:
  - Alzheimer's disease
  - 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)

Use of transcranial magnetic stimulation is contraindicated in the following populations, which could result in serious injury or death:

- 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 psychoses or with psychiatric emergencies where a rapid clinical response is needed, such as marked physical deterioration, catatonia, or immediate suicide risk.

The safety and effectiveness of TMS therapy has not been established in the following patient populations or clinical conditions through a controlled clinical trial. The use of TMS in these patients is therefore unproven:

- Individuals who are acutely suicidal.
- Individuals with a history of substance abuse, eating disorder, or post-traumatic stress disorder whose symptoms are the primary contributors to the clinical presentation
- Individuals with a history of or risk factors for seizures during TMS therapy
- Individuals with vagus nerve stimulators or implants controlled by physiologic signals, including pacemakers, and implantable cardioverter defibrillators
- Individuals who are pregnant or nursing

UTILIZATION MANAGEMENT CRITERIA

Transcranial Magnetic Stimulation Admission Criteria

- See "*Common Criteria and Best Practices for All Levels of Care*": AND

- 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

- See "*Common Criteria and Best Practices for All Levels of Care*":
- 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.

Transcranial Magnetic Stimulation Discharge Planning and Criteria

- See "*Common Criteria and Best Practices for All Levels of Care*":
- Maintenance Therapy is considered not medically necessary by device manufacturers, and is not supported by the clinical evidence.

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.

Theta burst stimulation (TBS) is 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 37 minutes whereas TBS sessions are shorter with an average session length of a few minutes.

Navigated transcranial magnetic stimulation (nTMS) is 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.

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. Patients who are candidates for ECT and instead receive TMS likely do so because TMS is regarded as less invasive.

Clinical Trials

In a randomized, double-blind controlled study, Benadhira et al. (2017) assessed the benefits of maintenance repetitive transcranial magnetic stimulation (rTMS) for patients with treatment-resistant depression (TRD). Fifty eight TRD patients received rTMS over one month in an open-labeled design study (phase I). Responder patients 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 patients were responders after one month of active rTMS (phase I), and 17 patients were randomized for the maintenance sessions (phase II). The Hamilton Depression Rating Scale (HDRS) scores demonstrated 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 represent a novel strategy for preventing relapse in TRD patients who respond to rTMS treatment. These results should be confirmed in a larger sample.

Zhang et al. (2019) investigated the efficacy and clinical outcome of add-on rTMS in a large sample of adolescent patients compared to adult patients in a naturalistic study. This study included 117 patients (42 adolescents vs. 75 adults) with mood or anxiety disorders who were treated with at least 10 sessions of rTMS. Symptoms of depression and anxiety were measured using the Hamilton Rating Scale for Depression (HAMD) and the Hamilton Rating Scale for Anxiety (HAMA) respectively, at baseline and after 2 and 4 weeks of follow-up. Comparisons of clinical improvement and rates of response/remission were made across age groups. All the age groups showed significant improvements in clinical symptoms. No safety or tolerability concerns were identified. Symptomatic improvements and response/remission rates were more significant in adolescent patients than in adults. Decrease in HAMD and HAMA scores after 2 weeks and 4 weeks of rTMS treatment were positively correlated in adolescents, but not in adults. General linear model repeated measures demonstrated significant effect of time × age group interaction on the HAMD score, in response to 10 sessions of rTMS. According to the authors, add-on rTMS is feasible, tolerable, effective and more applicable to adolescents with mood or anxiety disorders. Double-blinded and sham-controlled trials with long term follow-up are needed for validating this conclusion.

Yip and colleagues (2017) conducted a double-blind, placebo-controlled continuation TMS study to examine the response among acute-phase non-responders of deep repetitive transcranial magnetic stimulation (dTMS) monotherapy for depression. Participants were medication-free outpatients with a primary diagnosis of Major Depressive Disorder, single or recurrent episode, Clinical Global Impressions-Severity rating >4, and total score on the Hamilton Depression Rating Scale >20 initially. For this analysis, 33 participants that had received active treatment in a blinded fashion, but did not respond (>50% decrease in HDRS-21 total score relative to baseline) after 20 treatments were selected. Treatment included once daily dTMS, 5 days per week, for 20 minutes per session. Following the initial treatment (acute phase), the continuation phase consisted of twice-weekly dTMS sessions for up to 12 weeks. Results indicate that 61% of non-responders did respond to treatment after 4 weeks of daily dTMS treatment. In addition, 73% of participants were able to achieve responder status at least once, and 64% were able to achieve remission status at some point during continuation. The authors conclude that a significant number of non- responders to dTMS treatment can eventually respond to continued treatment. They further conclude that these results support the treatment beyond the acute treatment course for dTMS non-responders.

Haesebaert and colleagues (2016) conducted a 3-arm open-label study to investigate the clinical efficacy of repetitive transcranial magnetic stimulation (rTMS), venlafaxine, or a combination of both treatments as a maintenance treatment in patients with treatment-resistant depression (TRD). The study included 66 patients (of which 45 were remitters) who responded to rTMS (n =25), venlafaxine (n = 22), or a combination of both treatments (n = 19). The patients continued to receive the respective treatment as a maintenance treatment over a 12-month period. Maintenance rTMS was delivered twice per week for the first month, once per week for the next two months, and once every two weeks for the remaining nine months. Venlafaxine was maintained at the dose that induced a clinical response (either 150mg/day or 225mg/day). At month 12, a total of 36 patients had been lost to follow-up. Results found that after 12 months of follow-up, there was no difference between the three groups in terms of rates of remitters or rates of patients who had not relapsed. The authors conclude that the three maintenance approaches exhibited similar efficacies in relapse prevention and maintenance of remission in patients with TRD. The authors note several limitations of the study, including the open-label observational design, without control group or placebo condition. Additionally, approximately half of the sample size of patients was ultimately lost to follow-up.

Philip and colleagues (2016) conducted a pilot feasibility study investigating 12-month outcomes of two maintenance TMS approaches. After an acute treatment phase consisting of 30 sessions of TMS (5 days per week for 6 weeks plus a three-week taper), patients who met study-defined response criteria (HAMD17 total score < 15 and more than 25% improvement in total score HAMD17 compared with baseline) were randomized into a maintenance phase. Patients 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 (HAMD17 > 16 and > 25% worsening from HAMD17 score at entry into maintenance phase) received reintroduction TMS. All patients were antidepressant-free throughout the maintenance phase. A total of 67 patients 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). 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 nonsignificantly longer time to first TMS reintroduction (91 vs. 77 days). The authors conclude that maintaining treatment-resistant depressed patients off medications with periodic TMS appears feasible in some cases. The authors note that interpretations should be tempered by consideration of 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 dTMS for up to 4 months. At 20 sites, a total of 212 outpatients who had failed 1-4 antidepressant treatments within the current depressive episode were enrolled. Eligible subjects were aged 22-68 with DSM-IV diagnosed 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. Patients were randomly assigned to undergo dTMS using either H-coil or sham TMS, applied as a monotherapy after patients had tapered off antidepressant medications. Patients 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 patients 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 the event 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. The authors 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 either 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.

Harel and colleagues (2014) examined the safety and feasibility of deep TMS (dTMS) continuation treatment for major depressive disorder in 29 patients over the course of 18 weeks, following 4 weeks of acute treatment. The 22-week study was divided into three phases: an acute phase of 4 weeks in which daily sessions were conducted, for a total of 20 sessions; “continuation treatment I” of 8 weeks in which sessions were conducted twice a week for a total of 16 sessions; and “continuation treatment II” of 10 weeks, in which sessions were conducted once a week. Response was defined as > 50% decrease from baseline in HDRS score and remission as < 10 score on the HDRS. Relapse was defined as > 18 score on the HDRS for two consecutive weeks. Subjects were aged 18-65 and had a DSM-IV diagnosis of major depressive disorder. Participants also had a score of > 20 on the HDRS-21 at screening, and had either failed at least one adequate pharmacological trial during the current episode or had intolerance to two antidepressants. Twenty-six of the 29 patients completed the acute phase of treatment. Twelve (46.2%) of the subjects completing the acute treatment phase showed a significant response. Ten of the 26 subjects dropped out by the end of “continuation treatment I”. A total of 15 subjects completed the full length of the continuation phase. As this study was an open study with a small sample size and add-on design, the authors note it was not possible to rule out a possible placebo effect and expectancy bias, as well as improvement from result of other factors. Another limitation was a high dropout rate, perhaps partly due to the relative length of the study. The authors conclude that future studies should use a sham controlled randomized design with a large number of patients to further assess the efficacy of dTMS in the treatment of MDD.

Carpenter and colleagues (2012) conducted a naturalistic, observational study to summarize outcomes experienced by a large population of depressed patients treated with TMS therapy in 42 clinical practice settings. 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.

Mantovani and colleagues (2012) presented long-term follow-up of patients who were remitters from an acute double- blind controlled trial of TMS (George, et al 2010; n = 18) or from an open-label extension in patients who did not respond to the acute trial (McDonald, et al 2011; n = 43). Subjects were followed for 6 months, but retention from 3 to 6 months was too low (n = 20) to allow meaningful analysis. As a result, the authors chose to report the 3-month follow-up data. Relapse was the primary outcome and defined as HDRS-24 > 20. Of the 61 remitters in the acute trials, five entered naturalistic follow-up and 50 entered a TMS taper phase (three sessions the first 2 weeks, two sessions the second 2 weeks). A total of 32 patients completed the TMS taper and 1-, 2-, and 3-month follow-ups. At 3-month follow-up, 29 of the 50 (58%) were classified as in remission (HDRS-24 < 10), two of 50 (4%) were partial responders, and one of 50 (2%) met criteria for relapse. During the entire 3-month follow-up, five of the 37 patients relapsed (13.5%), with four of these patients regaining remission by the end of the study. The authors conclude that most patients experience persistence of benefit from TMS followed by pharmacotherapy or no medication, though they acknowledge that longer follow-up, lower drop-out rates, and more rigorous studies are needed to explore the true long-term durability of remission produced by TMS.

McDonald and colleagues (2011) conducted an open-label follow up to a larger controlled trial (George, et al 2010), first identifying those patients who failed to meet minimal response criteria in the controlled study, and then enrolling these individuals in treatment for an additional 3-6 weeks. Patients who failed to remit using fast TMS over the left dorsolateral prefrontal cortex (10 HZ @ 120% of motor threshold) could switch to slow right TMS (1 HZ @ 120 of motor threshold) for up to 4 additional weeks. The final outcome measure was remission, defined as a HAM-D score of < 3 or two consecutive HAM-D scores less than 10. Results found that 43 of the 141 patients (30.5%) who enrolled in the open phase study eventually met criteria for remission. Of the patients who failed fast left TMS, 26% remitted during slow right treatment. The authors conclude that the total number of TMS stimulations needed to achieve remission in treatment-resistant depression may be higher than is used in most studies. Noted is that the results of the study are limited by the open label trial.

Isserles and colleagues (2011) assessed the H1 deep TMS (dTMS) coil as an add-on to antidepressant medication in treating patients with major depression. The study enrolled 57 patients for 4 weeks of daily 20Hz stimulation sessions, and an additional 4 weekly sessions as a maintenance phase. Main entry criteria included a diagnosis of non-psychotic MDD with HDRS-24 score of > 21. Patients also had to have failed at least two antidepressant medications and been free from known TMS risk factors. Efficacy analyses were performed on 46 patients who had a baseline measurement and at least two additional weekly assessments (i.e., received at least 10 sessions of dTMS treatment). Response rate was defined as a decrease of at least 50% in the HDRS-24 score, and remission rate defined as a HDRS-24 score less than or equal to 10. Overall, treatment was reported as easy to tolerate, and most patients suffered no side effects nor complained of significant discomfort. Fifteen patients withdrew consent during the daily treatment phase. One patient suffered a short tonic-clonic generalized seizure during the second treatment session and was removed from the study. Overall, 21 of the 46 patients (46%) achieved response criterion, and 13 (28%) achieved remission criterion by the end of the daily treatment phase. Following the daily phase, 11 out of the 13 remitters continued to the four week maintenance phase. One patient left the study after 2 weeks of maintenance treatment, with the other 10 remitters concluding this phase and preserving remission criteria. The authors conclude that the positive results warrant a wider study that will include a sham control arm to confirm dTMS efficacy for resistant depression.

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. Using the randomized trial examining the acute efficacy and safety of TMS (O'Reardon, et al 2007) and a 6-week open trial of TMS (Avery, et al 2008), 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 1142 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.

Janicak and colleagues (2008) examined comprehensive acute and long-term safety data obtained from 3 sequentially conducted studies of TMS. The first study was a large randomized, multisite, double-blind comparison of active TMS vs. sham TMS (O'Reardon, et al 2007). The second study (Avery, et al 2008) was a 6-week, open-label, acute efficacy study of TMS monotherapy available to all enrolled subjects whose depression had not responded sufficiently during the double blind-study. The third study (unpublished data, 2007) allowed open-label TMS reintroduction for symptom re-emergence to augment maintenance antidepressant monotherapy over a 24-week period in responders during the first or second study. The authors determined that TMS was administered in over 10,000 cumulative treatment sessions in the study program, with no deaths or seizures. Most adverse events were mild to moderate in intensity. Transient headaches and scalp discomfort were the most common adverse events. Auditory threshold and cognitive function did not change. There was a 4.5% discontinuation rate due to adverse events during acute treatment.

Systematic Reviews/Meta-Analyses

Voight et al. (2019) conducted a systematic review to determine the clinical efficacy of repetitive transcranial magnetic stimulation (rTMS) in patients after ≤1 medication trials. Twenty two articles were assessed for eligibility and ultimately 10 articles were 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 authors concluded that the use of rTMS in patients 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.

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.

Magavi et al. (2017) examined the efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) as a treatment for treatment-resistant depression in adolescents. A systematic review of six databases was conducted. Ten multi-subject trials, all uncontrolled, and five case reports met inclusion criteria. Twelve studies focused on treatment efficacy, whereas three studies focused exclusively on adverse events. All efficacy studies focused on adolescents only; 10 of these studies indicated that rTMS may demonstrate some benefit. Improvement within 2-8 weeks was reported in most studies, with a few studies indicating potential long-term benefits. A variety of adverse events occurred including scalp pain, which was the most common, as well as seizures. According to the authors, controlled studies of rTMS are warranted to further examine whether this treatment is a potential option for adolescents with treatment-resistant depression.

Allan and colleagues (2011) conducted a meta-analysis of thirty-one studies on TMS for the treatment of depression. This provided a cumulative sample of 815 active and 716 sham TMS courses. Studies were included if they had a randomized parallel or cross-over design with sham control, both patients and investigators were unaware of the treatment conditions, samples consisted of > 10 patients in each group, participants in each treatment group had a diagnosis of major depressive episode, and the outcome was measured using a version of the HDRS or MADRS with baseline and follow-up scores. The authors found a moderately sized effect in favor of TMS, with a significant variability between study effect sizes. At 4 weeks' follow-up after TMS, the authors noted no further change in depression severity. The authors conclude that if the TMS effect is specific, only further large double-blind randomized controlled designs with systematic exploration of treatment and patient parameters will help to define optimum treatment indications and regimen.

Slotema and colleagues (2010) conducted a meta-analysis on the efficacy of rTMS in psychiatric disorders. A total of 57 TMS studies were selected for the meta-analysis, including diagnoses of depression (40 studies), auditory verbal hallucinations (AVH; 7 studies), negative symptoms of schizophrenia (7 studies), and obsessive-compulsive disorder (3 studies). Other diagnoses provided too small of a sample size to be included in the meta-analysis. The studies specific to depression were divided into (1) rTMS vs. sham (34 studies), and (2) rTMS vs. ECT (6 studies). The meta- analysis indicated that rTMS is more effective than sham treatment in the treatment of depression, and a trend that rTMS as a monotherapy was more effective than as an adjunctive treatment to priorly started antidepressants. Further analysis showed that ECT yielded more favorable results than rTMS. The authors note that the duration of effect using rTMS in the treatment of depression is unknown.

Schutter (2009) conducted a meta-analysis to study the antidepressant effects of rTMS in all available published clinical trials that applied at least five treatment sessions of high-frequency rTMS in double-blind sham-controlled designs. A total of thrity studies (n = 1164 patients) that compared change in depression score from baseline to endpoint of active rTMS (n = 606) vs. sham rTMS (n = 558) treatment were included. Among them, a total of 850 (73%) patients were considered resistant to medication. The meta-analysis findings showed that high-frequency TMS was found to be superior to sham in the treatment of depression. TMS was also found to be a safe method that was well tolerated by patients. The author cautions that integrity of blinding and a lack of proper control conditions are considered limitations of rTMS trials. The meta-analysis concludes that rTMS may be an alternative for patients with major depression, and in particular, those who are unable to tolerate antidepressant medication side effects.

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) 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 appropriate as a treatment in patients with MDD even if the patient is medication resistant or has significant comorbid anxiety.
- There is no 1 recommended maintenance antidepressant strategy for patients after a beneficial rTMS acute course. Rather, it is recommended that the following available evidence-based antidepressant strategies be used after successful acute rTMS treatment: repeat rTMS, pharmacotherapy, manualized psychotherapy, exercise and combination of those treatments. Further research is needed to develop evidenced-based antidepressant maintenance strategies following acute clinical benefits with rTMS.

- Regarding allowable psychotropic medications during TMS treatment the consensus statement indicates that the safety guidelines for rTMS were determined in study participants who were largely free of antidepressant medications. While it is possible 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 therapeutic 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, there is insufficient evidence to support routine clinical rTMS use in these populations.

The 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 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 for Other Conditions

Rehn et al. (2018) performed an updated systematic review and meta-analysis on the effectiveness of rTMS for the treatment of obsessive-compulsive disorder (OCD) and aimed to determine whether certain rTMS parameters, such as cortical target, may be associated with higher treatment effectiveness. After conducting a systematic literature review for randomized controlled trials (RCTs) on rTMS for OCD through to 1 December 2016, a random-effects meta-analysis with the outcome measure as pre-post changes in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores was performed. To determine whether rTMS parameters may have influenced treatment effectiveness, studies were analyzed according to cortical target, stimulation frequency, and length of follow-up. Data were obtained from 18 RCTs on rTMS in the treatment of OCD. Overall, rTMS yielded a modest effect in reducing Y-BOCS scores with Hedge's g of 0.79. Stimulation of the supplementary motor area yielded the greatest reductions in Y-BOCS scores relative to other cortical targets. Subgroup analyses suggested that low frequency rTMS was more effective than high frequency rTMS. The effectiveness of rTMS was also greater at 12 weeks follow-up than at four weeks follow-up. According to the authors, this meta-analysis implies that low frequency rTMS applied over the supplementary motor area may offer the greatest effectiveness in the treatment of OCD. The authors indicated that the therapeutic effects of rTMS also appear to persist post-treatment and may offer beneficial long-term effectiveness. The authors suggested that future large-scale studies focus on the supplementary motor area and include follow-up periods of 12 weeks or more.

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 concluded that active transcranial magnetic stimulation was superior to sham stimulation for the amelioration 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.

In a double-blinded randomized sham controlled trial, Arumugham et al. (2018) investigated the efficacy of low-frequency repetitive transcranial magnetic stimulation (rTMS) in patients with obsessive-compulsive disorder (OCD). Forty subjects with OCD, who were on stable medications with partial/poor response to pharmacotherapy were randomly divided into 2 groups (n = 20 in each group), to receive either active or sham low-frequency rTMS over bilateral pre-supplementary motor area (pre-SMA). Thirty-six patients were eligible for intent-to-treat analysis. There was no significant difference in relevant demographic and clinical variables between the 2 groups at baseline. There were no statistically significant differences between the 2 groups after 3 weeks of treatment in the Yale-Brown Obsessive Compulsive Scale score and other secondary outcome measures including responder rates and depressive and anxiety symptoms. The authors concluded that low-frequency rTMS over pre-SMA may not be effective as an augmenting agent in partial/poor responders to SRIs. This study underlines the need to explore alternate rTMS protocols in OCD.

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

- Alzheimer's disease, dementia and cognitive impairment (Lin et al., 2019; Dong et al., 2018; Vacas et al., 2018)
- Anxiety (Vicario et al., 2019; Dilkov et al., 2017)
- Autism spectrum disorder (Barahona-Corrêa et al., 2018)
- Bipolar disorders (Tavares et al., 2017)
- Borderline personality disorder (Reyes-López et al., 2018)
- Posttraumatic stress disorder (Yan et al., 2017)
- Schizophrenia (Aleman et al., 2018; Osoegawa et al., 2018)
- Substance use disorders (Kedzior et al., 2018; Su et al., 2017)

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.

Theta Burst Transcranial Magnetic Stimulation

In a systematic review and meta-analysis, Sonmez et al. (2019) examined accelerated TMS 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.

Mutz et al. (2018) conducted a systematic review and meta-analysis to examine the efficacy of non-invasive brain stimulation in adults with unipolar and bipolar depression. Randomized sham-controlled trials of transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS) and theta-burst stimulation (TBS), without co-initiation of another treatment were included. The effects on response, remission, all-cause discontinuation rates and continuous depression severity measures were analyzed. Fifty-six studies met the criteria for inclusion (N = 3058). Response rates demonstrated efficacy of high-frequency rTMS over the left DLPFC, right-sided low-frequency rTMS bilateral rTMS, deep TMS, intermittent TBS and tDCS; but not for continuous TBS, bilateral TBS or synchronized TMS (sTMS). There were no differences in all-cause discontinuation rates. The strongest evidence was for high-frequency

rTMS over the left DLPFC. The authors indicated that there is insufficient published data available to draw firm conclusions about the efficacy and acceptability of TBS and sTMS.

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 acceptable as sham. The estimated relative ranking of treatments suggested that priming low-frequency and bilateral rTMS might be the most efficacious and acceptable interventions among all rTMS strategies. However, results were imprecise 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.

Berlim et al. (2017) conducted a systematic review and exploratory meta-analysis of RCTs to evaluate the use of theta burst stimulation (TBS) for treating major depression. Data were obtained from 5 RCTs, totalling 221 subjects with major depression. The pooled Hedges' g for pre-post change in HAM-D scores was 1.0, indicating a significant and large-sized difference in outcome favoring active TBS. Furthermore, active TBS was associated with significantly higher response rates when compared to sham TBS (35.6% vs. 17.5%, respectively; p = 0.005), although the groups did not differ in terms of rates of remission (18.6% vs. 10.7%, respectively; p = 0.1) and dropout (4.2% vs. 7.8%, respectively; p = 0.5). Finally, subgroup analyses indicated that bilateral TBS and unilateral intermittent TBS seem to be the most promising protocols. The authors concluded that although TBS is a promising novel therapeutic intervention for major depression, future studies should identify more clinically-relevant stimulation parameters as well as neurobiological predictors of treatment outcome, and include larger sample sizes, active comparators and longer follow-up periods.

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).

In a randomized, multicentre 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. Dropout 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 event was headache in both groups (10 Hz rTMS: 131 [64%] of 204; iTBS: 136 [65%] of 208). The authors concluded that in patients 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.

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 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 differ statistically from the rate in the 2 other groups. There were no significant differences in reduction of 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.

Fitzgerald et al. (2009) investigated whether repetitive transcranial magnetic stimulation (rTMS) targeted to a specific site in the dorsolateral prefrontal cortex (DLPFC), with a neuro-navigational method based on structural MRI, would be more effective than rTMS applied using the standard localization technique. Fifty-one patients with treatment-resistant depression were randomized to receive a 3-week course (with a potential 1-week extension) of high-frequency (10 Hz) left-sided rTMS. Thirty trains (5 s duration) were applied daily 5 days per week at 100% of the resting motor threshold. Treatment was targeted with either the standard 5 cm technique (n=27) or using a neuro-navigational approach (n=24). This involved localizing the scalp location that corresponds to a specific site at the junction of Brodmann areas 46 and 9 in the DLPFC based on each individual subject's MRI scan. There was an overall significant reduction in the Montgomery-Asberg Depression Rating Scale scores over the course of the trial, and a better outcome in the targeted group compared with the standard localization group at 4 weeks. Significant differences were also found on secondary outcome variables. The authors concluded that the use of neuro-navigational methods to target a specific DLPFC site appears to enhance response to rTMS treatment in depression. Further research is required to confirm this in larger samples, or to establish whether an alternate method based on surface anatomy, including measurement from motor cortex, can be substituted for the standard 5 cm method.

Professional Societies

American Psychiatric Association (APA)

In a 2010 clinical practice guideline for the treatment of patients with major depressive disorder, the APA states that electroconvulsive therapy (ECT) remains the treatment of best established efficacy against which other stimulation treatments (e.g., vagus nerve stimulation, deep brain stimulation, transcranial magnetic stimulation, other electromagnetic stimulation therapies) should be compared. For patients whose symptoms have not responded adequately to medication, ECT remains the most effective form of therapy and should be considered [I]. [For these patients] Magnetic stimulation could also be considered [II]. According to the APA, a substantial number of studies of TMS have been conducted, but most have had small sample sizes, and the studies overall have yielded heterogeneous results. Further complicating the interpretation of the TMS literature is the variability in stimulation intensities (relative to the motor threshold), stimulus parameters (e.g., pulses/second, pulses/session), anatomical localization of stimulation, and number of TMS sessions in the treatment course. The three APA rating categories represent varying levels of clinical confidence: I: Recommended with substantial clinical confidence II: Recommended with moderate clinical confidence III: May be recommended on the basis of individual circumstances

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).

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 (MDD).

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.” The guidelines additionally state that “maintenance rTMS for depression has only been explored very rarely. To date there are no sham-controlled studies supporting its efficacy” (Bauer et al 2015).

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. Pediatric Medical Devices 2017. Available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ucm135104.htm. (Accessed March 29, 2019)
- U.S. Food and Drug Administration. 510(K) Summary: Rapid2 Therapy System 2015. 510(K) Number

K143531. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf14/K143531.pdf. (Accessed March 29, 2019)

- U.S. Food and Drug Administration. 510(K) Summary: MagVita TMS Therapy System 2015. 510(K) Number K150641. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf15/K150641.pdf. (Accessed March 29, 2019)
- U.S. Food and Drug Administration. 510(K) Summary: Brainsway Deep TMS System 2013. 510(K) Number K122288. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf12/k122288.pdf. (Accessed March 29, 2019)
- U.S. Food and Drug Administration. 510(K) Summary: NeuroStar TMS Therapy System 2014. 510(K) Number K133408. Available at: https://neurostar.com/pdf/FDA%20Clearance%20TMS%20All%20Dates.pdf. (Accessed March 29, 2019)
- U.S. Food and Drug Administration. 510(K) Summary: NeuroStar TMS Therapy System. 510(K) Number K083538. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf8/K083538.pdf. (Accessed March 29, 2019)

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/NewsEvents/Newsroom/PressAnnouncements/ucm617244.htm. (Accessed March 29, 2019)

In 2018, the FDA cleared theta burst stimulation using the MagVita TMS Therapy System.
See the following for more information: https://www.magventure.com/component/k2/5-news/124-fda-clearance-for-magventure. (Accessed March 29, 2019)

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/. (Accessed March 29, 2019)

CENTERS FOR MEDICARE AND MEDICAID SERVICES

Medicare does not have a National Coverage Determination (NCD). Local Coverage Determinations (LCDs) exist; see the LCDs for Transcranial Magnetic Stimulation (TMS), Repetitive Transcranial Magnetic Stimulation (rTMS) in Adults with Treatment Resistant Major Depressive Disorder, Transcranial Magnetic Stimulation and Transcranial Magnetic Stimulation for Major Depressive Disorder. (Accessed April 2, 2019)

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.

Diagnosis 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

Procedure 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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HISTORY/REVISION INFORMATION

Date	Action/Description
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