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Coverage Policy

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Transcranial Magnetic Stimulation

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Overview

This Coverage Policy addresses the various types of transcranial magnetic stimulation (TMS) for the treatment of unipolar major depressive disorder, obsessive-compulsive disorder, and other psychiatric and neurological conditions.

Coverage Policy

Initial Transcranial Magnetic Stimulation (TMS) for Treatment of Major Depressive Disorder

An initial regimen (i.e. 30-36 treatments) of transcranial magnetic stimulation administered in an outpatient office setting using a U.S. Food and Drug Administration (FDA) approved device is considered medically necessary for major depressive disorder when an individual meets ALL of the following criteria:

- age 18 years or older
- diagnosis of major depressive disorder (unipolar), moderate-to-severe, single or recurrent episode or acute relapse, without psychosis, as defined by the most recent edition of Diagnostic and Statistical Manual of Mental Disorders
- during the current episode of depression ALL of the following criteria are met:
  - failure of two or more trials of antidepressant medications from two separate classes of antidepressant medications. A failed trial is defined as EITHER of the following:
    - use of an antidepressant medication at adequate therapeutic doses for at least four weeks with no significant reduction in depressive symptoms
    - use of an antidepressant medication with documented intolerance or medical contraindication
  - an adequate trial of an evidence-based psychotherapy known to be effective in the treatment of major depressive disorder, without significant improvement in depressive symptoms
  - validated depression monitoring scales are administered at the beginning and at the end of the initial and each subsequent course of TMS

Repeat TMS for Treatment of Major Depressive Disorder

Repeat transcranial magnetic stimulation (TMS) (i.e. 30-36 treatments) administered in an outpatient office setting for a recurrence or an acute relapse of major depressive disorder is considered medically necessary when ALL of the following criteria are met:

- all of the above criteria for initial TMS therapy were met prior to the initial course of TMS
- individual had more than a 50% improvement as evidenced by one or more standard rating scales for depression at the end of the most recent course of TMS
- improvement has been maintained for at least two months after the most recent course of TMS

Initial TMS for Treatment of Obsessive-Compulsive Disorder

An initial regimen (i.e. 30-36 treatments) of deep transcranial magnetic stimulation (TMS) administered in an outpatient office setting using a U.S. Food and Drug Administration (FDA) approved device for obsessive-compulsive disorder (OCD) is considered medically necessary for OCD when an individual meets ALL of the following criteria:

- age 18 years or older
- diagnosis of OCD as defined by the most recent edition of Diagnostic and Statistical Manual of Mental Disorders
- failure of two or more trials of psychopharmacologic medications for the treatment of OCD. A failed trial is defined as EITHER of the following:
  - use of a psychopharmacologic medication at adequate therapeutic doses for at least eight weeks with no significant reduction in OCD symptoms
  - use of a psychopharmacologic medication with documented intolerance or medical contraindication
- an adequate trial of an evidence-based psychotherapy known to be effective in the treatment of OCD, without significant improvement in OCD symptoms
- the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) is administered at the beginning and at the end of the initial and each subsequent course of TMS

Repeat TMS for Treatment of Obsessive-Compulsive Disorder

Repeat deep transcranial magnetic stimulation (TMS) (i.e. 30-36 treatments) administered in an outpatient office setting for a recurrence or an acute relapse of OCD is considered medically necessary when ALL of the following criteria are met:

- all of the above criteria for initial TMS therapy were met prior to the initial course of TMS
- individual had more than a 30% improvement as evidenced by Yale-Brown Obsessive Compulsive Scale (Y-BOCS) at the end of the most recent course of TMS
- improvement has been maintained for at least two months after initial course of TMS

Not Medically Necessary

Transcranial magnetic stimulation (TMS), used as a maintenance therapy, is considered not medically necessary.

Transcranial magnetic stimulation (TMS) for any other indication, including but not limited to migraine headaches, is considered not medically necessary.

Experimental, Investigational or Unproven

Accelerated treatment protocols (e.g., Theta Burst Stimulation (TBS), Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT), Stanford Neuromodulation Therapy (SNT)), are considered experimental, investigational or unproven.

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

General Background

Transcranial magnetic stimulation (TMS) is a non-invasive neurostimulation technique that modulates cortical excitability. In repetitive TMS (rTMS), trains of several pulses are delivered through repeated stimulation over the same area with frequencies ranging from 1 to 20 Hz. The two most commonly used methods of TMS are repetitive transcranial magnetic stimulation (rTMS) and deep TMS (dTMS). Standard repetitive transcranial magnetic stimulation delivers a magnetic field to a maximal depth of approximately two centimeters (cm) below the cortical surface and is also called surface cortical TMS or superficial TMS. Surface cortical rTMS of the left dorsolateral prefrontal cortex (DLPFC) is the most widely used and studied form of TMS. The site most commonly used for the treatment of depression is the left prefrontal cortex. TMS is typically applied to the skull with an electromagnetic coil called a figure-of-eight coil (8-coil) (U.S. Food and Drug Administration [FDA], Aug 14, 2018; Feffer, et al., 2017).

Deep transcranial (dTMS) stimulates brain structures beneath the superficial prefrontal cortex using a magnetic Hesel-coil (H-coil). The H-coil is proposed to cause cortical excitability up to a maximum depth of six centimeters which causes modulation of the activity of the cerebral cortex and of deeper neural circuits making it more effective than surface stimulation. H-coils stimulate a larger area of the brain than the conventional figure-8 coils. There are 14 different H-coils designed to target specific brain regions (e.g., H1, H2, H1L) based on the area and method of stimulation. In H-coil therapy, the electromagnetic coil is contained in a helmet with multiple windings

in multiple planes. Although deep stimulation can also be accomplished with a large circular coil or a double cone coil, their electromagnetic field decays more rapidly and to reach significantly deep targets much higher intensities must be used on the surface. Reported side effects include headaches, facial pain, tooth pain, neck pain and seizure (Feffer, et al., 2017; Tendler, et al., 2017; Feifel, et al., 2016; Nordenskjold, et al., 2016; Tendler, et al., 2016; Bersani, et al. 2013).

The effects of TMS depend on the parameters of waveform, frequency, intensity, and duration of stimulation. Due to the lower energy requirements, a biphasic waveform is frequently used in stimulation. Frequency is one of the most important parameters in rTMS protocols that affect the clinical outcome. High frequency (HF) rTMS usually comprises frequencies ≥ 5 Hz, while low frequency (LF) rTMS includes frequencies ≤ 1 Hz. Evidence has suggested that LF-rTMS is ‘‘inhibitory’’ while HF-rTMS is ‘‘excitatory” (Guo, et al., 2017). The electromagnetic current repeatedly switches on and off for up to 10 times per second to produce the pulses. To determine the therapeutic magnetic strength, the amount of magnetic energy is adjusted until the motor threshold is reached (i.e., the patient’s fingers or hands start to twitch). The pulses are proposed to induce electric currents to depolarize neurons in a focal area of the surface cortex and alter brain activity in areas responsible for mood. rTMS is less invasive than vagal nerve stimulation and is not intended to induce seizures like electroconvulsive therapy (ECT). rTMS may cause some short-term side effects such as headache, tingling of facial muscles, scalp discomfort, lightheadedness, or discomfort from the noise that the device makes. Hearing loss and seizures have been reported as uncommon side effects. Symptom relief may not take place for several weeks (Guo, et al., 2017; Allan, et al., 2011).

Transcranial Magnetic Stimulation (TMS) for Depression

Initial rTMS is a treatment option for a patient who is age 18 years or older and has a diagnosis of unipolar, depressive disorder, moderate-to-severe, single or recurrent episode or acute relapse, without psychosis, as defined by the most recent edition of the Diagnostic and Statistical Manual (DSM) of Mental Disorders. Potential TMS candidates are those patients who have failed at least two trials of antidepressant medications, at adequate therapeutic doses, including at least two different classes for a period of at least four weeks. The regimen should have included one or more anti-depressant medications. Antidepressant classes include: selective serotonin reuptake inhibitors (SSRIs; e.g., sertraline, fluoxetine), serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., desvenlafaxine, duloxetine), tricyclic antidepressants (TCAs; e.g., amitriptyline, nortriptyline, desipramine) and monoamine oxidase inhibitors (MAOIs; e.g., isocarboxazid, phenelzine), and may be given in combination regimens. Following pharmacotherapy, TMS candidates are those who demonstrate no significant reduction in depressive symptoms which is documented by results of validated depression monitoring scales (e.g., Patient Health Questionnaire [PHQ-9], Beck Depression Inventory [BDI], Hamilton Depression Rating Scale [HAM-D], Montgomery-Asberg Depression Rating Scale [MADRS], Quick Inventory of Depressive Symptomatology Self-reported [QIDS], Inventory of Depressive Symptomatology Clinician-rated [IDS-SR score]). Adherence to the medication should be documented or it should be documented if the patient has intolerance to the medication or could not take the medication due to medical contraindications (Institute for Clinical Systems Improvement [ICSI], 2016; FDA, 2014).

A major depressive episode as defined in the DSM-5 implies a prominent and relatively persistent (e.g., nearly every day for at least two weeks) depressed or dysphoric mood that represents a change from previous functioning, and includes at least five of the following nine symptoms, one of which is either of the first two symptoms (Institute for Clinical Systems Improvement [ICSI], 2016):

- Depressed mood
- Markedly diminished interest or pleasure in usual activities
- Significant change in weight and/or appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Slowed thinking or impaired concentration
- Recurrent thoughts of death or suicidal ideation or a suicide attempt

Standard treatments for major depressive disorder (MDD) include psychotherapy, pharmacotherapy, and/or electroconvulsive therapy (ECT). Although the majority of individuals respond to standard treatments for depression, some do not benefit, or cannot tolerate these interventions. Therefore, alternate treatment options are being investigated, including transcranial magnetic stimulation (TMS), vagal nerve stimulation, cranial electrical stimulation and herbal/homeopathic remedies (Miniussi, et al., 2005).

TMS should also be preceded by evidenced-based psychotherapy (e.g., cognitive behavioral psychotherapy, interpersonal psychotherapy, psychodynamic therapy) known to be effective for the treatment of depression. TMS candidates are those who do not show significant improvement on depression monitoring scales following psychotherapy. Adequate therapy may include at least one weekly session for at least 12 weeks. A face-to-face psychiatric evaluation that establishes that the diagnostic criteria are met for major depressive disorder should be performed and documented. An assessment of currently prescribed medications and a medical assessment to evaluate for any medical conditions that might increase the risks associated with TMS and/or the presence of contraindications to TMS are indicated. The patient should be educated regarding potential risks and benefits of the procedure. Because TMS may be associated with an increased risk of a seizure, the benefits of TMS use must be carefully considered against the risk in individuals taking medications which may lower the seizure threshold (Hayes, 2014; reviewed 2018).

Response is clinically defined as an improvement in symptoms from the initial onset of depression. The term remission has typically been applied to being symptom free or having minimal symptoms, representing an end to the immediate episode. The DSM-5 defines remission as a period of two or more months with no symptoms or only 1-2 mild symptoms. Partial remission involves significant improvement but mild symptoms of MDD are still present or there are no longer any significant symptoms of a Major Depressive Episode, but the period of remission has been less than two months. Recovery is the absence of symptoms for at least four months following the onset of remission with periods of improvement. Relapse has been defined as the re-emergence or early return of the depressive episode of full or significant depressive symptoms after remission. In their study, Jang et al. (2013) defined relapse as subjects who had HAM-D 17 score of 14 or more, and CGI-S score of three or more (with at least a 2-point increase from double-blind baseline), and meeting protocol defined DSM-IV criteria for MDD. Recurrence refers to a subsequent, new depressive episode after full recovery has been achieved. (American Psychiatric Association, 2022; Gili, et al., 2015; Gelenberg et al., 2010; Dobson, et al., 2008; Paykel et al., 2008).

The initial course of TMS typically includes 30–36 total treatments, with one treatment per day, over a 4–6-week period. Six tapered treatments over the final three-week period may be included in the total 30-36 visits (Hutton, et al., 2023). A typical course of TMS does not include concurrent or overlapping courses of TMS for either Major Depressive Disorder (MDD) or Obsessive-Compulsive Disorder (OCD). Treatment will last for 30–60 minutes, and the entire session may take up to two hours. TMS is administered in an outpatient setting by a Board-certified or Board-eligible physician or advanced practice psychiatric nurse practitioner (within the scope of their license) who has completed specialized training for TMS administration. The procedure does not require anesthesia.

A history of a favorable response to TMS in a previous episode of depression with more than a 50% improvement is predictive of a favorable clinical outcome (Hayes, 2014, reviewed 2018; FDA, 2014; O'Reardon, et al., 2007). Repeat treatments may be appropriate for acute relapse or recurrence when the patient experienced more than a 50% improvement in the initial TMS regimen as noted by standard rating scales used to measure depressive symptoms (e.g. Patient Health Questionnaire [PHQ-9], Beck Depression Inventory [BDI], Hamilton Depression Rating Scale [HAM-D], Montgomery-Asberg Depression Rating Scale [MADRS], Quick Inventory of Depressive Symptomatology Self-reported [QIDS], Inventory of Depressive Symptomatology Clinician-rated [IDS-SR score]) (Fitzgerald, et al., 2013; Mantovan, et al., 2012a; Jacicak, et al., 2010).

Maintenance TMS has been proposed, but maintenance regimens have not been established, and reported outcomes are conflicting. One study suggested that clustered TMS maintenance (five sessions over two days, administered once a month) prevented relapse better than no maintenance. Another study reported that a single, monthly TMS session showed no advantage over observation only. There are no clearly recommended stimulus parameters for maintenance TMS. Although the protocol should be individualized according to the clinical picture, a tentative maintenance protocol following a TMS taper (four times weekly for one week, three times weekly for one week, two times weekly for 1–2 weeks) could be one session every two or three weeks for many

months to several years depending on the nature of the mood disorder. There is a lack of evidence supporting the long-term, maintenance effects of TMS. Studies are primarily in the form of case reports, case series and retrospective reviews with small patient populations. Controlled studies with increased statistical power, rigorous standards of randomization, blinding procedures, optimal stimulus parameters, and clinical outcome as well as global functioning measures are needed to support the long-term safety and efficacy of maintenance rTMS (Rachid, et al., 2018; Benadhira, et al., 2017; Philip, et al., 2016; Fitzgerald, et al., 2013).

Other proposed forms of administering repetitive TMS (rTMS) to patients with major depression and other psychiatric and neurological conditions include: accelerated rTMS, bilateral rTMS, high-dose rTMS, multifocal, priming LF-rTMS (pTMS) and theta-burst repetitive TMS. In addition, TMS is not recommended for use in the home nor are the devices FDA approved for in-home use.

Although the evidence investigating left dorsolateral prefrontal cortex (DLPFC) repetitive transcranial magnetic stimulation (rTMS) and deep transcranial magnetic stimulation (dTMS) for the treatment of major depressive disorder (MDD) primarily consists of small patient populations and short-term follow-ups, some randomized controlled trials and meta-analysis have reported that TMS had better outcomes than sham therapy and in some studies, outcomes were reported as good as electroconvulsive therapy (ECT) with fewer side effects. As a result, left DLPFC rTMS and dTMS have evolved into an accepted treatment option.

U.S. Food and Drug Administration (FDA): Transcranial Magnetic Stimulation (TMS) systems are FDA 510(k) approved as Class II devices. In July 2011, the FDA issued a Class II TMS guidance detailing special controls that should be combined with general controls to ensure safety and effectiveness of rTMS systems for treatment of patients with MDD.

The standard-of-care FDA approved TMS protocol for treatment of MDD uses repetitive transcranial magnetic pulses applied at a frequency of 10 Hz to modulate cortical excitability. The observed and documented increase in cortical excitability after high frequency (10 Hz rTMS) repetitive TMS (rTMS) has been shown to persist beyond the duration of the train of stimulation, and 10 Hz rTMS on the left dorsolateral prefrontal cortex (L-DLPFC) has been shown to be effective and safe in the treatment of MDD (FDA, Aug 14, 2018).

The Neurostar TMS Therapy® System (Neuronetics, Inc., Malvern, PA) was one of the first systems to be approved by the FDA. The System was originally FDA approved in 2008. Labeling was updated and approved in 2013 to comply with the FDA 2011 TMS guidance. In 2014, based upon the outcomes of a randomized controlled trial (n=197) (George, et al., 2010), a new 510(k) approval was issued to “expand the indicated population in major depression to adult patients who have failed to benefit from one or more prior antidepressant medications in the current episode”. The 2016 indications for use stated that the “NeuroStar TMS Therapy System is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode”. The FDA’s Neurological Devices Panel reviewed Neuronetics’ research comparing the NeuroStar TMS Therapy System device with electroconvulsive therapy (ECT) and concluded that the research did not establish a risk-to-benefit profile that was comparable to the risk to benefit profile of the predicate device, ECT, because effectiveness had not been demonstrated. The Panel agreed that the safety profile of the device was better than that of ECT devices but concluded that additional study was necessary to establish the device’s effectiveness. The NeuroStar Advanced Therapy was FDA approved November 2020 to perform intermittent theta burst stimulation.

Examples of other approved TMS devices “indicated for the treatment of major depressive disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode” include (FDA, 510(k), 2024):

- Apollo TMS Therapy System delivers high frequency (10HZ) stimulation via a figure-of-eight Stimulation Coil which is positioned to the left dorsolateral prefrontal cortex (DLPFC) by means of the coil positioning system.
- Brainsway Deep TMS System (Brainsway LTD., Jerusalem, Israel) was initially FDA approved in 2013 “for the treatment of depressive episodes in adult patients suffering from MDD who failed to achieve satisfactory improvement from previous anti-depressant medication treatment in the current episode”. The electromagnetic radiation emitted is at a low frequency of the order of 1-10 kHz using an H1 coil. In 2021, they added an FDA approved iTBS Protocol.

- Horizon TMS Therapy System and Horizon TMS Therapy System with Navigation (Magstim Company, Ltd., Philadelphia PA) (FDA, 2019) and Magstim Horizon 3.0 TMS Therapy System, Horizon 3.0 System, Horizon 3.0, Horizon 3.0 With Navigation (Magstim Company Ltd., Whitland GB).
- MagVita TMS Therapy with MagPro R20 (Tonica, Elektroni A/S, Farum, Denmark) was FDA approved in 2017 and was an update of the earlier MagVita TMS Therapy system. The MagPro has two MCF-B65 coils compared to the earlier MagVita TMS system that had one MCF-B70 coil. The MagVita TMS therapy w/MagPro R20 pulses are applied repetitively at a frequency of 10Hz on the left dorsolateral prefrontal cortex (DLPFC).
- Neurosoft TMS (also called Cloud TMS) (TleEMG, LLC, Salem, NH) uses a figure-of-eight coil with a frequency of 10Hz delivered to the prefrontal cortex. The modified device allows a range of inter-train intervals from 11–26 second rather than the fixed 26 second duration allowing treatment time to range from 18.8 minutes to 37.5 minutes. The device also allows for intermittent and continuous theta-burst stimulations.
- Nexstim Navigated Brain Therapy (NBT) System 2 (Nexstim Plc. Helsinki, FL)
- NQ TMS for MDD (NQv1-MU-01) (NeuroQore, Inc., Salem, NH)
- Rapid^2 Therapy System (Magstim Company, LTD., Philadelphia, PA) uses a figure 8 air film coil with a stimulus frequency of 10 Hz.
- Ultimate rTMS, Yingchi rTMS (Brain Ultimate, Inc., Salem, NH)

Literature Review - left dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation (rTMS): Systematic reviews and randomized controlled trials evaluating the safety and efficacy of left dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant, major depressive disorder in adults have been reported. Studies have compared TMS to electroconvulsive therapy (ECT) (Kedzior et al., Mar 2015; Ren, et al., 2014; Berlim et al., 2013b; Minichino, et al., 2012; Keshtkar, et al., 2011; Hansen, et al., 2011; Mcloughlin, et al., 2007; Eranti, et al., 2007; Rosa, et al., 2006) and TMS to sham (Liu, et al., 2014; Gaynes, et al., 2014; Allan, et al., 2011; Ray, et al., 2011; Pallanti, et al., 2010; Schutter, et al., 2009; Lam, et al., 2008; Mogg, et al., 2008; O'Reardon, et al., 2007; Herwig et al., 2007; Fitzgerald, et al., 2006a; Machii, et al., 2006). Prospective case series and randomized control trials have also investigated TMS as a therapeutic option for treatment-resistant depression (Sehatzadeh, et al., 2019; Dunner, et al., 2014; Carpenter, et al., 2012; Mantovani, et al., 2012a; Janicak, et al., 2010; Avery et al., 2008).

Outcome measures varied and included the Clinical Global Impressions-Severity of Illness scale (CGSI), patient reported inventory of Depressive Symptoms Self Report (IDS-SR), 9-Item Patient Health Questionnaire (PHQ-9), Clinical Global Impressions-Severity of Illness Scale (CGI-S), Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory-II, visual analogue mood scales (VAMS), and Brief Psychiatric Rating Scale. Reduction in depressive symptoms, suicide ideation and remission of depression were reported.

Although there are conflicting results, overall improvement or remission of symptoms of depression and/or suicidal tendencies following TMS were reported, especially when TMS was compared to sham. Other studies reported better outcomes with ECT. However, some studies reported that response and remission rates following TMS were as good as ECT with fewer side effects. TMS adverse events, which were typically mild and transient, included headaches and localized discomfort/pain of the scalp during stimulation. In rare cases, seizures and psychotic symptoms were reported following TMS. Studies were limited by small patient populations, short-term follow-ups and heterogeneity of treatment regimens. Additional research is needed to define optimal TMS treatment protocols. Peer-reviewed, published studies supporting TMS as a maintenance therapy and as a treatment option for young people less than age 18 years are lacking.

Leggett et al. (2015) conducted a systematic review of the literature to evaluate rTMS for treatment-resistant depression in young people, ages 13–25 years. Three prospective cohort studies with small patient populations (n=7–9) met inclusion criteria. Follow-ups ranged from one month to three years. Anxiety levels based on the Screen for Child Anxiety-Related Disorders Questionnaire were significantly lower, but no significant difference was reported in the Suicide Ideation Questionnaire. The three-year study was a follow-up of an earlier study and suggested that the subjects did not experience worsening or improvement in depression severity over time without repeat rTMS. The third study reported a decrease in the mean Children's Depression Rating Scale. Meta-analysis was not possible due to the limited data. The limited number and the low quality of the studies restrict the ability to draw generalized conclusions about the use of rTMS in this age group. The rTMS protocols

were heterogeneous. Currently, FDA approved TMS devices are only approved for use in adult patients, age 18 years and older.

Literature Review – Deep Transcranial Magnetic Stimulation (dTMS): Randomized controlled trials and case series investing deep TMS (dTMS) have reported significant improvement in depressive symptoms and scores following dTMS for treatment-resistant major depressive disorder (Feffer, et al., 2017; Levkovitz, et al., 2015; Rapinesi, et al., 2015; Isserles, et al., 2011; Levkovitz, et al., 2009; Levkovitz, et al., 2007).

Kedzior et al. (Nov 2015) conducted a systematic review and meta-analysis to investigate the acute antidepressant effect that dTMS had on major depression. Data from nine open-label studies (n=162) were included in the meta-analysis. Inclusion criteria were: studies that enrolled at least five patients with a primary diagnosis of a major depressive disorder or episode according to DSM-IV or ICD-10 criteria; administered dTMS treatment with H coils; assessed depression severity using any version of any standardized depression rating scale (e.g., Hamilton Depression Rating Scale, [HDRS]); and reported adequate data to compute effect sizes. The outcome measures included the change in depression scores on Hamilton Depression Rating Scale (HDRS), response rates, remission rates and dropout rates. The majority of studies utilized the H1-coil which induced greater stimulation over the left DLPFC, a high frequency of stimulation (18–20 Hz), intensity of 120% of the resting motor threshold, 1680–3000 stimuli per session applied in 42–75 trains, and 20 stimulation sessions. Compared to baseline HDRS scores, there was a large antidepressant effect after 20 acute, high-frequency DTMS sessions (n=150) (overall mean weighted d=2.04, 95% CI: 1.53–2.55). Overall weighted response rate (n=94) was 60% and varied from 43% to 96%. Response rates were higher in the four studies (n=68) with patients on concurrent antidepressants compared to the two studies (n=26) that used dTMS as a monotherapy. Thirty-five out of 124 patients in eight studies remitted after the acute dTMS treatment. Remission rates varied from 0% to 53% in eight studies and decreased over time. A total of 27 out of 162 patients dropped out with dropout rates varying from 0% to 67%. Limitations of the analysis includes the small patient population, short-term follow-up, lack of a comparator, different cut-off scores used to define remission, and two studies used dTMS as a monotherapy vs four studies that used TMS with as an adjunctive therapy.

Agency for Healthcare Research and Quality (AHRQ): The 2011 comparative effectiveness review on nonpharmacological interventions for treatment-resistant depression (TRD) in adults concluded that comparative clinical research on nonpharmacologic interventions in a TRD population is early in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data was hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence was for ECT and rTMS. However, the strength of the evidence was low for beneficial outcomes. ECT and rTMS did not produce different clinical outcomes in TRD, and ECT produced better outcomes than pharmacotherapy. No trials directly compared the likelihood of maintaining remission for nonpharmacologic interventions. The few trials addressing adverse events, subpopulations, subtypes, and health-related outcomes provided low or insufficient evidence of differences between nonpharmacologic interventions (Gaynes, et al., 2011).

Department of Veterans Affairs/Department of Defense (VA/DoD): In a clinical practice guideline for the management of MDD (2022), the VA/DoD gave a “weak” recommendation for the use of TMS for “patients who have demonstrated partial or no response to two or more adequate pharmacologic treatment trials”. The work group indicated that the quality of evidence is very low with limitations including: “small study effects, higher than optimal discontinuation, lack of measurement for allocation concealment, and/or other issues”. However, they concluded that the benefits of rTMS outweigh the harms.

Technology Assessments: A 2016 (reviewed 2018) Hayes technology brief on low frequency rTMS (LFrTMS) (1 Hz) included seven randomized controlled trials (n=26–170). The studies reported that LFrTMS, in addition to pharmacotherapy, produced antidepressant effects. However, results were mixed suggesting no difference between LFrTMS and sham therapy as an adjuvant therapy to antidepressant treatment. Results also suggested that there was no difference between LFrTMS and HFrTMS as an add-on therapy. The low-quality evidence did not allow definitive conclusions regarding the efficacy of LFrTMS as a monotherapy. The therapies appeared safe with mild adverse events (e.g., scalp discomfort, transitory headaches).

In a 2016 (updated 2020), directory report on comparative effectiveness of HFL-rTMS, Hayes reported that there was insufficient evidence to support the use of HFL-rTMS combined with ECT compared to ECT alone for treatment-resistant major depressive disorder. The conclusion was based on ten randomized controlled trials

with small patient populations (n=32–121). Various outcome criteria and treatment regimens for rTMS and ECT were used. The 2020 published review added six newly published studies that met the original inclusion criteria. With this new information, there was no change to Hayes recommendation.

Professional Societies/Organizations: The 2010 American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Major Depressive Disorder stated that evidence for TMS is currently insufficient to support its use in the initial treatment of major depressive disorder. Electroconvulsive therapy (ECT) remains the treatment of best-established efficacy against which other stimulation treatments (e.g., VNS, deep brain stimulation, TMS, other electromagnetic stimulation therapies) should be compared. 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. As an initial treatment in the acute phase of major depression the guideline reported that the goal of treatment in the acute phase should be aimed at remission of the major depressive episode and achieving a full return to the patient's baseline level of functioning. Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, combination therapies (e.g., medications and psychotherapy, or other somatic therapies such as ECT, TMS, or light therapy) (Gelenberg, et al., 2010). There has been no update to this guideline since 2010.

Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder (OCD):

Obsessive-Compulsive Disorder (OCD) is a common, chronic and long-lasting disorder. It is mainly characterized by obsessions, which are persistent and intrusive thoughts, urges or images that an individual finds distressing, and compulsions, which are repetitive, time-consuming behaviors or mental acts usually performed to prevent or reduce distress. OCD manifests as a heterogeneous clinical condition with the intensity and mix of obsessions and compulsions varying between patients. OCD can be severely incapacitating and associated with impaired social and occupational functioning, and reduced quality of life. OCD is typically diagnosed by age 19 years, but onset is also seen after age 35 years. The causes of OCD are unknown. Genetic and environmental factors are believed to contribute to the etiology of OCD (Cocchi, et al., 2018; Rehn, et al., 2018; National Institute of Mental Health, 2016, Updated 2022).

Treatment for OCD includes medication (selective serotonin reuptake inhibitor [SSRI], antidepressants, clomipramine, venlafaxine), psychotherapy (cognitive behavioral therapy) or a combination of both. Treatment-resistant OCD patients are defined as those who undergo satisfactory trials of first-line treatments without showing an adequate response, usually defined by a reduction in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score ≥ 25% with respect to baseline. For individuals who are resistant to pharmacotherapy, transcranial magnet stimulation has been investigated and studies have reported favorable clinical outcomes (Rehn, et al., 2018; National Institute of Mental Health, 2016, updated 2022).

U.S. Food and Drug Administration (FDA): The Brainsway Deep Transcranial Magnetic Stimulation System (Brainsway Ltd., Kfar Saba, Israel) was FDA approved on August 17, 2018 as a class II De Novo device. The Food and Drug Administration Modernization Act of 1997 (FDAMA) added the De Novo classification option, also known as Evaluation of Automatic Class III Designation, to provide an alternate pathway to classify novel devices of low to moderate risk that are not substantially equivalent to an existing FDA approved device (predicate device). Devices that are classified through the De Novo process may be marketed and used as predicates for future 510(k) submissions and are typically Class II devices. The Brainsway System is FDA approved "to be used as an adjunct for the treatment of adult patients suffering from Obsessive-Compulsive Disorder" (FDA, 2018; FDA, 2017).

According to the Manufacturer, the device was FDA approved on a multicenter randomized controlled trial of 94 patients who previously failed pharmacological or psychological treatment. Subjects received thirty-minute sessions, five times per week, over a course of six weeks with the Brainsway H7-deep-TMS system. The primary outcome measure was the OCD Yale–Brown Obsessive Compulsive Scale (Y-BOCS). Following the six-week treatment session, there was a statistically significant improvement in the Y-BOCS score for the active treatment group compared to sham (p=0.0157). In addition, 38.1% of patients in the active group achieved a response compared with 11.1% in the sham group (p=0.0033) and 54.8% of patients in the active group achieved a partial

response versus 26.7% in the sham group (p=0.0076). The improved clinical effect in Y-BOCS scores was maintained in the active group one month following treatment. Improvement was more pronounced than that achieved in the sham group (p=0.0459) (Brainsway Ltd, 2017).

Examples of other FDA approved TMS devices for the treatment of or adjunct treatment of obsessive-compulsive disorder include (FDA 510(k), 2024):

- CloudTMS for OCD (TeleEMG, LLC, Salem, NH)
- Magstim Horizon 3.0 TMS Therapy System, Horizon 3.0 System, Horizon 3.0, H3.0, Horizon 3.0 with StimGuide+ (Magstim Company Ltd., Whitland, Carmarthenshire, UK)
- MagVentrure TMS Therapy System (Tonica Elektronik A/S, Farum, Denmark)
- NeuroStar Advanced Therapy System (Neuronetics, Malvern, PA)

Literature Review – FDA Approved Devices for OCD: Studies investigating the safety and efficacy of TMS using an FDA approved device for the treatment of OCD are in the form of systematic reviews, randomized controlled trials, case series, case reports and retrospective reviews. Overall short-term results have reported statistically significant improvements in YBOCS scores when applying rTMS over the bilateral dorsolateral prefrontal cortex (B-DLPFC), right-DLPFC (R-DLPFC) and the supplementary motor area (SMA), along with applications with both LF-rTMS (p=0.001) and HF-rTMS (p=0.01). No serious adverse events have been identified in these studies. Therefore, TMS for the treatment of OCD is evolving into an accepted treatment option for this disease.

Carmi et al. (2019) conducted a prospective multicenter, randomized, double-blind, placebo-controlled trial (n=100, aged 22-69 years) to examine the therapeutic effect of deep TMS (dTMS) for patients diagnosed with obsessive-compulsive disorder. Deep TMS was administered using a Magstim Rapid2 TMS stimulator equipped with a unique H7, H-shaped coil design. When placed four centimeters anterior to the foot motor cortex and used at 100% of the leg resting motor threshold (RMT), the H7 coil stimulated the dorsal medial prefrontal cortex (mPFC) and anterior cingulate cortices (ACC) bilaterally. The active treatment group received 20 Hz dTMS at 100% of RMT, with two-second pulse trains and 20-second intertrain intervals, for a total of 50 trains and 2,000 pulses per session. At the posttreatment assessment, YBOCS decreased significantly from baseline in both the active (−6.0 points, 95% CI=4.0, 8.1) and sham (−3.3 points, 95% CI=1.2, 5.3). The difference in slopes of change in YBOCS score between the two groups was 2.8 points (p=0.01). At the one-month follow-up, YBOCS score had decreased by 6.5 points (95% CI=4.3, 8.7) in the active treatment group and by 4.1 points (95% CI=1.9, 6.2) in the sham treatment group (p=0.03). The rate of full response (a reduction ≥30% in YBOCS score) at the posttreatment assessment in the active treatment group was 38.1% (16/42), compared with 11.1% (5/45) in the sham treatment group (p=0.003).

Literature Review – FDA Approved Devices not Indicated for OCD: Additional studies have been conducted using TMS devices that are not FDA approved for OCD (Rapinesi, et al., 2019; Rehn, et al., 2018; Zhou, et al., 2017; Elbeh, et al., 2016; Pelissolo, et al., 2016; Trevizol, et al., 2016; Berlim, et al., 2013c). Limitations of the studies include: small patient populations, heterogeneity of treatment parameters, little or no follow-up after treatment, and heterogeneity of stimulation parameters and cortical targets. Outcomes are conflicting and inconclusive. Only an FDA approved device should be used to administer TMS for OCD.

Transcranial Magnetic Stimulation for Migraine

The Cerena Transcranial Magnetic Stimulator (TMS) (eNeura Therapeutics, Sunnyvale, CA) device is the same device as the Spring TMS™ Total Migraine System marketed by eNeura Therapeutics in Europe. The device is small enough to be placed inside a large purse and can be used in the home or office where a comfortable chair or couch is available to the individual during use. The individual activates the subscriber information module (SIM) chip inside his or her prescription card for the device. The chip works only with the individual's device, and the prescription must be renewed regularly. When the individual experiences the onset of a migraine attack, the individual places the device on a flat surface in the "on" mode, presses the power button, and places the device behind the head at the base of the skull. The device has folding handles, which the individual can hold during treatment. When in place, the individual slides the treatment delivery switches housed in the handles to administer a pulse; a second pulse completes the treatment in less than a minute. The system automatically records the treatment history and is used with a headache diary program on a personal computer. Both the

treatment history and headache diary can be uploaded to an online journal on the eNeura Therapeutics website. The device uses single-pulse transcranial magnetic stimulation (sTMS).

U.S. Food and Drug Administration (FDA): The Cerena Transcranial Magnetic Stimulator (TMS) (eNeura Therapeutics, Sunnyvale, CA) received FDA 510(k) approval via the de novo premarket review pathway. This is the first approved device proposed to relieve pain caused by migraine headaches that are preceded by an aura: a visual, sensory or motor disturbance immediately preceding the onset of a migraine attack (FDA, 2013). In 2016, eNeura received a Class II FDA 510(k) approval for the sTMS mini device. Per the FDA approval, "the sTMS mini is indicated for the acute treatment of pain associated with migraine headache with aura. The device is designed for patient use where treatments are self-administered and can be delivered in a variety of settings including the home or office" (FDA, 2016). The device is available by prescription only. The SpringTMS was FDA approved February 2019 for "the acute and prophylactic treatment of migraine headache in adolescents (age 12 and older) and adults (FDA, 2019).

On May 16, 2023, the prescription only SAVI Dual ™ Migraine Therapy device (eNeura, Inc., Orono, MN) received 510(k) approval for the "acute and prophylactic treatment of migraine headache in adolescents (age 12 and older) and adults".

Literature Review: There are a limited number of peer-reviewed published studies exploring the efficacy of TMS for the treatment of pain associated with migraine headaches. Methodological limitations of these studies include small sample sizes, limited follow-up intervals and high dropout rates. Additional randomized controlled trials are needed to determine optimal treatment parameters, including the range of doses and timing of treatment, to confirm the effectiveness and durability of TMS for the treatment of pain associated with migraine headaches (Rapinesi, et al., 2016; Misra, et al., 2012; Brighina, et al., 2004; Teepker, et al., 2010; Clarke, et al., 2006; Brighina, et al., 2004).

Lan et al. (2017) conducted a systematic review and meta-analysis of randomized controlled trials (RCT) to investigate the efficacy of TMS for the treatment of migraine headaches. To be included, the study had to be an RCT with quantitative outcomes. Five studies (n=313) met the inclusion criteria. Four studies included chronic migraine subjects and one study (n=164) investigated TMS for the acute treatment of migraine with aura. Data from the one study (Lipton, et al., 2010) reported that single-pulse TMS was significantly effective for the acute treatment of migraine with aura after the first attack (p=0.02). There was no statistically significant difference in effect between the active TMS group and sham TMS group for the treatment of chronic migraine (p=0.14). Author-noted limitations of the meta-analysis included: limited number of studies; small patient populations; possibility of publication bias; heterogeneity of treatment regimens including site stimulated; doses that improved headache were not identifiable; lack of a standard control group (sham and botulinum toxin-A injection); no comparison to conventional therapy; and subjects primarily came from general hospitals or major institutions limiting generalization to the general population.

The FDA clearance of the Cerena TMS device was based on a single multi-center randomized, double-blind, parallel-group, two-phase, sham-controlled study (Lipton, et al., 2010). Adults who met the International Classification Headache Disorders criteria for migraine headache with aura ranged in age from 18-70 years. Phase one of the trial enrolled 267 adults who experienced visual aura preceding at least 30% of migraines, followed by moderate or severe headache in more than 90% of those attacks. Participants in phase one were trained to use an electronic diary to verify prospectively the diagnosis of migraine with aura. Sixty-six participants (25%) dropped out after phase one of the trial. In phase two, 201 individuals randomized to either sham stimulation (n=99) or sTMS (n=102) self-applied the device to the back of the head, pressing a button to administer two pulses, each approximately 0.9 Tesla and lasting less than a millisecond, 30 seconds apart. Participants were instructed to treat up to three attacks over three months while experiencing aura. The primary outcome measure was pain-free response two hours after the first attack. Thirty-seven participants did not treat a migraine attack and were excluded from the outcome analyses. A total of 164 participants treated for at least one attack of migraine with aura with sTMS (n=82) or with sham stimulation (n=82) reported that pain-free response rates two hours after stimulation were significantly higher with sTMS (39%, 32 of 82) than with sham stimulation (22%, 18 of 82; p=0.018). Sustained pain-free response rates with no recurrence and no rescue drug use significantly favored sTMS at 24 hours (29% [24 of 82] versus 16% [13 of 82]; p=0.0405) and 48 hours (27% [22 of 82] versus 13% [11 of 82]; p=0.0327) after treatment. There were no significant differences in secondary outcomes (headache response at two hours, use of rescue drugs, Migraine Disability Assessment [MIDAS] score

and consistency of pain relief response) between groups. The study did not demonstrate that sTMS was effective in relieving the associated symptoms of migraine, including nausea, photophobia, and phonophobia. No device-related serious adverse events were reported. Limitations of this study include the high dropout rate during phase one of the trial (25%, 66 of 267), the potential for unblinding of the device after administration of treatment, and variations in the time intervals from the onset of aura to treatment and pain intensity at the time of treatment. Additional randomized controlled trials are needed to determine optimal treatment parameters, including the range of doses and timing of treatment, to confirm the safety and durability of sTMS for the treatment of pain associated with migraine headache with aura.

In a Prognosis Overview on Cerna, Hayes (2014) concluded that there was insufficient published evidence to draw conclusions regarding the efficacy of this device for the treatment of migraine headaches. The best available study was the Lipton et al. (2010) study discussed above.

Transcranial Magnetic Stimulation - Other Psychiatric or Neurological Disorders

Literature Review
There have been numerous studies and meta-analyses conducted that explored the efficacy of TMS for a selection of neuropsychiatric-related disorders. Some of the methodological limitations of these studies include small patient populations, short-term follow-ups, variability in technique and outcome measures, and varied diagnostic groups on and off pharmacotherapy. Also, the optimal TMS protocol have not been identified for these conditions. Therefore, the clinical utility and improvement in health outcomes of TMS in the treatment of other psychiatric or neurological disorders have not been clearly established. TMS has not been proven effective in the peer-reviewed published scientific literature for the following indications nor are the devices FDA approved for these conditions:

- addictions (Torres-Castaño, et al., 2021; Zhang, et al., 2019; Maiti, et al., 2017; Grall-Bronnec and Sauvaget, 2014)
- alcohol dependence (Mishra, et al., 2010)
- Alzheimer disease (Wang, et al., 2020; Lin, et al., 2019; Hayes, 2018, updated 2019; Liao, et al., 2015; Ahmed, et al., 2012; Cotelli, et al., 2011)
- amyotrophic lateral sclerosis (ALS) (Fang, et al., 2013; Di Lazzaro, et al., 2010)
- anorexia nervosa (McClelland, et al., 2016)
- anxiety disorder (Parikh, et al., 2022; Diefenbach, et al., 2016)
- attention deficit hyperactivity disorder (ADHD) (Bloch, et al., 2010)
- auditory hallucinations in schizophrenia (Li, et al., 2020; Freitas, et al., 2012; Slotema, et al., 2011; Cordes, et al., 2010; Loo, et al., 2010; Dlabac-de Lange, et al., 2010; Freitas, et al., 2009; Fitzgerald, et al., 2005; Schonfeldt-Lecuona, et al., 2004; Hoffman, et al., 2003; Aleman, et al., 2007)
- autism (Sokhadze, et al., 2010)
- bipolar depression (Nguyen, et al., 2021; Bulteau, et al., 2019)
- blepharospasm (Kranz, et al., 2010; Kahn, et al., 2010)
- bulimic disorders (Van den Eynde, et al., 2010)
- chronic pain (O'Connell, et al., 2018; Jin, et al., 2015; Galhardoni, et al., 2015; Boldt, et al., 2014; Taylor, et al., 2012; Sampson, et al., 2011)
- chronic tinnitus (Noh, et al., 2019; Folmer, et al., 2015; Meng, et al., 2011; Anders, et al., 2010; Lorenz, et al., 2010; Frank, et al., 2010; Marcondes, et al., 2010; Landgrebe, et al., 2008; Khedr, et al., 2008; Rossi, et al., 2007; Kleinjung, et al., 2005; De Ridder, et al., 2005; Plewnia, et al., 2003)
- children (Allen, et al., 2017)
- epilepsy (Walton, et al., 2021; Pereira, et al., 2016; Chen, et al., 2016; Brodbeck, et al., 2010)
- facial pain (Ferreira, et al., 2019; Hodaj, et al., 2015)
- fibromyalgia (Saltychev and Laimi, 2017; Knijnik, et al., 2016; Marlow, et al., 2013)
- focal dystonia (Schneider, et al., 2010)
- Huntington's disease (Medina, et al., 2010)
- multiple sclerosis (Korzhova, et al., 2019)
- neuropathic pain (Attal, et al., 2021; Kim, et al., 2020)
- obesity (Ferrulli, et al., 2019)
- panic disorder (Li, et al., 2014; Mantovani, et al., 2012b)

- Parkinson's disease (Li, et al., 2020b; Xie, et al., 2020; Trung, et al., 2019; Chung and Mak, 2016; Wagle, et al., 2016; Chou, et al., 2015; Shirota, et al., 2013; Benninger, et al., 2011; Arias, et al., 2010; Hartelius, et al., 2010; Pal, et al., 2010; Filipović, et al., 2010; Fregni, et al., 2004)
- postherpetic neuralgia (Pei, et al., 2019; Ma, et al., 2015)
- post-concussion syndrome (VA/DoD, 2021; Moussavi, et al., 2019)
- post-operative pain (Borckardt, et al., 2006; Khedr, et al., 2005)
- post-stroke aphagia (Li, et al., 2015)
- post-stroke aphasia (Ren, et al., 2019)
- post-stroke dysphagia (Zhong, et al., 2023; Ünlüer, et al., 2019; Du, et al., 2016)
- post-traumatic stress disorder (Philip, et al., 2019; VA/DoD, 2023; Yan, et al., 2017; Trevizon, et al., 2016; Berlim and Eynde, 2014; Karsen, et al., 2014; Boggio, et al, 2010; Cohen, et al., 2004)
- schizophrenia (Kumar, et al., 2020; He, et al., 2017; Wobrock, et al., 2015; Dougall, et al., 2015; Quan, et al., 2015; Bais, et al., 2014; Blumberger, et al., 2010; Matheson, et al., 2010; McNamara, et al., 2001)
- smell and taste dysfunction (Henkin, et al., 2011)
- spinal cord injury (Nardone, et al., 2015; Awad, et al., 2013; Soler, et al., 2010; Kumru, et al., 2010)
- stroke (Xu, et al., 2021; He, et al., 2020; Tung, et al., 2019; VA/DoD, 2019; Dos Santos, et al., 2019; Xiang, et al., 2019; Dionísio, et al., 2018; Zhang, et al., 2017; Graef, et al., 2016; Zheng, et al., 2015; Avenanti, et al., 2012; Corti, et al., 2012; Weiduschat, et al., 2011; Emara, et al., 2010; Takeuchi, et al., 2010; Chang, et al., 2010; Kim, et al., 2010; Khaleel, et al., 2010; Lim, et al., 2010; Khedr, et al., 2009, 2010; Fregni, et al., 2006)
- tardive syndromes (Khedr, et al., 2019)
- tension-type headache (Mattoo, et al., 2019)
- tic disorders (Wu, et al., 2014; Steeves, et al., 2012; Kwon, et al., 2011)
- tinnitus (Galal; et al., 2020; Soleimani, et al., 2016)
- Tourette syndrome (Landeros-Weisenberger, et al., 2015)

The Brainsway Deep TMS System and modified Brainsway Deep (DTMS) System (Brainsway Ltd, Jerusalem IL) are FDA approved "to be used as an aid in short-term smoking cessation for adults". Both use an H4/HADD-Coil to deliver 120% of the patient's observed motor threshold for 10 Hz to the prefrontal cortex and insula (FDA, 2020; updated 2021).

In 2022, both the BrainsWay Deep TMS™ System and the NeuroStar line of devices received 510(k) approval for the "treatment of depressive episodes and for decreasing anxiety symptoms for those who may exhibit comorbid anxiety symptoms in adult patients suffering from Major Depressive Disorder (MDD) and who failed to achieve satisfactory improvement from previous andidepressand medication treatment in the current episode (FDA, 2022a; FDA 2022b).

In evidence-based guidelines for the treatment of tinnitus, the American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNSF) recommended against the use of TMS for the routine treatment of persistent, bothersome tinnitus. The recommendation was based on inconclusive data from randomized controlled trials (Tunkel, et al., 2014).

In a meta-analysis, Slotema et al. (2010) examined if rTMS is effective for various psychiatric disorders. Data were obtained from randomized, sham-controlled studies of rTMS treatment for depression (34 studies, n=751 rTMS and n=632 sham), auditory verbal hallucinations (AVH, seven studies), negative symptoms in schizophrenia (seven studies), and obsessive-compulsive disorder (OCD, three studies). Studies included a comparison of rTMS versus electro-convulsive therapy (ECT, six studies) for depression. Standardized mean effect sizes of rTMS versus sham were computed based on pre-treatment versus post-treatment comparisons. The mean weighted effect size of rTMS versus sham for depression was 0.55 ($p<0.001$). Monotherapy with rTMS was more effective than rTMS as adjunctive to antidepressant medication. ECT was superior to rTMS in the treatment of depression (mean weighted effect size -0.47, $p=0.004$). In the treatment of AVH, rTMS was superior to sham treatment, with a mean weighted effect size of 0.54 ($p<0.001$). The mean weighted effect size for rTMS versus sham in the treatment of negative symptoms in schizophrenia was 0.39 ($p=0.11$) and for OCD, 0.15 ($p=0.52$). Side effects were mild, yet more prevalent with high frequency rTMS at frontal locations. The authors stated that although the efficacy of rTMS in the treatment of depression and AVH may be considered proven, the duration of the effect is as yet unknown. Effect sizes were measured immediately after the cessation of rTMS treatment. There are indications that the effects of rTMS may last for several weeks to months. The

authors reported that although rTMS cannot replace ECT in depressive patients, there may be subgroups in which rTMS can replace antidepressant medication.

Other Forms of Transcranial Magnetic Stimulation

Accelerated TMS (aTMS): aTMS refers to the administration of multiple sessions per day (e.g., 2–5) for less than four weeks in an effort to intensify antidepressant response. Some of the advantages of accelerated TMS are to improve accessibility by reducing disruption in daily living and commuting requirements.

Studies have included small patient populations (n=7–115) and two days to three weeks treatment sessions followed or not followed by conventional rTMS. Outcomes have been conflicting and, in some cases, reported that aTMS was not more effective than sham. Accelerated TMS has also been proposed for the treatment of attention deficit hyperactivity disorder (ADHD), alcohol addiction and suicidal patients (Fitzgerald, et al., 2018; Brunoni, et al., 2017; Theleritis, et al., 2017; Tor, et al., 2016; McGirr, et al., 2015; Baeken, et al., 2013; Holzheimer, et al., 2010; Loo, et al., 2007).

Fitzgerald, et al. (2018) conducted a parallel, randomized controlled trial (n=115) to evaluate outcomes achieved with an accelerated rTMS protocol compared to a standard rTMS protocol in patients with MDD. The mean age of participants was 49 ± 13.8 years and 66 were female. Participants were eligible for inclusion if they had a diagnosis of treatment resistant MDD. Participants were excluded if they: had a contraindication to TMS (e.g., metallic implants in the head, cardiac pacemakers, cochlear implants, or other implanted electronic devices), started a new antidepressant treatment within the preceding four weeks, had another Axis 1 psychiatric disorder, had a history of substance abuse or dependence in the preceding six months, or had a neurodegenerative disorder. The accelerated rTMS protocol consisted of three weeks of decreasing treatment intensity administered to the left DLPFC. Week one included three times daily treatment sessions for three days, week two included three treatment sessions over two days, and week three included three treatment sessions given in a single day. Sessions occurring on the same day were provided 15–30 minutes apart. The comparator consisted of a standard, daily treatment protocol provided in 20 daily sessions, five days per week, over four weeks. Outcome measures used were the Montgomery Asberg Depression Rating Scale (MADRS), the Beck Depression Inventory II (BDI), the Scale of Suicidal Ideation (SSI), and the Hamilton Depression Rating Scale (HDRS-17). Positive responses from the HDRS-17 and MADRS scales were defined as > 50% reduction in scores. Remission was defined as < 8 on the HDRS-17 or < 10 on the MADRS. Cognitive function (i.e., attention, speed of information processing, verbal and visual memory, and executive function) were assessed using the Digit Span, Digit Symbol Coding, Trail Making Test, Rey Verbal Auditory Learning Test, Stroop, Verbal Fluency, Brief Visuospatial Memory Test, and the Rey Complex Figure. Participants were assessed at baseline and at the end of weeks one, two, three, four, and eight. Out of the 115 participants included in the analysis, 111 completed baseline and at least week four assessments. Three participants withdrew in the accelerated treatment group, and one withdrew from the standard group. There were no differences in baseline scores for any domain. There were no significant differences in response or remission rates between the two groups on the HDRS-17 at four weeks or on the MADRS at four and eight weeks. A significant reduction in MADRS scores was observed in the accelerated group from baseline to week one ($p<0.001$) and from week one to week 2 ($p<0.05$) but not at any of the other time points. A significant reduction in MADRS scores was observed in the standard group from baseline to week one, three, and four ($p<0.001$, $p<0.01$, $p<0.01$ respectively). Significantly more participants in the accelerated group reported site discomfort compared to the standard group ($p=0.01$). More participants in the accelerated group (n=16) experienced headache following at least one treatment session compared to the standard group (n=9). Author noted limitations of the study included the non-blinding of participants and small sample size obtained from a single site. An additional limitation of the study is the short-term follow-up.

Theleritis, et al. (2017) conducted a parallel-group, randomized, sham controlled trial (n=96) from a single center to evaluate the efficacy of two high-frequency rTMS sessions per day compared to one for the treatment of MDD. Individuals were eligible for inclusion if they: were 18–59 years old; were right-handed; had a diagnosis of treatment resistant nonpsychotic MDD; had never undergone TMS before; were not pregnant, and did not have a history of seizures, head injury with loss of consciousness, brain surgery, metallic implants, dementia, or substance dependence or abuse within the previous six months. Participants were encouraged to discontinue the use of antidepressants prior to entry into the study. However, if this was not possible, participants were kept on a minimum antidepressant regimen and kept stable for a minimum of four weeks before study entry. The intervention consisted of high-frequency rTMS (Magstim ultrarapid stimulator; Magstim Company Ltd, Whitland,

UK) delivered with a figure-8 coil to the left prefrontal cortex consecutively on weekdays (starting on Monday) either one time per day (A1 group; n=27) or two times per day (A2 group; n=27) that continued for three weeks for a total of either 15 (A1) or 30 (A2) treatment sessions. Sham rTMS (i.e., lateral edge of an active coil was rotated 90 degrees away from the scalp) delivered on weekdays either one time per day (S1 group; n=20) or two times per day (S2; n=24) that continued for three weeks served as the comparator. Outcome measures used were the Hamilton Depression Rating Scale (HDRS) and the Clinician Global Impressions-Severity of Illness (CGI-S). HDRS response was defined as a decrease of 50% or more from baseline and remission as a score of < 8. CGI-S response was defined as an endpoint rating of ≤ 3 and remission as a score of ≤ 2. Patients were evaluated at baseline, at the end of the first, second, and third weeks of treatment, and again after treatment sessions were complete at the fifth week. Nine participants did not complete the trial due to: protocol violation, exacerbation of a preexisting headache, inability to attend treatment sessions because of work or financial reasons, and hospitalization with influenza. Analysis took place on the intent-to-treat sample (n=96). Differences in baseline measures were not significant between the four groups. Significant improvement in the HDRS and CGI-S scores were noted in the active treatment group compared to the sham group (p<0.001). The likelihood of remission in the active treatment groups was found to be significantly associated with baseline scores (p=0.001) but not significantly associated with the number of rTMS sessions per day (p=0.066). Adverse events included discomfort at the site of stimulation and exacerbation of a preexisting headache in both the active in sham groups. Author noted limitations of the study included: non-blinding of the individuals administering treatment, absence of a sham coil capable of delivering rTMS-like sensations, the fact that the authors did not evaluate the impact rTMS has on cognitive function, and short-term follow-up. Additional limitations of the study include the unknown effect pharmacotherapy had on outcomes. Additional, well-designed studies are needed to evaluate the safety and efficacy of rTMS delivered more than one time per day.

Bilateral Transcranial Magnetic Stimulation: Bilateral TMS combines high frequency stimulation of the left dorsolateral prefrontal cortex (DLPFC) with low frequency stimulation of the right DLPFC (either simultaneously or sequentially) during one TMS session. It is hypothesized that stimulation of each side may activate complementary mechanisms that would enhance efficacy. Bilateral TMS has been proposed for the treatment of treatment-resistant major depressive disorder, attention deficit hyperactivity disorder (ADHD), stroke, schizophrenia, tinnitus, and Parkinson's disease (Brunoni, et al., 2017; Zhang, et al., 2015; Chen, et al., 2014).

Overall, systematic reviews, meta-analysis, randomized controlled trials and comparative studies have reported that sequential bilateral rTMS is not more effective than unilateral rTMS. Galletly et al. (2017) conducted a comparative study to assess the effectiveness of sequential bilateral rTMS (n=57) and right unilateral rTMS (n=78) for the treatment of depression. There were no statistically significant differences in response and remission rates between the two groups. The authors concluded that right unilateral rTMS may be a better choice than bilateral treatment given the shorter treatment time and the greater safety and tolerability of unilateral TMS. In a randomized controlled trial comparing the efficacy of sequential bilateral rTMS to right-sided unilateral rTMS using a priming protocol (n=179), the authors concluded that the results of the study did not support superior efficacy of bilateral rTMS (Fitzgerald, et al., 2013).

Blumberger et al. (2016) conducted a randomized controlled trial (n=121) comparing sequential bilateral rTMS (n=40) (600 pulses at 1 Hz followed by 1500 pulses at 10 Hz), unilateral high-frequency left (HFL)-rTMS (n=40) (2100 pulses at 10 Hz) or sham rTMS (n=41) 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 measure was the remission rate. Remission rates differed significantly among the three groups: 8/40 (20%) subjects in the bilateral group; 3/40 (7.5%) in the unilateral group; and 1/41 (2.4%) in the sham group (p=0.027). Response rates did not differ significantly between the three groups. Regarding dropout rates, four occurred (10.0%) in the bilateral group, seven (17.5%) in the unilateral group and five (12.1%) in the sham group. Headache was the most frequently reported adverse event (n=21) followed by pain (seven subjects in the bilateral group, eight in the unilateral group and two in the sham group). Limitations of the study include the small patient populations, short-term follow-ups and concurrent use of antidepressants by most subjects during the trial. The authors noted that this was the first RCT comparing sequential bilateral and unilateral rTMS using cortical co-registration, adjusting intensity for coil-to-cortex distance and providing up to six weeks of treatment. There was no statistically significant difference in overall depression change scores. Enhanced efficacy rates were not seen using the enhanced techniques of adjusting MT for coil-to-cortex distance or MRI targeting of the DLFPC.

Zhang et al. (2015) conducted a systematic review and meta-analysis of ten randomized controlled trials (n=634) to evaluate the efficacy of bilateral TMS compared with unilateral rTMS and sham rTMS in patients with treatment resistant depression (TRD). Inclusion criteria were as follows: subjects had a diagnosis of adult MDD based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, DSM-III or DSM-III-R) or the International Classification of Diseases (ICD-9 or ICD-10) criteria and had failed to respond to at least one course of adequate treatment for MDD during the current illness episode. Treatment resistant patients with comorbid neurological disorders and psychotic disorders or specific types of depression (e.g., child and adolescent depression or postpartum depression) were excluded. The primary outcome was the change in depression scores at the end of treatment. Remission was the secondary outcome. The cut-off points of response were ≥ 50% from the baseline score to the end of treatment score on the Hamilton Depression Rating Scale (HDRS) or the Montgomery and Asberg Depression Rating Scale (MADRS), or ‘‘much improved’’ or ‘‘very much improved’’ on the Clinical Global Impression (CGI) scale. Clinical remission was defined as a depression rating scale score within the normal range at the end of treatment. Three trials investigated unilateral rTMS, four evaluated sham rTMS, and three assessed both unilateral and sham rTMS. Treatment duration was 1–6 weeks. The primary and secondary outcomes of bilateral rTMS showed no significant improvements in outcomes compared to unilateral rTMS (p=0.22). There was a significant improvement in the change in depression scores at the end of treatment for bilateral rTMS compared to sham, but not for bilateral compared to unilateral. Limitations of the study include the limited number of studies and small patient populations. The data from this meta-analysis showed that bilateral rTMS is not a useful treatment for patients with TRD.

Chen et al. (2014) conducted a systematic review and meta-analysis to compare the efficacy of bilateral vs. unilateral repetitive transcranial magnetic stimulation (rTMS) in the treatment of major depressive disorder (MDD). Seven randomized controlled trials (RCTs) (n=509) met inclusion criteria. RCTs were included that investigated MDD patients aged 18 years or older without metallic implants or foreign bodies, epileptic seizures, severe suicidal risk, substance abuse, alcohol or drug dependence and had a mood assessment by the Hamilton Depression Rating Scale (HDRS), the Montgomery–Asberg Depression Rating Scale (MADRS), or the Clinical Global Impression (CGI). The primary outcome measures were the response rate and remission rate. The response rate was 117/248 in bilateral subjects and 120/261 in unilateral subjects showing no significant difference (p=0.86) between the two types of TMS at three- and six-weeks follow-up. Five RCTs reported remission rates. A total of 75/214 bilateral subjects and 71/213 unilateral subjects remitted showing no significant difference (p=0.09) between the groups. No significant difference was seen in the drop-out rates (bilateral subjects 29/219 vs. 38/232 unilateral subjects). Limitations of the studies include the small patient populations, short-term follow-ups, and heterogeneity of the patient populations. The authors noted that bilateral TMS usually involves a greater number of stimuli than unilateral, and the efficacy of bilateral may be the result of the number of stimulation pulses vs. the bilateral nature. Additional large-scale randomized trials are needed to investigate the clinical advantage of bilateral TMS over unilateral TMS.

High dose Transcranial Magnetic Stimulation: High-dose TMS is a new method of brain stimulation proposed to rapidly improve depressive symptoms. High-dose TMS uses rapid repeated bursts of magnet pulses to stimulate the brain by delivering more pulses than usual over the same treatment time frame (e.g., 6000-6800 pulses per session rather than 3000 pulses) (Pan, et al., 2018). Studies are primarily in the form of case series (n=7) and case reports (Pan, et al., 2018; George, et al., 2014; Hadley, et al., 2011).

Multi-Locus Transcranial Magnetic Stimulation (mTMS): mTMS is an investigational form of TMS that is proposed to provide a means to administer tailored pulse sequences in which stimulus locations are electronically controlled and would allow selection of different stimulation targets without any physical movement of the transducer. mTMS may involve the use of 2-5 coils and an algorithm to enable the user to select a target location from within a region of the cortex, stimulate it in any desired direction and obtain adequate control over the target location without coil movement. Koponen et al. (2018) used an algorithm that yielded a set of five overlapping coils: two figure-of-eight coils at a 90° angle; a circular coil; and two four-leaf-clover coils at a 45° angle. mTMS is considered experimental for all indications. Clinical trials investigating mTMS are lacking.

Priming Transcranial Magnetic Stimulation (pTMS): Despite consistent and large treatment effects, the average reduction in depression scores with conventional rTMS has been reported as low as 37% with few patients meeting the criteria for response. Methods are being investigated for enhancing response rates to rTMS. A number of potential modalities have been suggested, including optimizing pulse number and intensity, increasing the treatment duration, selecting appropriate patients, bilateral stimulation, and alternative treatment

sites (e.g., parietal cortex, cerebellum) (Nongpiur, et al., 2011). Priming of the LF-rTMS (pTMS) has been proposed as an enhancing therapy and consists of “priming” the rTMS by delivering high-frequency rTMS (5 Hz-6Hz) before LF-rTMS (1 Hz), theoretically boosting LF-rTMS efficacy. There is a paucity of studies with small patient populations and short-term follow-up (Fitzgerald, et al., 2008; Nongpiur, et al., 2011; Iyer, et al., 2003).

Theta burst stimulation (TBS): TBS is a newer form of repetitive transcranial stimulation (rTMS) by which magnetic pulses are applied in bursts. The standard theta burst pattern consists of three bursts of pulses given at 50 Hz and repeated every 200 ms. TBS may be delivered as continuous (cTBS) or intermittent (iTBS) magnetic pulses and are intended to mimic endogenous theta rhythms of the brain. cTBS typically uses a 40 second train of uninterrupted TBS to the right dorsolateral prefrontal cortex and typically 600 pulses. Intermittent TBS (iTBS) sessions deliver two seconds of stimulation on the left dorsolateral prefrontal cortex followed by an 8 second pause (e.g., for a total of 190 seconds and typically 600 pulses). Studies in healthy participants have reported that the cTBS is inhibitory while the iTBS is excitatory. The effects of cTBS or iTBS are hypothesized to be due to the mimicking of long-term potentiation or long-term depression of synaptic transmission. TBS is proposed to exert longer lasting effects upon motor cortex excitability than conventional repetitive TMS and requires less stimulation time (e.g., 6 minutes per session vs. 30 to 40 minutes). TBS protocols have a potentially higher risk of triggering a seizure than traditional TMS protocols due to the high-frequency bursts (FDA, 2018; Abujadi, et al., 2018; Brunoni, et al., 2017; Guo, et al., 2017).

U.S. Food and Drug Administration (FDA): Brainsway Deep TMS System (with iTBS Protocol) (Brainsway Ltd., Jerusalem IL) is FDA 510(k) approved “for the treatment of depressive episodes in adult patients suffering from Major Depressive Disorder who failed to achieve satisfactory improvement from previous anti-depressant medication treatment in the current episode”. A deep TMS coil delivers pulses to the prefrontal cortex (FDA, 2021).

The Mag Vita TMS Therapy System w/Theta Burst Stimulation (Tonica, Elektroni A/S, Farnum, Denmark) is FDA 510(k) approved “for the treatment of major depressive disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode”. The device uses a Cool-B70 figure 8 coil to deliver TBS to the left dorsolateral prefrontal cortex (L-DLPFC) using intermittent pulses (FDA, 2018). The Neurosoft TMS (Also called Cloud TMS) (TleEMG, LLC, Salem, NH) can be used to deliver continuous or intermittent theta-bursts TMS. Per the manufacturer the device is FDA approved for intermittent theta burst but not continuous (Cloud Neuro, 2018).

Literature Review: Studies investigating TBS for the treatment of major depressive disorder are lacking. TBS has been investigated for the treatment of other conditions including autism spectrum disorder, schizophrenia, spinal cord injury, complex regional pain syndrome (CRPS), neuropathic pain, epilepsy, tinnitus, Parkinson’s, and obsessive-compulsive disorder. Studies have primarily been in the form of pilot studies, case series and randomized controlled trials with small patient populations and short term-follow-ups (Naro, et al., 2019; Abujadi, et al., 2018; Koc, et al., 2017; Garg, et al., 2016; Oberman, et al., 2011). TMS devices are not FDA approved for the treatment of these other conditions.

Harika-Germaneau et al. (2019) conducted a six-week randomized, sham-controlled, double blind, parallel group trial (n=28, aged 18-65 years) comparing the effect of cTBS on obsessive-compulsive disorder (OCD) symptoms. Eligibility requirements included: DSM-IV-TR OCD diagnosed using the Mini-International Neuropsychiatric Interview (MINI), total Y-BOCS score of 20 or more, a total duration of the disease of at least two years and had received at least two 12-week adequate sequences and dose of treatment with SRIs but treatment resistant. Patients were excluded if they had: a diagnosis of schizophrenia; current major depressive disorder (Montgomery Asberg Depression Rating Scale [MADRS] > 21); other psychotic disorders; bipolar I disorder; substance and alcohol dependence within the prior six months; suicidal (score ≥ 3 in MADRS, moderate or severe stage in MINI); metallic implant in the cranium (except teeth); severe or unstable medical conditions; history of TMS; history of epilepsy; neurological disorders leading to increased intracranial pressure; abnormal findings in brain MRI; and severe cardiac disorder and/or with intracardiac lines, cardiac pacemakers and other contraindication to MRI. Thirty rTMS sessions were delivered once a day, five days a week, for a total of six weeks. The cTBS treatment was administered with the MagPro® X100 with Option stimulator (MagVenture, Inc.) using the cool B-65 Active/Placebo (A/P) coil which could be configured in active or sham mode by flipping the coil over. cTBS stimulation consisted of three single biphasic pulses separated by 0.02 seconds (s) (50 Hz) repeated every 0.2 s (5 Hz) for a total of 600 pulses delivered in a 40 s session. Trained psychiatrists blind to the

patient stimulation group completed clinical assessments including the Y-BOCS (primary outcome measure), Clinical Global Impression Severity (CGI-S), MADRS, the Brief Anxiety Scale (BAS), Global Assessment of Functioning (GAF), Brown Assessment of Belief Scale (BABS), and Hospital Anxiety and Depression scale (HAD). Patients were assessed at baseline, post-cTBS treatment (after six week of treatment), and at six-week follow-ups (12 weeks after baseline). No significant differences between the two groups were found with any of the outcome measures at any of the assessments. The only adverse event noted was a mild headache. Limitations of the study include: small patient population, lack of previous research and knowledge of cTMS for OCD, and heterogeneity of patient population as they were all on different types of medication regimens while in the trial. The conclusion of the clinical trial was that cTMS over the supplemental motor area had no clinically significant effect in treating OCD.

Oberman et al. (2011) conducted a systematic review of the literature to assess the safety of theta burst TMS. A total of 67 studies (n=1040) including 776 healthy control participants and 225 clinical patients met inclusion criteria. Diagnoses included: autism spectrum disorders (n=27), chronic pain (n=6), stroke (n=42), tinnitus (n=67), Parkinson's disease (n=37), dystonia (n=14), amyotrophic lateral sclerosis (ALS) (n=20), Fragile X (FX) (n=2) and multiple sclerosis (MS) (n=10). Areas of stimulation included: primary motor cortex (n=632); prefrontal cortex (n=235) supplementary motor area (SMA) (n=150); dorsal lateral prefrontal cortex (DLPFC) (n=97); frontal eye fields (FEF) (n=20); primary sensory cortex (n=98); other parietal loci (n=56); temporal cortex (n=67) including 46 to primary auditory cortex, 20 to inferior temporal cortex, and one to temporal-parietal junction; occipital cortex (n=102) and cerebellum (n=44). Multiple studies stimulated more than one site in separate sessions. Adverse events included: 1) one seizure in a healthy control subject during cTBS; 2) mild headaches; 3) nonspecific discomfort; 4) mild discomfort due to cutaneous sensation and neck muscle contractions; 5) worsening tinnitus; 6) nausea; 7) light headedness or vagal responses; and 8) unilateral eye pain and lacrimation. Limitations of the studies included: small, heterogeneous patient populations (n=1–50); heterogeneity of TBS protocols (e.g. cTBS, iTBS, other modified TBS protocols); no long-term follow-up; and lack of standardized methods for reporting adverse events. Due to the heterogeneity of the data, the safety of TBS could not be established. The authors recommended that future experiments proceed with caution and systematically document adverse events until more formal safety guidelines have been established.

Stanford Accelerated Intelligent Neuromodulation Therapy Protocol (SAINT): The SAINT protocol, also known as Stanford Neuromodulation Therapy (SNT), for administration of TMS is a novel form of iTBS delivered via an accelerated treatment schedule consisting of 50 sessions with 1800 pulses per session, 50-minute intersession interval, and delivered as 10 daily sessions over five consecutive days (Cole, et al., 2022; Cole, et al., 2020). This differs from traditional TMS protocols which are typically administered over the course a 4–6-week period with one treatment per day, for a total of 30–36 treatments. Six tapered treatments over the final three-week period may be included in the total 30-36 visits (Hutton, et al., 2023).

U.S. Food and Drug Administration (FDA): An example of an FDA cleared TMS device that utilizes the SAINT protocol is the Magnus Neuromodulation System (MNS) with SAINT Technology (Model Number 1001K) (Magnus Medical, Inc., Burlingame, CA). The FDA issued 510(k) clearance on September 1st, 2022. The device is "indicated for the treatment of Major Depressive Disorder (MDD) in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode."

Literature Review: There is insufficient evidence in the peer reviewed literature evaluating the safety and efficacy of the SAINT protocol for the delivery of TMS for the treatment of TRD. Evidence is limited to two studies (i.e., RCT, open label without comparator) with short-term follow-ups and small patient populations conducted at the same institution (Cole, et al., 2022; Cole, et al., 2020).

The studies conducted by Cole and colleagues (Cole, et al., 2022; Cole, et al., 2020) were completed at the same institution and aimed to evaluate the safety and efficacy of the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) and Stanford Neuromodulation Therapy (SNT) protocols (i.e., 50 iTBS sessions consisting of 1800 pulses per session, 50-minute intersession interval, delivered as 10 daily sessions over five consecutive days at 90% resting motor threshold) for the treatment of treatment-resistant depression. The first of the two studies (n=21) had a prospective, open label design (Cole, et al., 2020) without a comparator. The second study (n=29) had a double-blind randomized controlled trial design (Cole, et al., 2022) that utilized sham accelerated iTBS as the comparator. The primary outcome measure in both studies was the change in depression severity assessed using the Montgomery-Asberg Depression Rating Scale (MADRS). Response and

remission rates, safety, and tolerability were evaluated as secondary outcome measures. Follow-up occurred in the 2020 study at the end of each day's 10 stimulation sessions and in the 2022 study at 4-weeks. Improvements in all outcome measures were reported by the authors in both studies however, the authors concluded in the RCT that "further trials are needed to determine SNT's durability and to compare it with other treatments". Limitations for both studies included the small sample sizes and short-term follow-up. Additional limitations for Cole, et al. (2020) included the open label design and lack of a comparator.

Systematic Review of All TMS Methods: Brunoni et al. (2017) conducted a systematic review and meta-analysis to establish a clinically meaningful hierarchy of efficacy and acceptability of the different rTMS modalities for the treatment of MDD. A total of 81 randomized clinical trials (RCTs) (n=4233) enrolling subjects with a primary diagnosis of an acute unipolar or bipolar depressive episode, including those that were not precluded due to comorbidities (e.g., anxiety or personality disorders), were analyzed. Included studies compared at least two of the following interventions:

- Low frequency (LF-rTMS) over the right dorsolateral prefrontal cortex (DLPFC)
- High frequency (HF-rTMS) over the left DLPFC
- Bilateral rTMS (LF over the right DLPFC and HF over the left DLPFC)
- Theta burst stimulation (TBS) including intermittent TBS over the left DLPFC, continuous over the right DLPFC or bilateral
- Priming TMS (pTMS) over the right DLPFC
- Accelerated TMS (aTMS) over the left DLPFC
- Synchronized TMS (sTMS) over the left DLPFC
- Deep TMS (dTMS) (H-Coil) over the left DLPFC
- Sham

Exclusion criteria were other study designs, trials performing less than 10 rTMS sessions, using frequencies between 2–4 Hz, or comparing only one modality of rTMS. The primary outcome measures were response rates and acceptability (dropout rate), and remission rates were a secondary outcome. Priming TMS, bilateral, HF-rTMS, TBS, and LF-rTMS were superior to sham for response and pTMS, bilateral, HF-TMS, and LF-TMS were superior to sham for remission. Bilateral rTMS appeared to be superior to sTMS. The estimated relative ranking of treatments implied that pTMS and bilateral rTMS performed the best of all the interventions in terms of efficacy. However, findings were imprecise for most comparisons between active interventions, and no definite evidence of superiority could be supported for any particular intervention. Acceptability of all active interventions was similar to sham showing that they were well tolerated. pTMS was more acceptable (i.e., with smaller dropout rate) than HF-rTMS, LF-rTMS, sTMS, and sham. TBS was more effective than sham, but the authors noted that further clinical investigation is needed because the TBS sessions lasted approximately five minutes compared with thirty 30 minutes or longer for other strategies. Deep, synchronized, and accelerated TMS were not more effective than sham. Limitations of the studies include: small sample size (n=12–199); overall unclear to high risk of bias in the majority of the studies; lack of data on the different TMS approaches; and heterogeneity in treatment strategies. The authors concluded that clinical efficacy and acceptability between rTMS modalities could not be confirmed. High-quality RCTs are necessary to establish the efficacy of these modalities with a higher degree of credibility.

Diagnostic Navigated Transcranial Magnetic Stimulation (nTMS)

Navigated transcranial magnetic stimulation (nTMS) is being investigated as a noninvasive modality to map essential functional motor cortex areas for diagnostic indications and for preoperative treatment planning. It uses electromagnetic pulses to stimulate points of the patient's brain and then records the motor output (if any) on a standard electromyogram. Direct electrical stimulation (DES) is the gold standard for brain mapping and is used intraoperatively but is not used preoperatively. DES cannot be replaced by a noninvasive method due to its unique capability to stimulate subcortical structures accurately and to monitor function during surgery. Preoperative functional brain imaging is used widely in the context of rolandic (the motor area of the cerebral cortex lying just anterior to the central sulcus and comprising part of the precentral gyru) brain tumor surgeries. The most widely adopted method is functional magnetic resonance imaging (fMRI), but magnetoencephalography (MEG), PET, and electroencephalography have also been used for preoperative mapping (Takahashi, et al., 2013; Pitch, et al., 2012).

U.S. Food and Drug Administration (FDA)

In 2009, the Nexstim eXimia Navigated Brain Stimulation System (NexStim, North Attelboro, MA) received 510(k) FDA approval. The 510(k) summary indications for use state, “The Nexstim eXimia Navigated Brain Stimulation System (NBS System) is indicated for non-invasive mapping of the primary motor cortex of the brain to its cortical gyrus. The NBS System provides information that may be used in the assessment of the primary motor cortex for pre-procedural planning. The NBS System is not intended to be used during a surgical procedure. The NBS System is intended to be used by trained clinical professionals” (FDA, 2009).

Literature Review-navigated transcranial magnetic stimulation (nTMS)
There is limited evidence at this time to permit conclusions regarding the impact of nTMS testing on health outcomes. Several comparative studies with small sample sizes suggest that nTMS may be useful as a mapping modality of the motor cortex. Studies are primarily in the form of case series with small patient populations and lack a comparator. Additional well-designed clinical studies with larger patient populations are required (Krieg, et al., 2014; Krieg, et al., 2013; Coburger, et al., 2013; Tarapore, et al., 2012; Forster, et al., 2012; Krieg, et al., 2012; Picht, et al., 2012; Frey, et al., 2012; Makela, et al., 2012; Picht, et al., 2011).

Raffa et al. (2019) conducted a systematic review and meta-analysis of the current literature on the use of nTMS mapping and planning for surgery of motor-eloquent intrinsic brain tumors and to objectively evaluate and summarize the impact of the nTMS-based approach (occurrence of postoperative new permanent motor deficits, gross total resection [GTR] rate, size of craniotomy, length of surgery) as compared to standard surgery performed without using nTMS. Eight studies (n=1,233), including prospective observational controlled, prospective series, and retrospective series studies, met inclusion. Seven of the eight studies were included in analysis of the outcome GTR rate, four in assessment of craniotomy size, and three for the length of surgery. Inclusion criteria included: studies that reported a comparison between patients operated using the nTMS motor mapping and planning vs. patients operated without using nTMS, and data on the occurrence of postoperative new permanent motor deficits, and on the GTR rate. Results between all eight studies suggested that there was a possibility of reducing the occurrence of postoperative new permanent motor deficits following nTMS. Seven of the studies reported a higher GTR rate using nTMS motor mapping, four reported a reduced size in craniotomy, and one reported longer duration of surgery using nTMS while two others reported shorter duration. Limitations of the analysis include: lack of well-conducted randomized control trials, heterogeneous patient populations, and limited data of effects on craniotomy size and length of surgery. The authors concluded that the meta-analysis demonstrated that nTMS motor mapping may be associated with a reduced risk of postoperative new permanent motor deficits and a higher probability to achieve a gross total resection of the tumor, but well-designed randomized control studies from multiple institutions are needed.

Hayes (2017; reviewed 2019) conducted a systematic review of the literature to evaluate nTMS for mapping of the primary motor cortex to provide information that may be used for presurgical planning for brain tumors. Seven studies met inclusion criteria including one retrospective review. Although the overall body of evidence suggested that nTMS may be beneficial, a definitive conclusion could not be made due to the poor quality of the evidence. Limitations of the studies included: small, heterogeneous patient populations; retrospective study design; lack of power analysis; difference in sample sizes between groups; short- term follow-ups; various follow-up durations; and limited statistical analyses. The 2019 review revealed no new studies on nTMS.

In a systematic review of observational studies, Takahashi et al. (2013) studied the spatial accuracy and clinical utility of nTMS in rolandic brain tumor surgery in or near the motor cortex. Eleven reports in which adult patients were examined with nTMS prior to surgery met the inclusion criteria. For mapping of the motor cortex, most studies used a biphasic TMS pulse (250–280 μsec pulse length) from a figure-eight coil with an outer diameter of 70 mm applied at 110% of the resting motor threshold and a maximum frequency of 0.25 Hz.2–5,7–9,12,14–17,20,21. For lower-extremity stimulation the intensity was adapted on an individual basis. Quality criteria consisted of documentation of the influence of nTMS brain mapping on clinical decision making in a standardized prospective manner and/or performance of intraoperative direct electrical stimulation (DES) and comparison with nTMS results. Cross-observational assessment of nTMS accuracy was established by calculating a weighted mean distance between nTMS and DES. All studies reviewed concluded that nTMS correlated well with the “gold standard” of DES. The mean distance between motor cortex identified on nTMS and DES by using the mean distance in 81 patients described in six quantitatively evaluated studies was 6.18 mm. The nTMS results changed the surgical strategy based on anatomical imaging alone in 25.3% of all patients, based on the data obtained in 87 patients in two studies. The nTMS technique spatially correlates well with the gold standard of DES. Its functional information benefits surgical decision making and changes the treatment strategy in one-

fourth of cases. The studies included in the review were limited by small sample sizes. The impact of nTMS on the operation was not reported in the majority of the studies.

In a 2016 search and summary report on nTMS, Hayes reported that although there was a moderate amount of published evidence, well-designed, large randomized controlled trials are lacking. A review of the abstracts showed conflicting findings. There was considerable overlap of authorship in the retrieved abstracts, and the majority of the published studies consisted of small patient populations with various diagnosis.

Professional Societies/Organizations
Professional society opinion on this technology is lacking.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD		No Determination Found	
LCD	CGS Administrators, LLC	Repetitive Transcranial Magnetic Stimulation (rTMS) in Adults with Treatment Resistant Major Depressive Disorder (L36469)	1/6/2022
LCD	First Coast Service Options, Inc.	Transcranial Magnetic Stimulation for Major Depressive Disorder (L34522)	11/28/2019
LCD	National Government Services, Inc.	Transcranial Magnetic Stimulation (L33398) (DL33398)	10/1/2020
LCD	Noridian Healthcare Solutions, LLC	Repetitive Transcranial Magnetic Stimulation (rTMS) in Adults with Treatment Resistant Major Depressive Disorder (L37086) (L37088)	12/1/2019
LCD	Novitas Solutions, Inc.	Repetitive Transcranial Magnetic Stimulation (rTMS) in Adults with Treatment Resistant Major Depressive Disorder (L34998)	9/26/2019
LCD	Palmetto GBA	Repetitive Transcranial Magnetic Stimulation (rTMS) in Adults with Treatment Resistant Major Depressive Disorder (L34869)	6/9/2022
LCD	Wisconsin Physicians Service Insurance Corporation	Transcranial Magnetic Stimulation (TMS) (L34641)	7/30/2020

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:
1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare and Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* 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

Considered Not Medically Necessary when used to report transcranial magnetic stimulation for any other indication, including presurgical mapping:

CPT®* Codes	Description
64999	Unlisted procedure, nervous system

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
0889T	Personalized target development for accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation derived from a structural and resting-state functional MRI, including data preparation and transmission, generation of the target, motor threshold-starting location, neuronavigation files and target report, review and interpretation
0890T	Accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation, including target assessment, initial motor threshold determination, neuronavigation, delivery and management, initial treatment day
0891T	Accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation, including neuronavigation, delivery and management, subsequent treatment day
0892T	Accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation, including neuronavigation, delivery and management, subsequent motor threshold redetermination with delivery and management, per treatment day

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Revision Details

Type of Revision	Summary of Changes	Date
Focused Review	No clinical policy statement changes.	11/15/2024
Annual Review	No clinical policy statement changes.	3/15/2024
Focused Review	Added a policy statement for accelerated treatment protocols.	7/15/2024