Medical Coverage Policy

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Transcranial Magnetic Stimulation

Table of Contents

Related Coverage Resources

Attention-Deficit/Hyperactivity Disorder (ADHD): Assessment and Treatment
Complementary and Alternative Medicine
Deep Brain, Motor Cortex and Responsive Cortical Stimulation
Electrical Stimulation Therapy and Devices
Vagus Nerve Stimulation (VNS)

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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 and other psychiatric and neurological conditions.

Coverage Policy

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 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:

- 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/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 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
- improvement has been maintained for at least two months after initial course of TMS

Transcranial magnetic stimulation (TMS) for any other indication, including but not limited to migraine headaches or as a maintenance therapy, is considered experimental, investigational or unproven.

General Background

Transcranial Magnetic Stimulation (TMS) for Depression

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 (rTMS) 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 (Holtzheimer, 2018, Updated 2019; 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 (Holtzheimer, 2018, Updated 2019; Guo, et al., 2017; Allan, et al., 2011).

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 (Thase, et al., 2017, Updated 2019; 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; Neuronetics, Inc., 2015):

- 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 (Simon, 2017, Updated 2019; 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 (Holtzheimer, 2015; 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, 2018; 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 over a 4–6 week period. Six tapered treatments over the final three week period may be included in the total 30-36 visits. 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 (Holtzheimer, 2015; Lebow, et al., 2015; 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]) (Holtzheimer, 2015; 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; Philip, et al., 2016; Health Quality Ontario, 2016; Holtzheimer, 2015; 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 (Holtzheimer, 2018). 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.

While the majority of clinical trials on TMS have evaluated its use in depression, numerous other conditions have been studied, including, but not limited to: Alzheimer disease, Parkinson's disease, post-traumatic stress disorder, acute ischemic stroke, obsessive-compulsive disorders, schizophrenia, alcohol dependence, tinnitus, migraines, chronic neuropathic pain, and spinal cord injury. There is insufficient published evidence to support the effectiveness of TMS for these other conditions nor are the devices FDA approved for these indications.

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 (FDA, 2008-2016).

Examples of other recently 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:

- 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 (FDA, 2013; updated 2018).
- 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 (FDA, 2018).
- MagVita TMS Therapy with MagPro R20 (Tonica, Elektroni A/S, Farnum, 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) (FDA, 2017).
- Neurosoft TMS (also called Cloud TMS) (TleEMG, LLC, Salem, NH) uses a figure-of-eight coil with a frequency of 10Hz (FDA, 2017) 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.
- Rapid^2 Therapy System (Magstim Company, LTD., Philadelphia, PA) uses a figure 8 air film coil with a stimulus frequency of 10 Hz (FDA, 2017).
- Horizon TMS Therapy System and Horizon TMS Therapy System with Navigation (Magstim Company, Ltd., Philadelphia PA).
- Nexstim Navigated Brain Therapy (Nbt) System 2 (Nexstim Plc. Helsinki, FL).

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 have also investigated TMS as a therapeutic option for treatment-resistant depression (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).

Technology Assessments: A 2016 (reviewed 2017) 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; Simpson, Oct 2017, Updated 2019; National Institute of Mental Health, 2016, Updated 2019).

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 novel therapies such as deep brain stimulation and transcranial magnet stimulation are being investigated (Rehn, et al., 2018; Simpson, 2017 Updated 2019; National Institute of Mental Health, 2016, Updated 2019).

As rTMS can modulate cortical activity, it has been utilized in the treatment of OCD due to the neurophysiological abnormalities proposed to underlie the disorder. Currently, TMS is largely administered as a one size fits all therapy, without customizing the choice of cortical stimulation according to a patient's specific clinical profile or imaging-based estimates of dysregulation of cortical network activity. Studies investigating rTMS for the treatment of OCD have reported conflicting outcomes. No improvements in symptoms over sham following high frequency and low frequency TMS have been reported. However, some meta-analyses have reported that active rTMS is superior to sham rTMS. The heterogeneity in protocols and conflicting results in the limited literature have made it difficult to conclude whether rTMS is efficacious and to identify the most effective target area and treatment regimen. It is unknown whether the therapeutic effects are maintained after cessation of rTMS (Cocchi, et al., 2018; Lusicic, et al., 2018; Rehn, et al., 2018).

U.S. Food and Drug Administration: 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 YBOCS 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 YBOCS 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, 2018).

Literature Review: Studies investigating the safety and efficacy of TMS for the treatment of OCD are in the form of randomized controlled trials, case series, case reports and retrospective reviews. 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. Depending on the area of stimulation no significant difference was seen between TMS and sham TMS (Rehn, et al., 2018; Lee, et al., 2017; Zhou, et al., 2017; Elbeh, et al., 2016; Hawken, et al., 2016; Pelissolo, et al., 2016; Trevizol, et al., 2016; Berlim, et al., 2013c; Mansur, et al., 2011; Sachdev, et al., 2007). Overall, systematic reviews and meta-analysis agree that additional studies are needed to establish the efficacy and treatment parameters of TMS for the treatment of OCD. Future randomized controlled trials should include larger sample sizes and be more homogeneous in terms of demographic/clinical variables as well as stimulation parameters and brain targets.

Because of the historical conflicting results of the effectiveness of TMS for the treatment of OCD, Rehn et al. (2018) conducted a systematic review and meta-analysis to determine if certain rTMS parameters (e.g., cortical target) were associated with higher treatment effectiveness. Studies were included if they met the following criteria: 1) subjects aged 18–75 years with a primary diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental disorders (DSM-IV) or the Diagnostic and Statistical Manual of Mental disorders (DSM-IV-TR) or the International Classification of Diseases; 2) randomized, sham-controlled trials with either single- or double-blinding or parallel or crossover design; 3) greater than five subjects randomized per study arm; 4) low frequency (LF)-(≤ 1 Hz) or high frequency (HF)-rTMS (≥ 5 Hz) given for ≥ 5 sessions either as monotherapy or as an augmentation strategy; 5) reported pre- and post-rTMS Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores and standard deviation (SD) to evaluate the severity of symptoms as the outcome. A total of 18 randomized controlled trials (n=484) met inclusion criteria with 262 subjects being randomized to active rTMS and 222 randomized to sham. The mean number of rTMS sessions delivered was 14.63 ± 6.0. rTMS was used as an augmentation strategy for OCD in all RCTs and most enrolled subjects had some degree of treatment-resistance. Overall, active rTMS was significantly superior to sham rTMS in reducing Y-BOCS scores ($p<0.001$) but there was moderate heterogeneity of the studies ($p<0.001$). RCTs applying active rTMS over the bilateral dorsolateral prefrontal cortex (B-DLPFC), right-DLPFC (R-DLPFC) and the supplementary motor area (SMA) yielded significant improvements in Y-BOCS scores over sham rTMS. Targeting the SMA produced the greatest effect size ($p=0.041$), followed by B-DLPFC ($p=0.002$), and R-DLPFC ($p=0.003$). Active rTMS was not significantly superior to sham rTMS in improving Y-BOCS scores in studies targeting the left DLPFC (L-DLPFC) ($p=0.253$). RCTs targeting the orbitofrontal cortex (OFC) did not reach statistical significance in Y-BOCS scores ($p=0.059$). Statistically significant improvements in Y-BOCS scores were found in studies using LF-rTMS ($p=0.001$) and HF-rTMS ($p=0.01$). In six studies that reported Y-BOCS scores at ≤ 4 weeks, active rTMS was statistically significantly superior to sham ($p=0.047$). Y-BOCS scores at 12 weeks post-rTMS from three studies maintained significant scores ($p=0.008$). However, there was high heterogeneity of these studies ($p=0.008$). rTMS applied over the SMA yielded greater improvements in OCD severity than rTMS applied over the DLPFC or OFC, which has not been found in previous meta-analysis. Studies targeting the OFC and SMA were few in number preventing conclusions from being made regarding the effectiveness of stimulations of these areas. rTMS targeted at the DLPFC offered greater improvements in OCD symptoms than sham. rTMS applied over the DLPFC was less effective in improving OCD symptoms than rTMS applied over the SMA. Author-noted limitations of the studies included the heterogeneity of clinical variables and stimulation parameters (target areas, frequencies, total pulses, rTMS strategy, number of sessions). It was noted that many of the enrolled subjects had resistant OCD, which limits the ability to draw definitive conclusions about the effectiveness of rTMS in the treatment of OCD with other characteristics, such as early illness course or drug-nativity. Also, many of the patients were maintained on pharmacological treatments throughout rTMS trials making it possible that there existed a synergistic effect between rTMS and the medications. Additional limitations of the studies include the small patient populations; short-term treatment duration (2–6 weeks); no or short-term follow-up after treatment; absence of drop-out rates; and significant possibility of a publication bias. The authors noted that this was the first meta-analysis to assess whether the effectiveness of rTMS in improving OCD symptoms is moderated by its application over different cortical targets. Most of the RCTs included in this meta-analysis had patients with comorbid anxiety and depression and rTMS applied over the DLPFC may have produced improvements in OCD symptoms that were secondary to improvements in depression and anxiety. Additional studies are needed to identify the most effective stimulation target and long-term effects of rTMS for the treatment of OCD.

Zhou et al. (2017) conducted a systematic review and meta-analysis to assess the short-term therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) for the treatment of obsessive-compulsive disorder (OCD) and to examine potential influencing factors (e.g., the clinical characteristics of subjects and rTMS parameters). Twenty studies with 791 patients met inclusion criteria. Inclusion criteria were as follows: 1) subjects were diagnosed with OCD; 2) rTMS was performed as the intervention, 3) active rTMS was compared with sham rTMS; 4) Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used to evaluate the severity of symptoms; 5) studies were randomized, single-blind or double-blind design; and 6) articles provided the statistical parameters necessary for calculations. Studies using single TMS, deep rTMS, priming rTMS, or theta-burst rTMS were excluded. Compared to sham the following target areas showed a significant improvement:

- supplementary motor area (SMA) ($p<0.001$) (four studies)
- left dorsolateral prefrontal cortex (DLPFC) ($p=0.02$) (three studies)
- bilateral DLPFC ($p<0.001$) (six studies)
- right DLPFC ($p<0.001$) (nine studies)
- low-frequency rTMS ($p<0.001$) (ten studies)
- high frequency rTMS ($p<0.001$) (ten studies)

There was no significant difference in outcomes between low and high frequency rTMS ($p=0.85$). There was no significant improvement following stimulation of the orbitofrontal cortex (OFC) ($p=0.07$) (n=3 studies). Targeting the right DLPFC resulted in the highest effect size, followed by targeting the bilateral DLPFC and the left DLPFC. Subgroup analysis of subjects who were not treatment-resistant and who did not have MDD showed larger therapeutic effects than their corresponding subgroups but was not statistically significant ($p=0.40$, $p=0.11$, respectively). Subgroup analysis according to sham strategy showed that tilted coils yielded larger effects than sham coils ($p=0.03$). The risk difference of all-cause dropouts was not significantly different between active and sham TMS ($p=0.38$). Limitations of the studies included: small patient populations (n=10–95); heterogeneity of patient population (with vs without MDD) and treatment targets; medium and long-term effects were not assessed; two studies included non-treatment resistant subjects; and potential publication bias. The authors noted that given the lack of an ideal sham condition, the therapeutic effects of rTMS may be overestimated in relation to current sham conditions and that these findings are only exploratory. Due to the methodological heterogeneity (different patient characteristics and rTMS parameters) and methodological shortcomings (most of studies performed per-protocol analysis), the results of this meta-analysis should be treated cautiously. Head-to-head RCTs with large patient populations reporting medium- and long-term effects are needed to verify the results of this analysis. rTMS protocols and patient selection criteria have not been established.

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". The device is available by prescription only.

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 aged 18-70 years who met the International Classification Headache Disorders criteria for migraine headache with aura. 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; 66 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 a number of studies and meta-analyses conducted that explored the efficacy of rTMS 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 rTIMS protocol have not been identified for these conditions. Therefore, the clinical utility and improvement in health outcomes of rTMS in the treatment of other psychiatric or neurological disorders have not been clearly established. rTMS 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 (Maiti et al., 2017; Grall-Bronnec and Sauvaget, 2014)
- alcohol dependence (Mishra, et al., 2010)
- Alzheimer disease (Hayes, 2018; Liao, et al., 2015; Ahmed, et al., 2012; Cotelli, et al., 2010)
- amyotrophic lateral sclerosis (ALS) (Fang, et al., 2013; Guo, et al., 2011; Di Lazzaro, et al., 2010)
- anorexia nervosa (McClelland, et al., 2016)
- anxiety disorder (Diefenback, et al., 2016)
- attention deficit hyperactivity disorder (ADHD) (Bloch, et al., 2010)
- auditory hallucinations in schizophrenia (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, Shonefldt-Lecuona, et al., 2004; Hoffman, et al., 2003; Aleman, et al., 2007)
- autism (Sokhadze, et al., 2010)
- 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; 2010)
- chronic tinnitus (Folmer, et al., 2015; Meng, et al., 2011; Anders, et al., 2010; Lorenz, et al., 2010; Frank, et al., 2010; Marcondes, et al., 2010; Langrebe, 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 (Pereira, et al., 2016; Chen, et al., 2016; Brodbeck, et al., 2010)
- facial pain (Hodaj, et al., 2015)
- fibromyalgia (Saltychev and Laimi, 2017; Knijnik, et al., 2016; Marlow, et al., 2012, 2013)
- focal dystonia (Schneider, et al., 2010)
- Huntington's disease (Medina, et al., 2010)
- panic disorder (Li, et al., 2014: Mantovani, et al., 2012b)
- Parkinson's disease (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 (Ma, et al., 2015)
- post-operative pain (Borckardt, et al., 2006; Khedr, et al., 2005)
- post-stroke aphagia (Li, et al., 2015)
- post-stroke dysphagia (Du, et al., 2016)
- post-traumatic stress disorder (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 (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 (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)
- tic disorders (Wu, et al., 2014; Steeves, et al., 2012; Kwon, et al., 2011)
- tinnitus (Soleimani, et al., 2016)
- Tourette syndrome (Landeros-Weisenberger, et al., 2015)

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.

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).

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=7–38) and two days to two weeks treatment sessions 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 (Brunoni, et al., 2017; Tor, et al., 2016; McGirr, et al., 2015; Baeken, et al., 2013; Holzheimer, et al., 2010; Loo et al., 2007).

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 (Holtzheimer, 2018; 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 coregistration, 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 age 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) (Holtzheimer, 2018; 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 are 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, for example 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; Holtzheimer, 2018; Abujadi, et al., 2018; Brunoni, et al., 2017; Guo, et al., 2017).

The MagVita 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 Nuero, 2018)

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, and Parkinson's. Studies have primarily been in the form of case series and randomized controlled trial with small patient populations and short term-follow-ups (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.

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. Diagnosis 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.

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 intervention 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).

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 2018 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.

Use Outside of the US

Galician Agency for Health Technology Assessment: In the 2014 revised clinical practice guideline on the management of depression, the HTA Working Group stated that TMS is not currently recommended for the treatment of depression due to the uncertainly about its clinical efficacy.

Health Quality Ontario: The Ontario Health Technology Advisory Committee (OHTAC) (2016) conducted a technology assessment on rTMS for treatment-resistant depression. Twenty-three randomized controlled trials comparing rTMS with sham and six comparing rTMS with electroconvulsive therapy (ECT) met inclusion criteria. Repetitive TMS versus sham studies showed a statistically significant improvement in depression scores following rTMS, but follow-ups did not show that the effect continued for long periods of time. Trials comparing rTMS to ECT showed statistically and clinically significant improvements in favor of ECT.

National Institute for Health and Clinical Excellence (NICE): In the 2015 update of the interventional procedural guidance document on repetitive TMS for depression, NICE (United Kingdom) reported that there were no major safety concerns regarding TMS. The evidence on its efficacy in the short-term is adequate, although the clinical response is variable. According to NICE, clinicians should, in particular, inform patients about available treatment options, and make sure patients understand the procedure may not give them benefit. Further evidence on patient selection, details of the precise type and stimulation regime used, long-term outcomes and the use of maintenance treatment is needed.

In January 2014, NICE issued an interventional procedural guidance document on TMS for treating and preventing migraine. The authors reported that the evidence on the efficacy of TMS for the treatment of migraine and prevention of migraine is limited. Evidence on its safety in the short and medium term is adequate but there is uncertainty about the safety of long-term or frequent use of TMS. Nice concluded that the procedure should only be used with special arrangements for clinical governance, consent and audit or research.

Canadian Network for Mood and Anxiety Treatments (CANMAT): The 2016 update of the CANMAT clinical guidelines for the management of major depressive disorder in adults recommends rTMS as a first-line therapy for patients with MDD who have failed at least one antidepressant. Both high-frequency and low-frequency rTMS have demonstrated efficacy. A limited number of studies have suggested that long-term outcomes appear more favorable with maintenance rTMS, but maintenance schedules have not been established (Milev, et al., 2016).

Royal Australian and New Zealand College of Psychiatrists: The 2018 Royal Australian and New Zealand College of Psychiatrists position statement on repetitive transcranial magnetic stimulation included the following recommendations**:**

- In treating major depression, rTMS should be offered in a clinical settings with appropriate stimulation protocols, staff training and [Therapeutic Goods Administration] TGA-approved equipment. Assessment of appropriateness for patients to undergo rTMS should reflect evidence-based guidelines, such as the RANZCP Clinical Practice Guidelines for Mood Disorders (Malhi et al., 2015).
- rTMS may be offered on a restricted basis to carefully selected patients with schizophrenia who have auditory hallucinations that have not improved with adequate trials of antipsychotic medications. This should only be performed in tertiary referral centers or specialist centers with expertise and experience with this indication for rTMS ~~with appropriate expertise.~~
- Until the establishment of further empirical evidence, rTMS as a treatment of other neuropsychiatric disorders should only be within a research protocol which has had formal ethical review and approval by a relevant clinical research ethics committee.
- Ongoing research into rTMS should be undertaken, including a focus on further optimisation of treatment protocols, utility in different patient groups, and efficacy for other psychiatric conditions. Treatment outcomes and adverse events in specialty patient groups, e.g. pregnant populations, should be closely monitored and where possible employed to inform scientific understanding and evidence base.
- Clinical trials investigating outcomes in bipolar depression should be undertaken to increase the evidence base for the applicability of rTMS in this population group.
- Where rTMS is conducted, the outpatient or hospital based rTMS clinic should be suitably accredited by an accepted accreditation agency such as International Standards Organisation (ISO) or Australian Council of Healthcare Standards (ACHS).

- Psychiatrists supervising rTMS should have appropriate expertise and be credentialed by their institution for the delivery of rTMS treatment, and undertake continuing professional education to ensure they remain up to date on treatment advances.
- rTMS should be accessible in private and public mental health services and made available in addition to the current spectrum of treatment options. It should be affordable and, where appropriate, offered as a therapeutic option for the treatment of major depression.

The RANZCP clinical practice guidelines for mood disorders (Malhi et al., 2015) included the following recommendations for the treatment of depression:

- "A combination of psychological and pharmacological therapy should be considered when response to either modality alone has been suboptimal or unsuccessful. "
- "Optimal treatment for both acute severe depression and chronic depression is a combination of pharmacotherapy and psychotherapy. The combination can consequently be considered first line for treatment resistant depression."
- Patients with non-psychotic depression may be treated with rTMS once they have failed one or more trials of standard antidepressant medications and psychological therapies.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	No National Coverage Determination Found	
LCD	CGS Administrators, LLC	Repetitive Transcranial Magnetic Stimulation (rTMS) in Adults with Treatment Resistant Major Depressive Disorder (L36469)	12/26/2019
LCD	Noridian Healthcare Solutions, LLC	Repetitive Transcranial Magnetic Stimulation (rTMS) in Adults with Treatment Resistant Major Depressive Disorder (L37086) (L37088)	12/01/2019
LCD	Palmetto GBA	Repetitive Transcranial Magnetic Stimulation (rTMS) in Adults with Treatment Resistant Major Depressive Disorder (L34869) (DL34869)	01/12/2020
LCD	Novitas Solutions, Inc.	Repetitive Transcranial Magnetic Stimulation (rTMS) in Adults with Treatment Resistant Major Depressive Disorder (L34998)	09/26/2019
LCD	National Government Services, Inc.	Transcranial Magnetic Stimulation (L33398) (DL33398)	10/24/2019
LCD	Wisconsin Physicians Service Insurance Corporation	Transcranial Magnetic Stimulation (TMS) (L34641)	11/01/2019
LCD	First Coast Service Options, Inc.	Transcranial Magnetic Stimulation for Major Depressive Disorder (L34522)	11/28/2019

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
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 Experimental/Investigational/Unproven when used to report transcranial magnetic stimulation for any other indication, including presurgical mapping:

CPT®* Codes	Description
64999	Unlisted procedure, nervous system

***Current Procedural Terminology (CPT®) ©2019 American Medical Association: Chicago, IL.**

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