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MEDICAL POLICY – 2.01.526

Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders

BCBSA Ref. Policy:	2.01.50	
Effective Date:	April 4, 2024	RELATED MEDICAL POLICIES:
Last Revised:	Dec. 12, 2023	None
Replaces:	2.01.50	

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Introduction

Transcranial is a word that means passing through the skull. Transcranial magnetic stimulation is a treatment in which magnetic pulses travel through the skull and into the areas of the brain involved in mood control and depression. For this treatment, an electromagnetic coil is placed on the scalp. This coil creates magnetic fields that turn on and off very fast. The magnetic fields then travel into the brain, but only a small distance. As the pulses travel, they produce very weak electrical currents. It's believed that these currents stimulate cells that release neurotransmitters like serotonin and dopamine. Transcranial magnetic stimulation can be used for certain types of depression when other treatments haven't worked. This policy describes when transcranial magnetic stimulation may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

This policy addresses the following types of transcranial magnetic stimulation (TMS) and outlines when application may be considered medically necessary:

- Deep transcranial magnetic stimulation of the brain
- Standard/conventional repetitive transcranial magnetic stimulation of the brain
- Theta burst stimulation of the brain with the exceptions of accelerated theta burst stimulation and the SNT/SAINT protocol

The policy addresses when the types of transcranial magnetic stimulation (TMS) listed above may be considered medically necessary for treatment of the following conditions (click indication to navigate to that section):

- **Major depression as a component of Bipolar Disorder (bipolar depression)**
- **Major Depressive Disorder (unipolar depression)**
- **Obsessive-Compulsive Disorder**

Indication	Investigational
All other types of transcranial magnetic stimulation (TMS)	**All other types of transcranial magnetic stimulation (TMS) outside of those listed above, including but not limited to the following, are considered investigational:** • Accelerated TMS at 3 or more treatments per day • Any type of TMS with biomarkers • Computer-assisted transcranial magnetic stimulation of the prefrontal cortex (aka Group 8 Technology computer-assisted transcranial magnetic stimulation of the prefrontal cortex) • Functional MRI-guided TMS • Low field magnetic stimulation • Magnetic seizure therapy • MeRT (magnetic e-resonance therapy--TMS guided by quantitative EEG and EKG) • MRI-guided TMS • Multiarray TMS • Navigated TMS • Single pulse TMS • Synchronized TMS • The SNT/SAINT protocol (Stanford Neuromodulation Therapy aka Stanford Accelerated Intelligent Neuromodulation Therapy) • TMS with neuronavigation aka image-guided coil placement

Indication	Investigational
Theta burst stimulation • **Major depression as a component of Bipolar Disorder** • **Obsessive Compulsive Disorder**	**Theta burst stimulation is considered investigational for the treatment of major depression as a component of Bipolar Disorder (bipolar depression) and the treatment of Obsessive Compulsive Disorder.**
• **All other psychiatric disorders or conditions** • **Neurologic disorders and conditions** • **Substance abuse disorders and conditions**	**TMS and specific TMS protocols for all other psychiatric disorders or conditions, for all substance use disorders and conditions, and for all neurologic disorders or conditions, which are not addressed in this policy are considered investigational.**
TMS as an augmenting intervention	**Use of TMS to boost the effectiveness of other treatment modalities, including but not limited to drugs or other devices, is considered investigational.**
Technology computer-assisted TMS	**Technology computer-assisted transcranial magnetic stimulation of the prefrontal cortex is considered investigational.**

Indication	Medical Necessity
Major Depressive Disorder (unipolar depression)	**The following types of transcranial magnetic stimulation (TMS) may be considered medically necessary when policy criteria are met:** • Deep transcranial magnetic stimulation of the brain • Standard/conventional repetitive transcranial magnetic stimulation of the brain • Theta burst stimulation of the brain with the exceptions of accelerated theta burst stimulation and the SNT/SAINT protocol **TMS of the brain may be considered medically necessary for the treatment of Major Depressive Disorder (unipolar depression) without psychotic features when:** • The individual is at least 15 years old

Indication	Medical Necessity
	• The individual is experiencing a current episode of moderate to severe depression as demonstrated by documentation of the individual's symptoms and their severity or by one or more standardized depression rating scales • One of the following criteria are met: ○ Failure of at least 3 antidepressant medications from at least 2 different classes in separate trials **OR** ○ Failure of at least 2 different antidepressant medications from at least 2 different classes in separate trials, plus failure with the addition of an augmenting agent to at least one of the failed antidepressants **OR** ○ A positive clinical response to a previous course of treatment with TMS for Major Depressive Disorder **Note**: Please see **Additional Information** below.
Major depression as a component of Bipolar Disorder (bipolar depression)	**The following types of TMS may be considered medically necessary when policy criteria are met:** • Deep transcranial magnetic stimulation of the brain • Standard/conventional repetitive transcranial magnetic stimulation of the brain **TMS of the brain may be considered medically necessary for the treatment of bipolar depression (major depression as a component of Bipolar Disorder) without psychotic or manic features when:** • The individual is at least 18 years old • The individual is experiencing a current episode of moderate to severe depression as demonstrated by documentation of the individual's symptoms and their severity or by one or more standardized depression rating scales **AND** • One of the following criteria are met: ○ Failure of separate trials of at least 3 of the following medications: cariprazine/Vraylar; lamotrigine/Lamictal;

Indication	Medical Necessity
	lithium; lumateperone/Caplyta; lurasidone/Latuda; olanzapine-fluoxetine combination/Symbyax; quetiapine regular (immediate release) or XR/Seroquel; valproate/Depakote **OR** ○ A positive clinical response to a previous course of treatment with TMS for bipolar depression **Theta burst stimulation is considered investigational for the treatment of major depression as a component of Bipolar Disorder (bipolar depression).** **Note**: Please see **Additional Information** below.
Obsessive-Compulsive Disorder	**The following types of TMS may be considered medically necessary when policy criteria are met:** • Deep transcranial magnetic stimulation of the brain • Standard/conventional repetitive transcranial magnetic stimulation of the brain **TMS of the brain may be considered medically necessary for the treatment of Obsessive-Compulsive Disorder when:** • The individual is at least 18 years old • The individual has an Obsessive-Compulsive Disorder that is currently moderate to severe as demonstrated by documentation of the individual's symptoms and their severity or by a standardized rating scale **AND** • One of the following criteria are met: ○ Failure of separate trials of at least 3 of the following medications: clomipramine/Anafranil; all SSRIs **OR** ○ A positive clinical response to a previous course of treatment with TMS for Obsessive-Compulsive Disorder **Theta burst stimulation is considered investigational for the treatment of Obsessive-Compulsive Disorder.**

Indication	Medical Necessity
	Note: Please see **Additional Information** below.
Contraindications	**Transcranial magnetic stimulation (TMS) of the brain is considered not medically necessary when any of the following contraindications are present prior to initiation of a course of TMS of any length, or during any ongoing course of TMS including intensive TMS, a taper, or maintenance TMS:** • A history of or presence of a brain tumor • A history of repetitive or severe head trauma/traumatic brain injury • Acute or chronic psychotic disorder, including Schizophrenia, Schizoaffective Disorder, and Schizophreniform Disorder • Any condition with increased intracranial pressure • Current psychotic symptoms (acute or chronic) • Current substance abuse/excessive substance use • Dental implants (other than fillings) with magnetically sensitive material located on the side of the head on which TMS will be done • Non-removable conductive, ferromagnetic, or other magnetic-sensitive metals implanted or embedded in the head or neck within 30cm of where the TMS coil will be placed, except for dental fillings • Other implanted stimulators controlled by or that use electrical or magnetic signals • Seizure disorder or a history of a seizure disorder, unless stable and well-controlled on medication, or a history of isolated febrile seizures or ECT-induced seizures, or seizures were due to adverse drug side effects or interactions • Severe dementia • Substance use disorder unless in early or sustained remission (complete abstinence for at least the past three months) • Vagus nerve stimulator leads in the carotid sheath • Documentation that any type of medical clearance (e.g., cardiac) is required, until such clearance is obtained

Indication	Medical Necessity
Course of full intensive TMS	**Courses of intensive TMS (daily treatments 4-5 days/week) consist of either full courses, or brief courses (aka mini courses or booster courses), as explained in the criteria below.** **A full intensive course of standard/conventional repetitive transcranial magnetic stimulation or theta burst stimulation may be considered medically necessary when the criteria above are met and TMS is delivered as follows:** • A course of 30 treatments over 6-7 weeks, at a frequency of one treatment daily 4-5 days per week, with an optional 6 additional treatments for a taper over 3 weeks (3 treatments on separate days in the first week, 2 treatments on separate days in the second week, and 1 treatment in the third week), for a total of 30 or 36 treatments. The first treatment session may include treatment planning, cortical mapping, and initial motor threshold determination; 1-3 subsequent treatment sessions may include motor threshold re-determination. • More than one treatment session that includes treatment planning, cortical mapping, and initial motor threshold determination is considered not medically necessary except when there is an equipment problem that causes the initial cortical mapping and threshold determination to be done incorrectly, or there is a problem with TMS treatments which the provider suspects or determines is due to the initial cortical mapping and threshold determination not having been done correctly, or treatment is changed to a different TMS device. • More than three treatment sessions that include motor threshold re-determination are considered not medically necessary except when TMS is not being effective and the provider suspects or determines that the position of the TMS device or the strength of the magnetic pulse is not correct, or there is a medical problem or condition that could be adversely impacting the effectiveness of TMS, or there has been a medication change that could potentially impact cortical excitability, or there is a clinical event that could potentially lower the seizure threshold (e.g., sleep deprivation).

Indication	Medical Necessity
	A full intensive course of deep TMS may be considered medically necessary when the criteria above are met and TMS is delivered as follows: • A course of 20 treatments over 4 weeks, at a frequency of one treatment daily 5 days per week, called the intensive phase, followed by a course of 2 treatments weekly on separate days over 10-12 weeks, called the continuation phase, for a total of 40-44 treatments. The first treatment session may include treatment planning, cortical mapping, and initial motor threshold determination; 1-3 subsequent treatment sessions may include motor threshold re-determination. **OR** • A course of 30 treatments over 6-7 weeks, at a frequency of one treatment daily 4-5 days per week, with an optional 6 additional treatments for a taper over 3 weeks (3 treatments on separate days in the first week, 2 treatments on separate days in the second week, and 1 treatment in the third week), for a total of 30 or 36 treatments. The first treatment session may include treatment planning, cortical mapping, and initial motor threshold determination; 1-3 subsequent sessions may include motor threshold re-determination. **More than one TMS treatment session that includes treatment planning, cortical mapping, and initial motor threshold determination is considered not medically necessary except when:** • There is an equipment problem that causes the initial cortical mapping and threshold determination to be done incorrectly, **OR** • There is a problem with TMS treatments which the provider determines is due to the initial cortical mapping and threshold determination not having been done correctly, **OR** • Treatment is changed to a different TMS device

Indication	Medical Necessity
	More than three treatment sessions that include motor threshold re-determination are considered not medically necessary except when: • TMS is not being effective and the provider suspects or determines that the position of the TMS device or the strength of the magnetic pulse is not correct, **OR** • There is a medical problem or condition that could be adversely impacting the effectiveness of TMS, **OR** • There has been a medication change that could potentially impact cortical excitability, **OR** • There is a clinical event that could potentially lower the seizure threshold (e.g., sleep deprivation)
• **Extended intensive course** • **Extended intensive phase (deep TMS)**	**An extension of an intensive course of TMS (one treatment daily 4-5 days/week) beyond 30 treatments, or of the intensive phase of deep TMS (one treatment daily 5 days/week) beyond 20 treatments, may be considered medically necessary when:** • The individual has not experienced improvement. **OR** • The individual has had a partial response, but symptoms are still moderate or severe as demonstrated by documentation of the individual's symptoms and their severity or by a standardized rating scale. **OR** • The individual had minimal to no response until after the first 15 treatments ("slow/late responder'). **OR** • The individual had a positive response but then symptoms worsened during a taper or within a few days of completing treatment. **OR** • The individual has had a good response, symptoms have improved to mild, but the goal is to reach remission or as close as possible to remission. **AND**

Indication	Medical Necessity
	• The extension of the intensive course or phase consists of one treatment daily 4-5 days per week for a maximum of 10 total treatments if symptoms are mild, 15 total treatments if symptoms are moderate, or 20 total treatments if symptoms are severe. **AND** • If symptoms are mild or moderate, one session may include motor threshold re-determination; if symptoms are severe, 1-2 sessions may include motor threshold re-determination. **A second extension of TMS treatment may be considered medically necessary if symptoms are still moderate or severe after the first extension, or if symptoms are still mild or have improved to mild but the goal is to reach remission or as close as possible to remission.** **More than two extensions of TMS treatment are considered not medically necessary.** • Failing to attain desired results (symptom reduction to mild or remission) after two extensions is considered to indicate that TMS is not effective for the individual, TMS is not adequately effective for the individual, or a benefit plateau has been reached. **An extended intensive course or extended intensive phase (deep TMS) is considered not medically necessary if depression or obsessive-compulsive symptoms are in remission.**
Extended taper	**A taper at the completion of 30 intensive (4-5/week) treatments, or at the completion of an extended intensive course of TMS, is done with a maximum of 6 treatments over 3 weeks as noted above. More than 6 treatments over more than 3 weeks for an extended taper may be considered medically necessary when:** • The individual has had one or more previous courses of TMS with worsening of symptoms during tapering. **OR**

Indication	Medical Necessity
	• The individual has obtained maximum benefit from intensive TMS according to the provider but is at risk of worsening of symptoms during tapering as evidenced by symptoms not improving to mild or remission, or symptom severity fluctuating between improvement and worsening during intensive treatment. **OR** • Symptoms have improved, but the provider believes that the individual is at risk of worsening of symptoms during tapering based on a slower than expected response to TMS. **AND** • The extended taper will consist of no more than 10 additional treatments, for a maximum total taper of no more than 16 treatments, and with a maximum frequency of 3 treatments weekly on separate days. The frequency is expected to decrease every 1 to 3 weeks over the course of the taper. **An extended taper is considered not medically necessary if depression or obsessive-compulsive symptoms are in remission.**
Accelerated intensive TMS	**Accelerated intensive TMS consisting of 2 TMS treatments daily, but with no change in the total number of TMS treatments, to complete a course of TMS in a shorter period, may be considered medically necessary when:** • The individual resides at a significant distance from the location of TMS treatment such that traveling to treatment daily constitutes a hardship. **OR** • Other legitimate factors make daily treatment for an extended period of time a hardship for the individual, e.g., inability to be absent from work daily for an extended period of time, or lack of daily transportation for an extended period of time, or the individual is relocating prior to the time when a standard protocol would be completed, or the individual's schedule will cause a break in treatment of a week or longer prior to the time when a standard protcol would be completed.

Indication	Medical Necessity
	More than 2 treatments daily are considered not medically necessary. **More than two theta burst treatments daily via the SNT/SAINT protocol (Stanford Neuromodulation Therapy aka Stanford Accelerated Intelligent Neuromodulation Therapy aka accelerated intermittent theta burst stimulation) are considered investigational as noted above.**
Maintenance TMS	**Maintenance TMS (also referred to as relapse prevention) is a continuation of TMS after a full intensive course or after a brief intensive course (aka a mini-intensive course, a booster course, or a booster series), at reduced frequency, to maintain improvement. Maintenance TMS may be considered medically necessary when:** • Intensive TMS resulted in symptom improvement to moderate, mild, or remission. • The frequency is 2 treatments/week (on separate days) or less frequent. • One treatment session may include motor threshold re-determination no more frequently than every 10 treatment sessions. More frequent treatment sessions that include motor threshold re-determination are considered not medically necessary except when TMS is not being effective and the provider suspects or determines that the position of the TMS device or the strength of the magnetic pulse is not correct, or there is a medical problem or condition that could be adversely impacting the effectiveness of TMS, or there has been a medication change that could potentially impact cortical excitability, or there is a clinical event that could potentially lower the seizure threshold (e.g., sleep deprivation). • For continued authorization after the initial authorization of maintenance TMS, improvement is being maintained. **Initial authorization: Maintenance TMS may be approved for up to 12 weeks.**

Indication	Medical Necessity
	Subsequent reauthorizations may be approved for up to 12 weeks when the frequency is 2 treatments/week, for up to 16 weeks when the frequency is one treatment/week or one treatment every other week, and for up to 26 weeks if the frequency is one treatment/month or less. **Maintenance TMS is considered not medically necessary if the preceding course of intensive TMS was determined by the Company to be not medically necessary.**
Repeat full intensive course	**A repeat full intensive course of TMS may be considered medically necessary when:** • The individual had a positive response to a previous course of TMS, depression or obsessive-compulsive symptoms have worsened and are moderate to severe as demonstrated by documentation of the individual's symptoms and their severity or by a standardized rating scale, and the last TMS treatment was at least 90 days ago. **OR** • The individual has failed to respond adequately to a current course of TMS, depression or obsessive-compulsive symptoms are moderate to severe as demonstrated by documentation of the individual's symptoms and their severity or by a standardized rating scale, and a new course of TMS will be conducted with one of the other types of TMS (standard/conventional repetitive TMS, deep TMS, or theta burst stimulation, depending on what type was utilized for the failed trial) or with placement of the TMS coil in a different location on the individual's head. Only one repeat full intensive course of TMS is considered medically necessary when a course of TMS has failed. Failing to attain desired results after a second full intensive course of TMS is considered to indicate that TMS is not effective or is not adequately effective for the individual. **OR** • The individual failed to respond adequately to a prior course of TMS, depression or obsessive-compulsive symptoms are moderate to severe as demonstrated by documentation of the

Indication	Medical Necessity
	individual's symptoms and their severity or by a standardized rating scale, and the provider has documented a reason or reasons why a repeat course of TMS might be effective based on what is different about the member's clinical condition or how TMS will be applied differently than previously. Only one repeat full intensive course of TMS is considered medically necessary when a course of TMS has failed. Failing to attain desired results after a second full intensive course of TMS is considered to indicate that TMS is not effective or is not adequately effective for the individual. **A repeat full intensive course of TMS is considered not medically necessary if depression or obsessive-compulsive symptoms are mild or in remission.** **Desired results are usually symptom reduction to mild or remission, but in some cases may be symptom reduction from severe to moderate for individuals with severe symptoms who have not responded to any other treatments.** **A repeat full intensive course of TMS is considered not medically necessary if the preceding full intensive course of TMS was determined by the Company to be not medically necessary.**
Short or brief intensive course (aka mini-intensive course aka booster course or booster series)	**A short or brief intensive (one treatment daily 4-5 days/week) course of TMS, also referred to as a mini-intensive course or a booster course or a booster series, is an intensive course of shorter length than a full intensive course. A mini or brief or booster intensive course of TMS may be considered medically necessary when:** • The individual had a positive response to a previous course of TMS, and depression or obsessive-compulsive symptoms have worsened as demonstrated by documentation of the individual's symptoms and their severity or by a standardized rating scale. **OR**

Indication	Medical Necessity
	• The individual is undergoing maintenance TMS, and depression or obsessive-compulsive symptoms are getting worse as demonstrated by documentation of the individual's symptoms and their severity or by a standardized rating scale. **AND** • The individual has not had a short or brief intensive course of TMS in the past 90 days. **AND** • The course consists of one treatment daily 4-5 days per week for a maximum of 10 total treatments if symptoms are mild, 15 total treatments if symptoms are moderate, or 20 total treatments if symptoms are severe. **AND** • If symptoms are mild or moderate, one session may include motor threshold re-determination; if symptoms are severe, 1-2 sessions may include motor threshold re-determination. **A short or brief intensive course of TMS is considered not medically necessary if depression or obsessive-compulsive symptoms are in remission or are mild and not getting worse.** **A short or brief intensive course of TMS is considered not medically necessary if the preceding course of intensive TMS or maintenance TMS was determined by the Company to be not medically necessary.**
Consecutive or overlapping courses of TMS for different conditions	**Consecutive or overlapping courses of TMS for different conditions (e.g., for Major Depressive Disorder or bipolar depression, and then for Obsessive-Compulsive Disorder) are considered not medically necessary.**
TMS with more than one provider at the same time	**TMS with more than one provider/group/clinic at the same time is considered not medically necessary.**
TMS in conjunction with Spravato or ketamine or any other psychedelic drug	**Use of TMS in conjunction with Spravato or with any type of ketamine or any other psychedelic drug, regardless of the reason for which Spravato or ketamine or another psychedelic drug is being used, is considered investigational.**

Indication	Medical Necessity
TMS in conjunction with other neuromodulation modalities	**Use of TMS in conjunction with any other modality of neuromodulation, including but not limited to electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), deep brain stimulation (DBS), or cranial electrotherapy stimulation (CES), is considered not medically necessary.**
Continuation of TMS that was started under a non-Company plan	**Continuation of TMS that was started under a non-Company plan may be considered medically necessary when criteria for TMS were met at the time that TMS was started, and all other criteria for the type of TMS are met.**

Additional Information

For Major Depressive Disorder, bipolar depression, and Obsessive-Compulsive Disorder:

- Failure of a medication trial means that medication was not effective, was partially but inadequately effective, was effective for some period but then lost effectiveness, had to be stopped due to adverse effects, or doses could not be increased to potentially therapeutic levels due to adverse effects.
- Each medication that failed must be individually identified, and the reason or reasons for failure must be specified for each medication.
- Unless stopped because of intolerable adverse effects, a minimum of thirty continuous days with no or inadequate improvement is required before a medication trial is considered to be a failed trial.

For Major Depressive Disorder and bipolar depression:

- A diagnosis code that includes a numeral for severity, or a diagnosis with the descriptor moderate or severe, is not sufficient to establish severity; documentation of symptoms and their severity or score on a standardized rating scale is required.
- Standardized rating scale scores of moderately severe are considered to be equivalent to severe.

For Major Depressive Disorder:

- Addition of a second antidepressant to an antidepressant trial is considered to be addition of an augmenting agent, not a separate antidepressant trial.
- Second generation antipsychotics, lithium, and anticonvulsants that are utilized as mood stabilizers are considered to be augmenting agents, not antidepressants.
- Trials of antidepressants that are commonly used for insomnia are considered to be failed trials only if the dose was at minimum antidepressant dose (amitriptyline: 150 mg; doxepin: 150 mg;

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mirtazapine: 15 mg; trazodone: 150 mg), not at lower doses that are used for insomnia, or, if titration up to an antidepressant dose was planned but could not be done due to intolerable adverse effects.

For bipolar depression:

- Mixed episodes of Bipolar Disorder (concurrent depression and hypomanic or manic symptoms) are not equivalent to depressive episodes of Bipolar Disorder (bipolar depression). Transcranial magnetic stimulation is considered investigational for mixed episodes.

For Obsessive-Compulsive Disorder:

- A diagnosis with a descriptor of moderate or severe is not sufficient to establish severity; documentation of symptoms and their severity or score on a standardized rating scale is required.

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Diagnosis
- Severity of symptoms
- Brief history of the diagnosis
- Medication trials, including the outcome of the trial for each medication
- Age of individual
- Contraindications, if any, to TMS
- CPT codes and the number of sessions for each CPT code

Coding

Code	Description
CPT	
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

Code	Description
90869	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold re-determination with delivery and management

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Definition of Terms

Clinical response: Improvement of 50% or more in the Hamilton Depression Rating Scale

Remission: Score of 7 or less on the Hamilton Depression Rating Scale

Evidence Review

Description

Transcranial magnetic stimulation (TMS) is a non-invasive method of delivering electrical stimulation to the brain. A magnetic field is delivered through the skull, where it induces electric currents that affect neuronal function. Repetitive TMS (rTMS) is being evaluated as a treatment of depression and other psychiatric/neurologic brain disorders.

Background

Transcranial magnetic stimulation (TMS) was first introduced in 1985 as a new method of noninvasive stimulation of the brain. The technique involves placement of a small coil over the scalp; a rapidly alternating current is passed through the coil wire, producing a magnetic field that passes unimpeded through the scalp and bone, resulting in electrical stimulation of the cortex. TMS was initially used to investigate nerve conduction; for example, transcranial magnetic stimulation over the motor cortex will produce a contralateral muscular-evoked potential. The motor threshold, which is the minimum intensity of stimulation required to induce

a motor response, is empirically determined for each individual by gradually increasing the intensity of stimulation. The stimulation site for treatment is usually 5 cm anterior to the motor stimulation site.

Interest in the use of transcranial magnetic stimulation as a treatment for depression was augmented by the development of a device that could deliver rapid, repetitive stimulation. Imaging studies had showed a decrease in activity of the left dorsolateral prefrontal cortex (DLPFC) in depressed individuals, and early studies suggested that high frequency (e.g., 5–10 Hz) TMS of the left DLPFC had antidepressant effects. Low frequency (1–2 Hz) stimulation of the right DLPFC has also been investigated. The rationale for low frequency TMS is inhibition of right frontal cortical activity to correct the interhemispheric imbalance. A combination approach (bilateral stimulation) or deep stimulation with an H1 coil, are also being explored. In contrast to electroconvulsive therapy, transcranial magnetic stimulation does not require anesthesia and does not induce a convulsion.

Repetitive transcranial magnetic stimulation (rTMS) is also being tested as a treatment for a variety of other disorders including alcohol dependence, Alzheimer disease, neuropathic pain, obsessive-compulsive disorder (OCD), post-partum depression, depression associated with Parkinson's disease, stroke, posttraumatic stress disorder, panic disorder, epilepsy, dysphagia, Tourette's syndrome, schizophrenia, migraine, spinal cord injury, fibromyalgia, and tinnitus (see **Related Policies**). In addition to the potential for altering interhemispheric imbalance, it has been proposed that high frequency rTMS may facilitate neuroplasticity.

Depression

Over the last decade, there has been a trend to increase the intensity, trains of pulses, total pulses per session, and number of sessions.[1] Unless otherwise indicated in the trials described next, stimulation was set at 100% to 120% of motor threshold, clinical response was defined as an improvement of 50% or more on the Hamilton Rating Scale for Depression (HAM-D), and remission was considered to be a score of 7 or less on the HAM-D. Refer to the 2009 meta-analysis by Schutter for a summary of study characteristics and stimulation parameters used in trials conducted prior to 2008.[2]

The Blue Cross and Blue Shield Technology Evaluation Center (TEC) published an assessment of repetitive TMS (rTMS) for depression in 2009, 2011 and 2013.[3-5] These TEC Assessments concluded that the available evidence did not permit conclusions regarding the effect of TMS on health outcomes. Limitations of the evidence included:

- Equivocal efficacy in the largest sham-controlled trial of TMS,

- Uncertain clinical significance of the short-term anti-depressant effects found in meta-analyses, which are also at high risk of bias due to the inclusion of numerous small trials and potential for publication bias,
- Limited evidence beyond the acute period of treatment, and
- Lack of comparison with standard therapy (a second course of antidepressant therapy) in the population for whom TMS is indicated (individuals who have failed one 6-week course of antidepressant medication).

The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review on nonpharmacologic interventions for treatment-resistant depression (TRD) in adults in 2011.[6] Findings for the key questions (KQ) of the review follow.

Efficacy of Nonpharmacologic Interventions Against Other Nonpharmacologic Interventions (KQ 1a)

Direct Evidence

The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions for Tier 1 TRD was limited to two fair trials (both in major depressive disorder [MDD]-only populations). One compared ECT and rTMS, and the other compared ECT and ECT plus rTMS. They showed, with low strength of evidence, no differences between treatment options for depressive severity, response rates, and remission rates. No trial involved a direct comparison of psychotherapy with another nonpharmacologic intervention.

Indirect Evidence

Identified trials that compared a nonpharmacologic intervention, generally rTMS, VNS [vagus nerve stimulation], or psychotherapy, with a control or sham procedure in Tier 1 populations (i.e., individuals had 2 or more prior treatment failures with medications). The number of these trials with the same or similar control group was very small, so they could not pool them quantitatively. They assessed the potential benefits of nonpharmacologic interventions versus controls by calculating mean changes in depressive severity, relative risks of response, and relative risks of remission.

rTMS was beneficial relative to controls receiving a sham procedure for all 3 outcomes (severity of depressive symptoms, response rate, remission rate). rTMS produced a greater decrease in depressive severity (high strength of evidence). Specifically, rTMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than 5 points relative to sham control, and this change meets the minimum threshold of the 3-point HAM-D difference that is considered clinically meaningful. Response rates were greater with rTMS than sham (also high strength of evidence); those receiving rTMS were more than three times as likely to achieve a depressive response as individuals receiving a sham procedure. Finally, rTMS was also more likely to produce remission than the control procedure (moderate strength of evidence); individuals receiving rTMS were more than six times as likely to achieve remission as those receiving the sham.

Efficacy of Nonpharmacologic Interventions Compared with Antidepressant Pharmacotherapies (KQ 1b)

Direct Evidence

No direct evidence was identified for rTMS.

Maintenance of Remission or Prevention of Relapse (KQ 2)

Direct Evidence

With respect to maintaining remission (or preventing relapse), there were no direct comparisons involving ECT, rTMS, VNS, or CBT.

Indirect Evidence

Three fair trials compared rTMS with a sham procedure and found no significant differences. However, too few individuals were followed during the relapse prevention phases in two of the three studies, and individuals in the third received a co-intervention providing insufficient evidence for a conclusion.

AHRQ Author's Conclusions

The evidence review suggests 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 is substantially hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence is for ECT and rTMS. However, even for the few comparisons of treatments that are supported by some evidence, the strength of evidence is low for benefits, reflecting low confidence that the evidence reflects the true effect and indicating that further research is likely to change our confidence in these findings. This finding of low strength is most notable in two cases: 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. The most urgent next steps for research are to apply a consistent definition of TRD, to conduct more head-to-head clinical trials comparing nonpharmacologic interventions with themselves and with pharmacologic treatments, and to carefully delineate the number of treatment failures following a treatment attempt of adequate dose and duration in the current episode.

High Frequency rTMS of the Left DLPFC for Treatment-Resistant Depression (TRD)

There is a large body of evidence for the use of rTMS in the treatment of depression. The largest study (23 study sites) to date is included in the meta-analysis was a double blind multicenter trial with 325 TRD individuals randomized to daily sessions of high frequency active or sham rTMS (Monday to Friday for 6 weeks) of the left dorsolateral prefrontal cortex (DLPFC).[7] Treatment-resistant depression was defined as failure of at least one adequate course of antidepressant treatment. Individuals had failed an average of 1.6 treatments in the current episode, with approximately half of the study population failing to benefit from at least 2 treatments. Loss to follow-up was similar in the 2 groups, with 301 (92.6%) individuals completing at least one post-baseline assessment and an additional 8% of individuals from both groups dropping out before the 4-week assessment. Intent-to-treat (ITT) analysis showed a trend favoring the active rTMS group in the primary outcome measure (2 points on the Montgomery-Asberg Depression Rating Scale [MADRS]; p = 0.057) and a modest (2-point) but significant improvement over sham treatment on the HAM-D. The authors reported that after 6 weeks of treatment the subjects in the active rTMS group were more likely to have achieved

remission than the sham controls (14% vs. 5% respectively), although this finding is limited by loss-to-follow-up.

In 2010, George et al. reported a randomized sham-controlled trial that involved 190 individuals treated with left- prefrontal rTMS.[8] This was a multi-centered study involving individuals with a moderate level of treatment resistance. The response rate using an ITT analysis was 14% for rTMS and 5% for sham (p=0.02). In this study, the site for stimulation was determined through pre-treatment magnetic resonance imaging (MRI). In a 3-week, open-label, follow-up phase of the study in which all individuals received active therapy but remained masked to their original treatment arm, the remission rates rose to 30.2% in the originally active group and 29.6% in the original sham group.

Another randomized sham-controlled double-blind trial was conducted in 68 individuals who had failed at least 2 courses of antidepressants.[9] Three individuals in each group did not complete the 15 treatment sessions or were excluded due to a change in medication during treatment, resulting in 91% follow-up. Independent raters found a clinical response in 31% (11 of 35) of the active rTMS individuals and 6% (2 of 33) of the sham group. The average change in HAM-D was 7.8 for the active group and 3.7 for the control group. The Beck Depression Inventory (BDI) decreased by 11.3 points in the active rTMS group and 4.8 points in controls. Remission was observed in 7 individuals (20%) in the active rTMS group and 1 individual (3%) in the control group. Regarding effectiveness of blinding; 15% of subjects in each group guessed that they were receiving active TMS after the first session. After the 15th session, 58% of the rTMS group and 43% of the sham group guessed that they had received active TMS; responders were more likely than non-responders (85% vs. 42%) to think that they had received the active treatment. The 11 responders were treated with antidepressant medication and followed for 6-months. Of these, 1 was lost to follow-up, 5 (45%) relapsed, and 5 (45%) did not relapse.

Rossini and colleagues randomized 54 individuals who had failed at least two adequate courses of antidepressants to sham control or active rTMS at 80% or 100% of motor threshold (MT) for 10 sessions over a 2-week period.[10] Double-blind evaluation found an intensity-dependent response with 6% (1 of 16) of the sham, 28% (5 of 18) of the 80% MT, and 61% (11 of 18) of the 100% MT groups showing improvement of 50% or more over a 5-week evaluation. All the individuals reported that they were unaware of the differences between sham and active stimulation.

In a 2008 report, Mogg et al. randomized 59 individuals with major depression who had failed at least one course of pharmacotherapy for the index depressive episode.[11] In this study population, 78% of the individuals had failed 2 treatment courses and 53% had failed 3. The sham coil, which was provided by Magstim, was visually identical to the real coil and made the same clicking sound but did not deliver a magnetic field to scalp or cortex. Blinded assessments

were measured 2 days after the 5th and final (tenth) sessions (97% follow-up), with additional assessments at 6 weeks (90% follow-up) and 4 months (83% follow-up). The mean group difference was estimated to be 0.3 points in HAM-D scores for the overall analysis. Interpretation of this finding is limited since 7 sham individuals (23%) were given a course of real rTMS after the 6-week assessment and analyzed as part of the sham group in the ITT analysis. The study was powered to detect a difference of 3.5 points in the HAM-D between the active and sham groups, and the 2.9 point group difference observed at the end-of-treatment was not significant. A higher percentage of individuals in the active rTMS group achieved remission criteria of 8 points or less on the HAM-D (25% vs. 10% control), and there was a trend for more individuals to achieve clinical response in the active rTMS group (32% vs. 10%, $p = 0.06$). All the 12 individuals who met the criterion for clinical response (9 active and 3 sham) thought that they had received real rTMS, with more individuals in the active group (70%) than the sham group (38%) guessing that they had received the real treatment. Interpretation of this finding is also limited, since the reason the subjects guessed that they had active treatment was not reported, and the subjects were not asked to guess before they began to show a clinical response.

A small double-blind randomized trial from 2009 suggests that specific targeting of Brodman areas 9 and 46 may enhance the anti-depressant response compared with the standard targeting procedure, i.e., measuring 5 cm anterior from the motor cortex.[12] Fifty-one individuals who had failed at least two 6-week courses of antidepressant medication (average 5.7 failed courses) were randomized to a standard localization procedure or to structural magnetic resonance imaging (MRI)-aided localization for 3 weeks (with one-week extension if > 25% reduction on the MADRS). Six individuals in the targeted group and 10 in the standard group withdrew due to lack of response. A single individual in the targeted group and 5 in the standard group withdrew for other reasons, resulting in 17 individuals in the targeted group and 12 in the standard group continuing for the full 4 weeks of treatment. To adjust for the imbalance in discontinuation rates, a mixed model statistical analysis was used. There was a significant difference between the groups in the overall mixed model analysis, and planned comparisons showed significant improvement in MADRS scores for the targeted group at 4 weeks. Response criteria were met by 42% of the targeted group and 18% of the standard group. Remission criteria were met by 30% of the targeted group and 11% of the standard group. Although encouraging, additional trials with a larger number of subjects are needed to evaluate this procedure.

Comparison with ECT

Several studies have compared the outcomes of rTMS with those from electroconvulsive therapy. In one study, 40 individuals with nonpsychotic major depression were treated over the course of 1 month (20 total sessions) and evaluated with the HAM-D, in which a response was defined as a 50% decrease with a final score of less than or equal to 10.[13] There was no difference in response rate between the 2 groups; 12 of 20 responded in the electroconvulsive therapy group compared to 11 of 20 in the magnetic stimulation group. A United Kingdom National Institute for Health Research health technology assessment compared efficacy and cost-effectiveness of rTMS and electroconvulsive therapy.[14] Forty-six individuals who had been referred for electroconvulsive therapy were randomly assigned to either electroconvulsive therapy (average of 6.3 sessions) or a 15-day course (5 treatments per week) of rTMS of the left DLPFC. Electroconvulsive therapy resulted in a 14-point improvement in the HAM-D and a 59% remission rate. Repetitive TMS was less effective than electroconvulsive therapy (5-point improvement in HAM-D and a 17% remission rate). Another study reported no significant difference between electroconvulsive therapy and rTMS in 42 individuals with TRD; however, response rates for both groups were low.[15] The number of remissions (score of 7 or less on the HAM-D) totaled 3 (20%) for electroconvulsive therapy and 2 (10%) for rTMS.

A 2013 systematic review by Berlim et al identified 7 RCTs with a total of 294 individuals that directly compared rTMS and ECT treatment for individuals with depression. After an average of 15.2 sessions of high-frequency rTMS over the left DLPFC, 33.6% of individuals were classified as remitters. This compared with 52% of individuals who were classified as remitters following an average of 8.2 ECT sessions. The pooled odds ratio was 0.46, indicating a significant difference in outcome favoring ECT. There was no significant difference in dropout rates for the 2 treatments.

Deep TMS of the Left Dorsolateral Prefrontal Cortex for Treatment-Resistant Depression

The randomized controlled trial leading to 510k clearance of the Brainsway deep TMS system was conducted at 20 centers in the US (n=13), Israel (n=4), Germany (n=2), and Canada (n=1).[16] The study included 229 individuals with major depressive disorder who had not received benefit from 1 to 4 antidepressant trials or were intolerant to at least 2 antidepressant treatments. Per protocol analysis, which excluded 31 individuals who did not receive adequate TMS treatment and 17 individuals who did not meet the inclusion/exclusion criteria, showed a significant benefit for both response rate (38.4% vs 21.4%) and remission rate (32.6% vs 14.6%). Modified intent-to-treat analysis, which excluded the 17 individuals who did not meet the inclusion/exclusion

criteria, showed a significant benefit in both response rate (37% vs 22.8%) and remission rate (30.4% vs 15.8%). At the end of the maintenance period (16-week follow-up), the response rate remained significantly improved by deep TMS. Remission rates were not reported. Intent-to-treat analysis found no significant benefit of treatment at 4 or 16 weeks.

Low Frequency rTMS of the Right DLPFC or Bilateral Stimulation for Treatment-Resistant Depression (TRD)

Fitzgerald et al. randomized 60 individuals who had failed a minimum of at least 2 six-week courses of antidepressant medications into one of 3 groups; high frequency left rTMS, low frequency right rTMS, or sham stimulation over 10 sessions.[17] All individuals who entered the study completed the double-blind randomized phase, which showed no difference between the two active treatments (left: 13.5% reduction; right: 15% reduction) and greater improvements in the MADRS scores compared to the sham group (0.76% reduction). Only 1 individual achieved 50% improvement during the initial 2 weeks. Then, only the subjects who showed at least 20% improvement at the end of the 10 sessions (15 active and 2 sham) continued treatment. Individuals who did not respond by at least 20% were switched to a different active treatment. From week-2 to week-4 there was greater improvement in the low frequency right rTMS group compared with the high frequency left rTMS group (39% vs. 14% improvement in MADRS, respectively). Seven individuals (18% of 40) showed a clinical response of greater than 50% by the end of the 4 weeks.

In a subsequent study Fitzgerald and colleagues randomized 50 individuals with TRD to sequential bilateral active or sham rTMS.[18] After 2 weeks of treatment, 3 subjects had dropped out of the sham treatment group and there was a slight but non-significant improvement favoring the active group for the MADRS (26.2 vs. 30.9, respectively) and the BDI (18.3 vs. 21.6, respectively). At this time point, 60% of subjects receiving active rTMS and 50% of subjects receiving sham treatment guessed that they were in the active group. The clinical response was reported by subjects as the major reason for their guess, with 11 of 13 responders (9 active and 2 sham) guessing that they were in the active group. As in the earlier study, only the subjects who showed at least 20% improvement at the end of each week continued treatment. Treatment on week 3 was continued for 15 subjects in the active group and 7 subjects in the sham group. By week six, 11 subjects in the active rTMS remained in the study, with no control subjects remaining. Final ratings for the 11 subjects who continued to respond through week 6 were 8.9 on the MADRS and 9.2 on the BDI.

Another multicenter double blind trial randomized 130 individuals with treatment-resistant depression to 5 sessions per week of either 1- or 2-Hz rTMS over the right DLPFC.[19] Sixty-eight individuals (52%) completed 4 weeks of treatment; there was an approximate 30% improvement in depression scales, with no differences between the 1- or 2-Hz groups. Due to the potential for placebo effects for this type of intervention, the absence of a sham control group limits interpretation.

A small randomized, sham-controlled trial was published in 2010 that involved either right or left rTMS in 48 individuals with TRD.[20] Overall reductions in the HAM-D-24 from baseline to 3 months were not significantly different between rTMS and sham treatment groups. In this small study, right cranial stimulation was significantly more effective than left cranial stimulation (sham or rTMS).

rTMS as an Adjunctive Treatment for Moderate to Severe Depression

Schutter conducted a meta-analysis of 30 double-blind randomized sham-controlled trials (1,164 individuals) of high frequency rTMS over the left DLPFC in individuals with major depression.[5] The pooled weighted mean effect size for treatment was calculated with Hedges' g, a standardized mean difference that adjusts for sampling variance, to be 0.39 (95% confidence interval 0.25-0.54), which is considered moderate. For 27% of the population rTMS was used as a primary/adjunctive treatment; 3 trials were included that used rTMS as a primary/adjunctive treatment for depression and enrolled more than 40 subjects.[21-23] Repetitive TMS has also been examined in individuals with clinical evidence of cerbrovascular disease and late-life depression.[24]

A 2012 study examined the efficacy of ultra-high frequency (30Hz) rTMS over the left prefrontal cortex in moderate to severely depressed individuals who were taking medication.[25] Sham treatment consisted of low frequency stimulation to the left prefrontal cortex. No benefit of rTMS was found to improve performance on the trail-making test, which covaried with improvement of psychomotor retardation.

Additional research on whether adjunctive rTMS can improve response to pharmacologic treatment as a first-line therapy is also needed.

Maintenance Therapy

Demirtas-Tatlidede et al. reported durability of the antidepressant response to rTMS and efficacy of retreatment for relapses in a prospective series of 16 individuals.[26] Individuals who initially had clinically significant antidepressant responses to rTMS were enrolled in the study and followed for 4 years. During this period there were a total of 64 episodes of relapse. Relapses were treated with a 10-day course of rTMS, with an average of 4 treatment courses per individual (range, 2-10) and a mean treatment interval of 4.9 months (range, 1.5 to 24.0). About one half of the individuals had a clinically significant response to repeated courses of rTMS and continued in the study. These individuals had a medication-free interval of 33 months (range, 26 to 43 months) and a mean response on the HAM-D of 64.8%. Other subjects terminated the study due to non-response after the second (n=3), third (n=1), fourth (n=2), or fifth (n=1) treatment course.

A variety of maintenance schedules are being studied. Richieri et al. used propensity-adjusted analysis of observational data and found that the group of individuals who had maintenance rTMS tapered over 20 weeks (from 3 times per week to once a month) had a significantly reduced relapse rate compared with individuals who had no additional treatment (37.8% vs. 81.8%).[27] Connolly et al. reported that in the first 100 cases treated at their institution the response rate was 50.6% and the remission rate was 24.7%.[28] At 6 months after the initial rTMS treatment, 26 of 42 individuals (62%) who received tapered maintenance therapy (from 2 sessions per week for the first 3 weeks to monthly) maintained their response. In another study, individuals who met criteria for partial response during either a sham–controlled or open-label phase of a prior study were tapered from rTMS and simultaneously started on maintenance antidepressant monotherapy.[29] During the 24 week follow-up, 10 of 99 individuals relapsed, 38 had symptom worsening, and of these 32 (84%) had symptomatic benefit with adjunctive rTMS.

Fitzgerald et al. reported a prospective open-label trial of clustered maintenance rTMS for individuals with refractory depression.[30] All individuals had received a second successful course of rTMS following relapse and were then treated with monthly maintenance therapy consisting of 5 rTMS treatments over a 2.5-day period (Friday evening, Saturday and Sunday). Individuals were treated with maintenance therapy of the same type that they had initially received (14 high frequency to the left dorsolateral prefrontal cortex, 12 low frequency to the right dorsolater prefrontal cortex, and 9 bilateral). The primary outcome was the mean duration until clinical relapse, addition or change of antidepressant medication, or withdrawal from maintenance treatment to pursue other treatment options. Out of 35 individuals, 25 (71%) relapsed at a mean of 10.2 months (range, 2 to 48 months), which was substantially shorter than the interval (< 3 months) for relapse from the initial treatment.

A 2015 meta-analysis examined durability of the antidepressant effect of high frequency rTMS of the left DLPFC in the absence of maintenance treatment. Included were 16 double-blind sham controlled RCTs with a total of 495 individuals. The range of follow-up was 1-16 weeks, but most studies reported follow-up of only 2 weeks. The overall effect size was small with a standardized mean difference (Cohens d) = -.48, and the effect sizes were lower in RCTs with 8-16 week follow-up (d = -.42) compared to 1 - 4 week follow-up (d = -0.54). The effect size was higher when antidepressant medication was started concurrently with rTMS (5 RCTs, d = -.56) than when individuals were on a stable dose of medication (9 RCTs, n = -.43) or were unmedicated (2 RCTs, d = -.26).

Alzheimer Disease

Ahmed et al. randomized 45 individuals with probable Alzheimer disease to 5 sessions of bi-lateral high-frequency rTMS, bi-lateral low-frequency rTMS, or sham TMS over the dorsolateral prefrontal cortex.[31] Thirty-two individuals had mild to moderate dementia and 13 had severe dementia. There were no significant differences between groups at baseline. Measures of cortical excitability immediately after the last treatment session showed that treatment with high-frequency rTMS reduced the duration of transcallosal inhibition. At 3 months after treatment, the high-frequency rTMS group improved significantly more than the other 2 groups in standard rating scales, and subgroup analysis showed that this was due primarily to improvements in individuals with mild/moderate dementia. Individuals in the subgroup of mild to moderate dementia who were treated with high-frequency rTMS improved from 18.4 to 22.6 on the Mini Mental State Examination (MMSE), from 20.1 to 24.7 on the Instrumental Daily Living Activity (IADL) scale and from 5.9 to 2.6 on the Geriatric Depression Scale (GDS).

Rabey et al. reported an industry-sponsored randomized double-blind trial of rTMS with cognitive training (NeuroAD system) in15 individuals with probable mild to moderate Alzheimer's disease.[32] Individuals received 5 sessions per week for 6 weeks over 6 different brain areas, followed by biweekly sessions for 3 months. Specific cognitive tasks were designed for the 6 targeted brain regions. These included syntax and grammar for Broca's area, comprehension and categorization for Wernicke's area, action naming, object naming and spatial memory tasks for the right and left dorsolateral prefrontal cortex, and spatial attention tasks for the right and left somatosensory association cortex. After 6 weeks of treatment there was an improvement in the average Alzheimer Disease Assessment Scale, cognitive subsection (ADAS-cog) score of 3.76 points in the rTMS group compared to 0.47 in the placebo group. After 4.5 months of treatment the ADAS-cog score in the rTMS group had improved by 3.52 points compared to a worsening of 0.38 in the placebo group. The Clinical Global Impression of Change improved significantly by

an average of 3.57 after 6 weeks and 3.67 after 4.5 months compared to 4.25 and 4.29 in the placebo group.

Attention-Deficit/Hyperactivity Disorder

In 2012, Weaver et al. reported a randomized sham-controlled crossover study of rTMS in 9 adolescents/young adults with attention-deficit/ hyperactivity disorder (ADHD).[33] rTMS was administered in 10 sessions over 2 weeks, with 1 week of no TMS between the active and sham phases. The clinical global impression and ADHD-IV scales improved in both conditions over the course of the study, with no significant differences between the active and sham phases.

Bulimia Nervosa

In 2008, Walpoth et al. reported no evidence of efficacy of rTMS in a small trial (n=14) of individuals with bulimia nervosa.[34]

Dysphagia

rTMS for the treatment of dysphagia following stroke has been examined in small randomized controlled trials. One study randomized 26 individuals to rTMS or sham over the affected esophageal motor area of the cortex.[35] Ten minutes of rTMS over 5 days reduced both dysphagia on the Dysphagic Outcome and Severity scale and disability measured by the Barthel Index. There was a trend for improved hand grip strength in the rTMS group. Blinded assessment showed that the effects were maintained at 1 month and 2-month follow-up. Another study randomized 30 individuals with dysphagia following stroke or traumatic brain injury to high frequency rTMS, low frequency rTMS, or sham stimulation.[32] Active or sham rTMS was administered bilaterally over the anterolateral scalp over a period of 2 weeks. Swallowing scale scores improved in both the low-frequency and sham groups. Improvement in videofluoroscopic evaluation was greater in the low frequency rTMS group than the other 2 groups. Blinding of evaluators was not described.

Study in a larger number of subjects is needed to determine the efficacy of this treatment with greater certainty.

Epilepsy

In 2012, Sun et al. reported a randomized double-blind controlled trial of low frequency rTMS to the epileptogenic zone for refractory partial epilepsy.[37] Sixty individuals were randomized into 2 groups; one group received 2 weeks of rTMS at 90% of resting motor threshold and the other group received rTMS at 20% of resting motor threshold. Outcomes were measured for 8 weeks after the end of treatment. With intent-to-treat analysis, high intensity rTMS resulted in a significant decrease in seizures when compared to baseline (from 8.9 per week at baseline to 1.8 per week at follow-up) and when compared to low intensity rTMS (from 8.6 at baseline to 8.4 per week at follow-up). High intensity rTMS also decreased interictal discharges (from 75.1 to 33.6 per hour) and improved ratings on the Symptom Checklist-90. These initial results are promising but require substantiation in additional trials.

Fibromyalgia

A 2012 systematic review included 4 studies on transcranial direct current stimulation and 5 on rTMS for treatment of fibromyalgia pain.[38] Three of the 5 trials were considered to be high quality. Four of the 5 were double-blind randomized controlled trials; the 5th included study was a case series of 4 individuals who were blinded to treatment. Quantitative meta-analysis was not conducted due to variability in brain site, stimulation frequency/intensity, total number of sessions, and follow-up intervals, but 4 of the 5 studies on rTMS reported significant decreases in pain. Greater durability of pain reduction was observed with stimulation of the primary motor cortex compared to the dorsolateral prefrontal cortex.

One of the studies included in the systematic review was a small 2011 trial that was conducted in the US by Short et al.[39] Twenty individuals with fibromyalgia, defined by the American College of Rheumatology criteria, were randomized to 10 sessions of left prefrontal rTMS or sham TMS along with their standard medications. At 2 weeks after treatment, there was a significant change from baseline in average visual analog scale (VAS) for pain in the rTMS group (from 5.60 to 4.41) but not in the sham-treated group (from 5.34 to 5.37). There was also a significant improvement in depression symptoms in the active group compared to baseline (from 21.8 to 14.10) but not in the sham group (from 17.6 to 16.4). There were no statistically significant differences between the groups in this small trial.

Additional study is needed to determine effective treatment parameters in a larger number of subjects and to evaluate durability of the effect.

Migraine Headache

A pivotal randomized, double blind, multi-center, sham-controlled trial was performed with the Cerena TMS device to demonstrate safety and effectiveness for the De Novo application.[41] Enrolled in the study were 201 individuals with a history of an aura preceding more than 30% of headaches with moderate or severe headache severity for approximately 90% of migraine attacks. Following a month baseline phase to establish the frequency and severity of migraine, individuals were randomized to a treatment phase consisting of three treatments or three months, whichever occurred first. Individuals were instructed to treat their migraine headache during the aura phase and to record their pain severity (0-3), severity of associated migraine symptoms (photophobia, phonophobia, nausea), presence of vomiting, and use of rescue medications at the time of treatment and at 1, 2, 24, and 48 hours after treatment. The primary endpoint was the proportion of individuals who were pain free 2 hours after treatment. Of the 201 individuals enrolled, 164 recorded at least 1 treatment and 113 recorded at least 1 treatment when there was pain. Post-hoc analysis of these 113 individuals showed a benefit of the device for the primary endpoint (37.74% pain free after 2 hours for Cerena and 16.67% for sham, p=0.0181) and for the proportion of subjects who were pain free after 24 hours (33.96% for Cerena and 10% for sham, p=0.0025). Active treatment was not inferior to sham for the proportion of subjects free of photophobia, suggesting that the device does not worsen photophobia. However, the device was not non-inferior to sham for the proportion of subjects free of nausea and phonophobia.

These results are limited by the 46% drop-out rate and post-hoc analysis. According to the FDA labeling, the device has not been demonstrated as safe or effective when treating cluster headache, chronic migraine headache, or when treating migraine headache during the aura phase. The device has not been demonstrated as effective in relieving the associated symptoms of migraine (photophobia, phonophobia, and nausea).[41]

Obsessive Compulsive Disorder

A 2013 meta-analysis included 10 small randomized controlled trials totaling 282 individuals with obsessive compulsive disorder (OCD).[42] Response rates of rTMS augmentation therapy were 35% for active and 13% for sham rTMS. The pooled odds ratio (OR) was 3.39 and the number needed to treat (NNT) was 5. There was no evidence of publication bias. Exploratory subgroup analysis suggested that the two most promising stimulation parameters were low frequency-rTMs and non-DLPFC regions (i.e., orbitofrontal cortex or supplementary motor area). Further study focusing on these stimulation parameters is needed.

Panic Disorder

In 2013, Mantovani et al. reported a randomized double-blind sham-controlled trial of low frequency rTMS to the right dorsolateral prefrontal cortex in 21 individuals with panic disorder with comorbid major depression.[43] Response was defined as a 40% or greater decrease on the panic disorder severity scale (PDSS) and a 50% or greater decrease on the HAM-D. After 4 weeks of treatment, the response rate for panic was 50% with active rTMS and 8% with sham. There was no significant difference in the response rate for depressive symptoms (25% active rTMS vs. 8% for sham). After an additional 4 weeks of open-label treatment, the response rate was 67% for panic and 50% for depressive symptoms. Five of 12 responders returned for 6-month follow-up and showed sustained improvement.

Parkinson Disease

A systematic review from 2009 included 10 randomized controlled trials with a total of 275 individuals with Parkinson disease.[44] Seven of the studies were double-blind, one was not blinded and 2 of the studies did not specify whether the raters were blinded. In studies that used high frequency rTMS there was a significant improvement on the Unified Parkinson's Disease Rating Scale (UPDRS) with a moderate effect size of -0.58. For low frequency rTMS the results were heterogeneous and did not significantly reduce the UPDRS. The analyzed studies varied in outcomes reported, rTMS protocol, individual selection criteria, demographics, stages of Parkinson disease and duration of follow-up, which ranged from immediate to 16 weeks after treatment.

In 2012, Benninger et al. reported a randomized double-blind sham-controlled trial of brief (6 sec) very high frequency (50 Hz) rTMS over the motor cortex in 26 individuals with mild to moderate Parkinson disease.[45] Eight sessions of 50 Hz rTMS did not improve gait, bradykinesia, or global and motor scores on the UPDRS compared to the sham-treated group. Activities of daily living were significantly improved a day after the intervention, but the effect was no longer evident at 1 month after treatment. Functional status and self-reported well-being were not affected by the treatment. No adverse effects of the very high frequency stimulation were identified.

Another study from 2012 randomized 20 individuals with Parkinson disease to 12 brief sessions (6 min) of high frequency (5-Hz) rTMS or sham rTMS over the leg area of the motor cortex followed by treadmill training.[46] Blinded evaluation showed a significant effect of rTMS

combined with treadmill training on neurophysiological measures, and change in fast walking speed and the timed up and go task. Mean treadmill speed improved to a similar extent in the active and sham rTMS groups.

A 2013 exploratory multicenter double-blind trial randomized 106 individuals to 8 weeks of 1 Hz rTMS, 10 Hz rTMS, or sham stimulation over the supplementary motor area.[47] At 9 weeks all groups showed a similar amount of improvement. At the 20-week follow-up only the 1 Hz group showed a significant improvement (6.84 points) in the primary outcome measure, the UPDRS part III. There was no significant improvement in other outcome measures.

A meta-analysis from 2015 included 20 sham-controlled RCTs with a total of 470 individuals with Parkinson disease. Sample sizes ranged from 8 to 102. The total effect size of rTMS on Unified Parkinson's Disease Rating Scale (UPDRS) part III score was 0.46, which is considered a small to medium effect size, and the mean change in the UPDRS-III score (-6.42) was considered to be a clinically important difference. The greatest effect on motor symptoms was from high frequency rTMS over the primary motor cortex (standardized mean difference [SMD] of 0.77, $p<0.001$) and low-frequency rTMS over other frontal regions (SMD: 0.50, $p=0.008$). High frequency rTMS at other frontal regions and low frequency rTMS over the primary motor cortex did not have a statistically significant benefit.

Additional study with a larger number of subjects and longer follow-up is needed to determine if rTMS improves motor symptoms in individuals with Parkinson disease.

Postpartum Depression

Myczkowski et al. conducted a double-blind sham-controlled study of 14 individuals with postpartum depression randomized to 20 sessions of active or sham rTMS over the left dorsolateral prefrontal cortex.[48] A positive response to treatment was defined as a reduction of at least 30% in the HAM-D and Edinburgh Postnatal Depression Scale (EPDS). At 2 weeks after the end of treatment, the active rTMS group showed significant improvements in the HAM-D, Global Assessment Scale, Clinical Global Impression and Social Adjustment Scale. The difference in the EPDS (reduction of 39.4% vs. 6.2% for sham) did not reach statistical significance in this small study, and there were marginal cognitive and social improvements. In addition, results were presented as mean values, rather than by the proportion of individuals who showed clinically meaningful improvement.

Posttraumatic Stress Disorder

The efficacy of rTMS for posttraumatic stress disorder (PTSD) has been examined in several small randomized controlled trials.

A 2004 study randomized 24 individuals with PTSD to 10 sessions of low frequency (1 Hz), high frequency (10 Hz) or sham rTMS over the right dorsolateral prefrontal cortex.[49] Blinded assessment 2 weeks after the intervention found that high frequency rTMS improved the self-reported PTSD checklist (PCL) by 29.3%, the clinician evaluation on the Treatment Outcome PTSD scale by 39.0%, the HAM-D by 25.9%, and the Hamilton Anxiety Rating Scale by 44.1%. Scores for the sham and low-frequency group were not significantly improved.

In 2012, Watts et al. reported a double-blind trial with 20 individuals randomized to low frequency rTMS or sham over the right dorsolateral prefrontal cortex.[50] Blinded evaluation at the end of treatment showed clinically significant improvements in the Clinician Administered PTSD Scale (CAPS) and the PCL compared with sham. Depressive and anxiety symptoms also improved in the rTMS group. Six of the 10 rTMS individuals showed a degradation of symptoms between the immediate post-treatment assessment and the 2-month post-treatment follow-up.

In another double-blind trial, 30 individuals with PTSD were randomized to deep, high frequency rTMS after brief exposure to a script of the traumatic event, rTMS after a script of a non-traumatic event, or sham stimulation after a brief script of the traumatic event.[51] Individuals received 3 treatment sessions per week for 4 weeks, and response was defined as a 50% or greater improvement in CAPS score. Intent-to-treat analysis showed a significant improvement in the total CAPS score in the exposure + stimulation group (24.3) compared to rTMS alone (7.9) or traumatic exposure with sham rTMS (9.1). The greatest improvement was in the intrusive component of the CAPS scale. Heart rate responses to the traumatic script were also reduced over the 4 weeks of treatment. The proportion of individuals who showed a response to treatment was not reported and the durability of the response was not assessed.

Conclusions

Several small randomized controlled trials have reported improvement of PTSD with rTMS over the right dorsolateral cortex. Results of high frequency versus low frequency stimulation are conflicting, and durability of the response has not been assessed. Additional study is needed.

Schizophrenia

The largest area of TMS research outside of depressive disorders appears to be treatment of auditory hallucinations in schizophrenia resistant to pharmacotherapy. In 2011, TEC published an Assessment of TMS as an adjunct treatment for schizophrenia.[52] Five meta-analyses were reviewed, along with randomized controlled trials (RCTs) in which measurements were carried out beyond the treatment period. A meta-analysis of the effect of TMS on positive symptoms of schizophrenia (hallucinations, delusions, and disorganized speech and behavior) did not find a significant effect of TMS. Four meta-analyses that looked specifically at auditory hallucinations showed a significant effect of TMS. It was noted that outcomes were evaluated at the end of treatment, and the durability of the effect is unknown. The Assessment concluded that the available evidence is insufficient to demonstrate that TMS is effective in the treatment of schizophrenia.

A 2012 meta-analysis included 17 randomized double blind sham-controlled trials (n=337) of the effect of rTMS on auditory hallucinations.[53] When measured at the end of treatment, the mean effect size of rTMS directed at the left temporoparietal area was 0.40 (moderate) and the effect size of rTMS directed at all brain regions was 0.33 (small). For the 5 trials that examined outcomes of rTMS one month after treatment, the effect was no longer significant.

Blumberger et al. examined the efficacy of priming stimulation (6 Hz) prior to low frequency stimulation (1 Hz) of Heschl's gyrus within the left temporoparietal cortex.[54] Fifty-four individuals with medication resistant auditory hallucinations were randomized to receive 20 sessions of left-sided stimulation, priming, or sham rTMS. Response rates on the Psychotic Symptoms Rating Scale did not differ between the 3 treatment groups. A small (n=18) double-blind randomized sham-controlled trial from 2012 found no significant effect of deep rTMS with an H1 coil on auditory hallucinations.[55]

A 2015 Cochrane review included 41 studies with a total of 1,473 participants. Based on very low-quality evidence, there was a significant benefit of temporoparietal TMS compared to sham for global state (7 RCTs) and positive symptoms (5 RCTs). The evidence on cognitive state was equivocal. For prefrontal rTMS compared to sham, the evidence on global state and cognitive state was of very low quality and equivocal. The authors concluded that there is insufficient evidence to support or refute the use of TMS to treat symptoms of schizophrenia, and although there is some evidence to suggest that temporoparietal TMS may improve certain symptoms such as auditory hallucinations and positive symptoms of schizophrenia, the results were not robust enough to be unequivocal.

Conclusions

The evidence on rTMS for the treatment of auditory hallucinations in schizophrenia consists of several small randomized controlled trials. Evidence to date shows small to moderate effects on hallucinations when measured at the end of treatment, but evidence suggests that the effect is not durable.

Stroke

A 2013 Cochrane review included 19 trials with a total of 588 participants on the effect of transcranial magnetic stimulation for improving function after stroke.[56] The 2 largest trials showed that rTMS was not associated with a significant improvement in function. The review concluded that current evidence does not support the routine use of rTMS for the treatment of stroke.

Hsu et al. reported a meta-analysis of the effect of rTMS on upper limb motor function in individuals with stroke in 2012.[57] Eighteen randomized-controlled trials with a total of 392 individuals were included in the meta-analysis. Most of the studies were double blind (n=11) or single blind (n=3). Eight studies applied low frequency (1 Hz) rTMS over the unaffected hemisphere, 5 applied high frequency (5 Hz) rTMS over the affected hemisphere, and 2 used both low- and high-frequency stimulation. Outcomes included kinematic motion analyses (5 trials), hand grip (2 trials), and the Wolf Motor Function Test (2 trials). Meta-analysis of results showed a moderate effect size (0.55) for rTMS on motor outcome, with a greater effect size of rTMS in individuals with subcortical stroke (mean effect size, 0.73) compared to non-specified lesion sites (mean effect size, 0.45), and for studies applying low frequency rTMS (mean effect size, 0.69) compared to high frequency rTMS (effect size, 0.41). Effect size of 0.5 or greater was considered to be clinically meaningful.

In 2012, Seniow et al. reported a randomized double-blind sham-controlled pilot study of low frequency rTMS (1 Hz at 90% of resting motor threshold for 30 min) to the contralesional motor cortex combined with physiotherapy in individuals with moderate upper extremity hemiparesis following stroke.[58] Power analysis indicated that a sample size of 129 individuals would be required to detect changes in functional motor ability, but only 40 individuals met eligibility criteria over the 4 years of the study. Blinded analysis showed no significant difference in hand function or level of neurological deficit between active or sham rTMS when measured either immediately after the 3-week intervention or at 3-month follow-up

A 2015 meta-analysis included 4 RCTs on rTMS over the right pars triangularis for individuals (N=137) with aphasia after stroke. All the studies used double-blinding, but therapists were not blinded. Every study used a different outcome measure, and the sample sizes were small (range from 12 to 40). Meta-analysis showed a medium effect size for naming (p=0.004), a trend for a benefit on repetition (p=0.08), and no significant benefit for comprehension (p=0.18). Additional study in a larger number of individuals is needed to determine with greater certainty the effect of this treatment on aphasia after stroke.

Conclusions

Evidence consists of several randomized controlled trials and a meta-analysis of the effect of rTMS on recovery from stroke. Results are conflicting, and efficacy may depend on the location of the stroke and frequency of the rTMS. Additional study is needed to determine whether rTMS facilitates standard physiotherapy in individuals with stroke.

Other Psychiatric/Neurologic Disorders

For other psychiatric/neurologic conditions, the evidence is insufficient to determine whether rTMS leads to improved outcomes. The available clinical trials are small and report mixed results for a variety of conditions other than depression. There are no large, high-quality trials for any of these other conditions. Therefore, rTMS is considered investigational for other psychiatric/neurologic conditions.

2012 Update

Re-examination of the George et al. study[8] reveals the following additional information: This was an NIMH- sponsored, industry-independent trial. As such, it was the first major published study of rTMS that was not industry-sponsored and therefore free of potential industry bias. This was also the first major published study of rTMS with the sham treatment modified so that the experience of actual rTMS was duplicated, thereby creating a significantly more reliable sham effect than in the previous published trials. Although the response rate for rTMS subjects in Phase I was only 14.1%, the statistical effect size is significant and comparable to the best medication efficacy data. In addition, in the Phase II follow-up, although open-label, the response rate increased to 30%. The retention rate of 88% was higher than in most situations of actual clinical practice with antidepressant medication. The patient sample consisted of

individuals who had either failed 3 or more research-quality antidepressant medication trials, or had tried and were intolerant to at least 3 antidepressant medications. In patients who have failed 2 medication trials, open-label studies (the STAR*D trials) have shown that remission rates with another medication or with augmentation are less than 20%, and in patients with 3 failed medication trials, remission rates with another medication trial are 10% to 20%. Thus, the 30% remission rate in Phase II of this trial compares favorably with continued medication trials, and demonstrates effectiveness for treatment-resistant depression that is exceeded only by electroconvulsive therapy (ECT), which remains the most effective treatment for treatment-resistant depression. This study indicates that rTMS is an effective antidepressant treatment for Major Depression in patients who do not respond to or cannot tolerate antidepressant medications.

A study by Ray et al.[64] that was also not industry-funded, in which none of the investigators had any ties to industry, and which also utilized realistic sham treatment, demonstrated remission in 75% of patients receiving actual rTMS as an add-on to antidepressant medication compared to 10% of patients who received sham rTMS. This study also included patients with psychotic depression, and in that population, 87.5% of patients receiving actual rTMS as an add-on to antidepressant medication achieved remission as compared to 7.7% of patients who received sham treatment. The study did lack rater blinding, which may have allowed for some degree of rater bias, but the effect size was substantial and would still be quite large even if rater bias could be accounted for.

Two more recent, naturalistic studies have demonstrated the effectiveness of TMS in real world practice settings without the constraints of research-based patient selection criteria. Carpenter et al.[65] studied the effectiveness of TMS with 339 consecutive patients at 42 different practice sites (academic and community). Patients had failed at least one antidepressant trial (average 2.5). The clinician-assessed response rate was 58% and remission rate was 37.1%. The patient-assessed response rate was 41.5%-56.4% and remission rate was 26.5%-28.7%. These rates are greater than those in earlier academic center studies. Although, as is typical of naturalistic studies, the study lacked sham treatment (placebo) and blinded rater assessment, it approximated real-world clinical practices to a much greater extent than prior studies Connolly et al.[66] conducted a retrospective chart review of 100 consecutive TMS patients at an academic medical center. Although done at an academic center, this study approximated real-world practice because patients were treated without applying research criteria. The patient population had failed an average of 3.4 adequate antidepressant trials in the current depressive episode. The clinician-measured response rate was 50.6% and the remission rate was 24.7%. This study and the Carpenter et al study, despite the absence of placebo controls and blinded rating, demonstrate real-world effectiveness of TMS in the treatment of Major Depression that has not responded to adequate trials of antidepressant medication.

Summary

Although questions still need to be answered about TMS, including the optimal length of treatment and the usefulness of maintenance treatment, the most recent studies demonstrate efficacy and real-world effectiveness of TMS in the treatment of unipolar Major Depression and psychotic depression (i.e., Major Depression with psychotic features). Antidepressant medication remains the biological treatment of first choice for Major Depression. ECT continues to be the most effective treatment for treatment-resistant depression, but the high incidence of functionally-impairing adverse cognitive effects renders ECT undesirable in many cases. In addition, there is a cohort of patients who have failed or cannot tolerate antidepressant medications and ECT. For those patients, with the possible exception of major chest surgery and its attendant potential complications (i.e., for a Vagus Nerve stimulator implant, for which the effectiveness data is weak), TMS is the only treatment option that remains, and that stands between possible relief of depression and continued indefinite suffering. That rationale, coupled with the results of the most recent studies, and with the knowledge that continued antidepressant medication trials after 3-4 trials have a high failure rate, leads to the conclusion that TMS is a reasonable and appropriate next intervention after 3 failed medication trials plus a failed ECT trial, or after 4 failed medication trials.

2015 Update

Evidence for the efficacy and effectiveness of TMS for adolescents is limited to anecdotal case reports and inadequately-sized studies. There are no large, high-quality trials of TMS for adolescents. Therefore, TMS is considered to be generally investigative for adolescent, though exceptions may be appropriate on a case-by-case basis for adolescents who have no other viable treatment options.

Alternate types of TMS that are under investigation include synchronized TMS, low field magnetic stimulation, and theta burst stimulation. There are no large, high-quality trials of these types of TMS, and they are therefore considered to be investigative.

2016 Update

See individual sections for 2016 literature and position statement updates.

2022 Update

Credible evidence[80-83] has been published in recent years demonstrating efficacy and effectiveness of theta burst stimulation for the treatment of Major Depressive Disorder. Credible evidence demonstrating effectiveness of theta burst stimulation for the treatment of bipolar depression[123] and Obsessive-Compulsive Disorder[124] is limited to absent due to small sample sizes, poor to mixed observational outcomes, and lack of significant differences in clinical response rates between active and sham treatment groups. Therefore, theta burst stimulation for the treatment of bipolar depression and Obsessive-Compulsive Disorder is still considered to be investigational.

Multiple alternate types of TMS continue to be under investigation. There are no large, replicated, high-quality trials of these types of TMS, and they are therefore considered to be investigational.

Credible open-label and uncontrolled evidence[84-88] has been published in recent years demonstrating efficacy and effectiveness of TMS for older adolescents. Although there is a need for the development of randomized controlled evidence, treatment of adolescents with Major Depressive Disorder with antidepressant medication has been less successful than in adults, and there is little likelihood of a positive response to a fourth antidepressant trial when trials of three antidepressants or two antidepressants plus an augmenting medication have failed[89]. Other biological treatment options for Major Depressive Disorder are ECT with its known potential adverse cognitive effects, in addition to being potentially frightening for adolescents; vagus nerve stimulation, which requires major surgery, has potential post-operative adverse effects, and has not been adequately studied in adolescents; and Spravato, which has also not been adequately studied in adolescents and has potential adverse effects that are more problematic than TMS. TMS has been demonstrated to be safe in this population with generally mild side effects like those experienced by adults. From a risk-benefit perspective, after three failed medication trials, TMS has a more positive risk-benefit profile than other biological treatment options. The available evidence is less compelling for TMS for younger adolescents. Therefore, TMS is still considered to be generally investigational for younger adolescents, though exceptions may be appropriate on a case-by-case basis for younger adolescents who have no other viable treatment options.

Credible evidence[89-91] has demonstrated that there is little likelihood of a positive response to a fourth antidepressant trial when trials of three antidepressants or two antidepressants plus an augmenting medication have failed.

Additional medications are available and feasible for the treatment of bipolar depression: lumateperone/Caplyta (good evidence)[92-93], cariprazine/Vraylar (good evidence)[94-97], and valproate/Depakote (moderate to good evidence depending on the study)[98-101].

Credible evidence[102-108] has been published in recent years demonstrating efficacy and effectiveness of standard/conventional TMS and deep TMS for the treatment of Obsessive-Compulsive Disorder in adults.

TMS continues to be under investigation for a variety of other psychiatric symptoms and disorders, and for some neurologic conditions. In the absence of large, replicated, high-quality trials, TMS is still considered to be investigational for conditions other than Major Depressive Disorder, bipolar depression, and Obsessive-Compulsive Disorder.

Credible evidence, expert consensus, and/or standard practice protocols have been published or emerged in recent years for, and extensive clinical experience has demonstrated the value of, TMS treatment extending or continuing beyond a single course of TMS, including extended full intensive courses[109-112], extended tapers, maintenance TMS[111, 112, 113-120], repeat full intensive courses[111, 112, 121], and brief (aka mini or booster) intensive courses[111, 112, 122].

The FDA approved the SNT/SAINT (Stanford Neuromodulation Therapy) method of theta burst stimulation in September 2022. SNT/SAINT consists of 10 theta burst stimulation treatment sessions daily for 5 consecutive days. Only 2 studies have been published which claim to show improvement of depression with the SNT/SAINT method of theta burst stimulation[125,, 126]. The first study was done so that all participants knew that they were receiving the SNT/SAINT treatment and was done without a comparison group that was receiving a sham version of the treatment, so it is not possible to conclude that any improvement was due to the treatment itself. Both studies were done with insufficient sample sizes to establish effectiveness. In the second study, which did include a comparison group that received a sham version of the treatment, only 29 patients finished the study, which was not a sufficient sample size to establish effectiveness. Also, the second study included only a small percentage of all potential subjects who were screened, suggesting the possibility of selection bias, and potentially failing to represent the general population that would seek treatment. In addition, neither study was done for a sufficient length of time to demonstrate durability. The published report of the second study specifically states that further trials are needed to determine durability. Furthermore, both studies were done at the same institution, and the studies have not been replicated at any other institutions or facilities or clinics. Therefore, SNT/SAINT is still considered to be investigational.

ICD-10 code X0Z0X18 indicates computer-assisted transcranial magnetic stimulation of the prefrontal cortex, aka Group 8 Technology computer-assisted transcranial magnetic stimulation of the prefrontal cortex. This TMS modality is being utilized only for research and only in

Europe[127, 128]. The manufacturer is Group 8 Technology, a company that makes devices which are used to calibrate and assess the performance of imaging systems in a variety of different fields, most of which are not related to healthcare[129].

Ongoing and Unpublished Clinical Trials

A search of **ClinicalTrials.gov** in August 2017 identified over 300 ongoing trials on rTMS.

Practice Guidelines and Position Statements

American Psychiatric Association (APA)

The APA 2010 practice guidelines for the treatment of patients with major depressive disorder states that treatment in the acute phase should be aimed at inducing remission of the major depressive episode and achieving a full return to the patient's baseline level of functioning [I, Recommended with substantial clinical confidence]. Acute phase treatment may include pharmacotherapy, depression- focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or light therapy. Several strategies are available when a change in the treatment plan seems necessary…. Transdermal selegiline, a relatively selective MAO B inhibitor with fewer dietary and medication restrictions, or transcranial magnetic stimulation could also be considered [II, Recommended with moderate clinical confidence].[59]

American Academy of Child and Adolescent Psychiatry

In 2013, the American Academy of Child and Adolescent Psychiatry (AACP) Committee on Quality Issues published practice parameters for the assessment and treatment of children and adolescents with tic disorders. AACP does not recommend repetitive transcranial magnetic stimulation, citing the limited evidence regarding safety, ethics, and long-term impact on development.

National Institute for Health and Care Excellence (NICE)

In 2007 the National Institute for Health and Care Excellence (NICE) published an Interventional Procedure Guideline (IPG) 242 which stated that current evidence suggests no major safety concerns for the use of TMS in the treatment of depression. There was uncertainty related to the clinical efficacy of TMS which may depend on several factors such as higher intensity, greater frequency, bilateral application, and /or longer treatment durations than have appeared in evidence to date. TMS should be performed in research studies designed to evaluate these factors.[60] The opinion was repeated in the NICE 2009 Clinical Guideline (CG) 90.[61]

NICE guidance in 2006 on the management of bipolar disorder in adults, children and adolescents in primary and secondary care states that TMS should not be routinely used for acute depressive episodes in people with bipolar disorder. The guidance states that TMS is not of proven efficacy for bipolar disorder and that when compared with sham TMS the participants receiving sham treatment had lower endpoint mania symptom scores.[62]

In December 2015, NICE updated its Interventional Procedure Guidelines [IPG542] which has the following recommendations:

- The evidence on repetitive transcranial magnetic stimulation for depression shows no major safety concerns. The evidence on its efficacy in the short term is adequate, although the clinical response is variable. Repetitive transcranial magnetic stimulation for depression may be used with normal arrangements for clinical governance and audit.
- During the consent process, clinicians should, in particular, inform patients about the other treatment options available, and make sure that patients understand the possibility the procedure may not give them benefit.
- NICE encourages publication of further evidence on patient selection, details of the precise type and regime of stimulation used, the use of maintenance treatment and long term outcomes.

American Academy of Neurology (AAN)

2006 Practice guidelines on the evaluation and treatment of depression, psychosis, and dementia in Parkinson disease from the AAN concluded that there is insufficient evidence to support or refute the efficacy of TMS or electroconvulsive therapy (ECT) in the treatment of depression associated with Parkinson disease (Level U; Data inadequate or conflicting given current knowledge, treatment is unproven).[63]

Canadian Network for Mood and Anxiety Treatments (CANMAT)

The CANMAT updated their clinical guidelines on neurostimulation therapies for the management of major depressive disorder in adults.[64] The evidence reviewed supported ECT as a first-line treatment under specific circumstances; when used in patients who have failed to respond to one or more adequate antidepressant medication trials, ECT response rates have been estimated to be 50-60%. The guidelines considered rTMS to be a safe and well-tolerated treatment, with no evidence of cognitive impairment. Based on the 2008 meta-analysis by Lam et al.[70], response (25%) and remission (17%) rates were found to be greater than sham but lower than for other interventions for TRD, leading to a recommendation for rTMS as a second- line treatment. The guidelines indicated that there is a major gap in the evidence base regarding maintenance rTMS, as only one open-label case series was identified.

Medicare National Coverage

There is a national coverage determination (NCD) and local coverage determinations that cover left prefrontal rTMS for patients diagnosed with severe Major Depression (single or recurrent episode) as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), and meet several other criteria.

Regulatory Status

Devices for transcranial stimulation have received clearance by the US Food and Drug Administration (FDA) for diagnostic uses include the following:

- NeoPulse (Neuronetics, Atlanta, GA) received approval in Canada, Israel and the United States as a therapy for depression. Initially examined by the FDA under a traditional 510(k) application, the NeoPulse,now known as NeuroStar TMS, received clearance for marketing as a "De Novo" device in 2008.
- NeuroStar TMS is indicated for the treatment of patients with depression who have failed one 6-week course of antidepressant medication.

Note: An FDA advisory panel met in January 2007 to determine if the risk to benefit profile for the NeoPulse was comparable to the risk to benefit profile of predicate electroconvulsive therapy (ECT) devices. The panel was not asked for a recommendation regarding the

regulatory determination of substantial equivalence for this 510(k) submission. Materials presented at the Neurological Devices Panel meeting are posted online at: **https://wayback.archive-it.org/7993/20170405055025/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4273b1_14-Bibliography-510kAppendix24.pdf** Accessed November 22, 2023.

FDA approved devices for transcranial stimulation treatment of major depression disorder include but may not be limited to the following:

- For standard repetitive TMS: NeuroStar TMS (formerly known as NeoPulse); MagPro "R" series stimulators; MagVita TMS Therapy system; Magstim Rapid Therapy System
- For deep TMS: Brainsway H-Coil Deep TMS device

The Brainsway H-Coil Deep TMS device (Brainsway Ltd.) received FDA clearance in 2013. This device is indicated for the treatment of depression in patients who have failed to respond to antidepressant medications in their current episode of depression and is a broader indication than that of the NeuroStar TMS, which specifies the failure of one course of antidepressant medication (product code: OBP).

Other TMS devices not FDA approved for the treatment of depression and other psychiatric disorders:

- The Cerena TMS device (Eneura Therapeutics) received De Novo marketing clearance in 2013 for the acute treatment of pain associated with migraine headache with aura. Warnings, precautions, and contraindications include the following:
    - The device is only intended for use by patients experiencing the onset of pain associated with a migraine headache with aura.
    - The device should not be used on headaches due to underlying pathology or trauma.
    - The device should not be used for medication overuse headaches.
    - The device has not been demonstrated as safe or effective when treating cluster headache or chronic migraine headache.
    - The device has not been shown to be effective when treating during the aura phase.
    - The device has not been demonstrated as effective in relieving the associated symptoms of migraine (photophobia, phonophobia, and nausea).
    - Safety and effectiveness have not been established in pregnant women, children under the age of 18, and adults over the age of 65.

The De Novo 510(k) review process allows novel products with moderate or low risk profiles and without predicates which would ordinarily require premarket approval as a class III device to be down-classified in an expedited manner and brought to market with a special control as a class II device.

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Appendix

Abbreviations	
BDI	Beck Depression Inventory
DLFPC	Dorsolateral prefrontal cortex
ECT	Electroconvulsive therapy
HAM-D	Hamilton Depression Rating Scale
MADRS	Montgomery-Asberg Depression Rating Scale
MT	Motor threshold
rTMS	Repetitive transcranial magnetic stimulation
TRD	Treatment-resistant depression

History

Date	Comments
01/14/13	New policy. Policy replaces 2.01.50 which is deleted. Previously considered investigational for all indications, policy statement created to consider TMS medically necessary for treatment resistant major depression when certain criteria are met. Added code 296.2x.
02/13/13	Replace policy. Added code 296.3x. Added literature review on multiple conditions: rTMS maintenance therapy, Alzheimer's, ADHS, Dysphagia, Epilepsy, Fibromyalgia, Panic Disorder, Parkinson Disease. Postpartum Depression, Posttraumatic Stress Disorder and Stroke.
07/25/13	Update Related Policies. Add 8.01.39.
06/19/14	Annual Review. Policy updated with an additional criterion of "bona-fide contraindication to ECT on the first medically necessary policy statement. An additional medically necessary policy for treatment of bipolar depression (Major Depression as a component of Bipolar Disorder or Schizoaffective Disorder) when criteria are met

Date	Comments
	(failed medication trials as outlined and a positive clinical response to a previous course of treatment with TMS). References reordered and
07/14/14	Interim Update. For treatment of bipolar depression (Major Depression as a component of Bipolar Disorder or Schizoaffective Disorder), medically necessary policy criterion "failure of trials of 4 antidepressant medications, or 3 antidepressant medications plus ECT, as indicated above for Major Depression, except that all trials must have reached the point of adequate dose and duration or intolerable effects without the emergence of mania or hypomania" removed.
02/25/15	Annual Review. Under Major Depressive Disorder policy statement removed criteria about failure of 3 medication trials or ECT trial contraindications/intolerance/poor response. Policy updated with literature review through October 2014; references 9, 15, 17, 25, 27, 36, 48, 52-53, 55 added; others renumbered/removed. Policy statement criteria removed as noted.
04/14/15	Interim Update. Medically necessary policy statement addressing Major Depressive Disorder updated with an additional criterion: failure of at least 3 different antidepressant medication trials, from at least 2 different classes, plus failure with the addition of an augmenting agent to at least one of the antidepressants. Policy Guidelines section updated with the removal of pregnancy as a contraindication to TMS; notation made of repeat course of TMS due to relapse to be determined on a case-by-case basis.
08/31/15	Update Related Policies. Remove 8.01.39 as it was archived.
11/10/15	Interim Update. Policy statements clarified in application to those 18 years and older. Policy section updated to types of TMS which are considered medically necessary (standard repetitive transcranial magnetic stimulation and deep transcranial magnetic stimulation only) versus investigational (all other types).
04/01/16	Annual Review, approved March 8, 2016. Policy updated with literature review; several references added. NICE recommendations updated. Clinical Trials section added. No change to the policy statement.
10/01/16	Interim Update, approved September 16, 2016 Updated Types of TMS and coding section.
09/01/17	Annual Review, approved August 22, 2017. Policy moved to new format. No changes to policy statement, minor grammatical updates.
10/01/17	Interim Review, approved September 21, 2017. Clarifications added that medical necessity is determined case-by-case for more than the indicated number of sessions with either treatment planning, cortical mapping, and initial motor threshold determination (CPT code 90867), or with motor threshold re-determination (CPT code 90869). Also added that an abbreviated repeat course of TMS is also known as a "mini-intensive."
12/01/18	Annual Review, approved November 21, 2018. No changes to policy statement.

Date	Comments
11/01/19	Annual Review, approved October 4, 2019. Literature review through September 2019, no changes to policy statements.
11/01/20	Annual Review, approved October 22, 2020. No changes to policy statements.
11/01/21	Annual Review, approved October 5, 2021. No changes to policy statements.
11/01/22	Annual Review, approved October 11, 2022. Policy changes will be effective Feb. 3, 2023 following 90-day provider notification. Major update, including: theta burst stimulation is medically necessary for the treatment of Major Depressive Disorder when medical necessity criteria are met; TMS is medically necessary for the treatment of Major Depressive Disorder in adolescents 15 years old and older when medical necessity criteria are met; reduction in the number of required failed medication trials for Major Depressive Disorder from four to three; increase in the number of required failed medication trials for bipolar disorder from two to three due to additional medication options for bipolar depression; standard/conventional TMS and deep TMS are medically necessary for the treatment of Obsessive-Compulsive Disorder when medical necessity criteria are met; additional contraindications of a history of repetitive or severe head trauma/traumatic brain injury and a history of or presence of a brain tumor (due to creating increased risk of seizures with TMS); more detailed specification of the types and numbers of treatment sessions that constitute a course of TMS; criteria for extended intensive courses of TMS, extended tapers, accelerated intensive TMS, maintenance TMS, repeat full intensive courses, and brief (aka mini or booster courses; investigational or not medically necessary status for consecutive or overlapping courses of TMS for different conditions, TMS with more than one provider at the same time, TMS in conjunction with Spravato or ketamine or any other psychedelic drug, TMS in conjunction with other neuromodulation techniques, and TMS as an augmenting intervention; miscellaneous additional clarifying information for the medical necessity criteria for the disorders for which TMS can be considered medically necessary; 2022 Update; 45 additional references. Policy reformatted for improved clarity. Changed the wording from "patient" to "individual" throughout the policy for standardization.
05/01/23	Interim Review, approved April 11, 2023. Clarification added that a seizure history is not a contraindication if seizures were due to adverse drug side effects or interactions. Added a contraindication of documentation that any type of medical clearance (e.g., cardiac) is needed, until such clearance is obtained. For accelerated TMS, added clarification that daily treatment is a hardship for an extended period of time,and added two additional examples: the individual is relocating prior to when a standard protocol would be completed, or the individual's schedule will cause a break in treatment of a week or longer prior to when a standard protocol would be completed. Added criteria for continuation of TMS that was started under a non-Company plan.
01/01/24	Annual Review, approved December 12, 2023, effective for dates of service on or after April 4, 2024, following 90-day provider notification.. Added critereia that (1) maintenance TMS is considered not medically necessary if the preceding course of intensive TMS was determined to be not medically necessary; (2) a repeat full intensive course of TMS is considered not medically necessary if the preceding full intensive

Date	Comments
	course of TMS was determined to be not medically necessary; and (3) a short or brief intensive course of TMS is considered not medically necessary if the preceding course of intensive TMS or maintenance TMS was determined to be not medically necessary. References validated.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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Language Assistance

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 844-722-4661 (TTY: 711).

注意：如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 844-722-4661（TTY：711）。

CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 844-722-4661 (TTY: 711).

주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 844-722-4661 (TTY: 711) 번으로 전화해 주십시오.

ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 844-722-4661 (телетайп: 711).

PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 844-722-4661 (TTY: 711).

УВАГА! Якщо ви розмовляєте українською мовою, ви можете звернутися до безкоштовної служби мовної підтримки. Телефонуйте за номером 844-722-4661 (телетайп: 711).

ប្រយ័ត្ន៖ បើសិនជាអ្នកនិយាយ ភាសាខ្មែរ, សេវាជំនួយផ្នែកភាសា ដោយមិនគិតឈ្នួល គឺអាចមានសំរាប់បំរើអ្នក។ ចូរ ទូរស័ព្ទ 844-722-4661 (TTY: 711)។

注意事項：日本語を話される場合、無料の言語支援をご利用いただけます。844-722-4661（TTY:711）まで、お電話にてご連絡ください。

ማስታወሻ: የሚናገሩት ቋንቋ አማርኛ ከሆነ የትርጉም እርዳታ ድርጅቶች፣ በነጻ ሊያግዝዎት ተዘጋጀተዋል፡ ወደ ሚከተለው ቁጥር ይደውሉ 844-722-4661 (መስማት ለተሳናቸው: 711).

XIYYEEFFANNAA: Afaan dubbattu Oroomiffa, tajaajila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bilbilaa 844-722-4661 (TTY: 711).

ملحوظة: إذا كنت تتحدث اذكر اللغة، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 844-722-4661 (رقم هاتف الصم والبكم: 711).

ਧਿਆਨ ਦਿਓ: ਜੇ ਤੁਸੀਂ ਪੰਜਾਬੀ ਬੋਲਦੇ ਹੋ, ਤਾਂ ਭਾਸ਼ਾ ਵਿੱਚ ਸਹਾਇਤਾ ਸੇਵਾ ਤੁਹਾਡੇ ਲਈ ਮੁਫਤ ਉਪਲਬਧ ਹੈ। 844-722-4661 (TTY: 711) 'ਤੇ ਕਾਲ ਕਰੋ।

ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 844-722-4661 (TTY: 711).

ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 844-722-4661 (TTY: 711).

ATANSYON: Si w pale Kreyòl Ayisyen, gen sèvis èd pou lang ki disponib gratis pou ou. Rele 844-722-4661 (TTY: 711).

ATTENTION : Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 844-722-4661 (ATS : 711).

UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 844-722-4661 (TTY: 711).

ATENÇÃO: Se fala português, encontram-se disponíveis serviços linguísticos, grátis. Ligue para 844-722-4661 (TTY: 711).

ATTENZIONE: In caso la lingua parlata sia l'italiano, sono disponibili servizi di assistenza linguistica gratuiti. Chiamare il numero 844-722-4661 (TTY: 711).

توجه: اگر به زبان فارسی گفتگو می کنید، تسهیلات زبانی بصورت رایگان برای شما فراهم می باشد. با 844-722-4661 (TTY: 711) تماس بگیرید.