Description

Transcranial magnetic stimulation (TMS) is a noninvasive method of delivering electrical stimulation to the brain. TMS involves the placement of a small coil over the scalp and passing a rapidly alternating current through the coil wire. The electrical current produces a magnetic field that passes unimpeded through the scalp and bone that stimulate neuronal function. Repetitive TMS (rTMS) is being evaluated for the treatment of treatment-resistant depression (TRD) and other psychiatric and neurologic disorders.

Transcranial magnetic stimulation (TMS), introduced in 1985 as a new method of noninvasive stimulation of the brain, involves placement of a small coil over the scalp, passing a rapidly alternating current through the coil wire, which produces 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; eg, TMS 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 person by localizing the
site on the scalp for optimal stimulation of a hand muscle, then gradually increasing the intensity of stimulation. The stimulation site for the treatment of depression is usually 5 cm anterior to the motor stimulation site.

In contrast to electroconvulsive therapy, TMS does not require general anesthesia and does not generally induce a convulsion. Interest in the use of TMS as a treatment for depression was augmented by the development of a device that could deliver rapid, repetitive stimulation. Imaging studies had shown a decrease in the activity of the left dorsolateral prefrontal cortex in depressed patients, and early studies suggested that high-frequency (eg, 5-10 Hz) TMS of the left dorsolateral prefrontal cortex had antidepressant effects. Low-frequency (1-2 Hz) stimulation of the right dorsolateral prefrontal cortex 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, is also being explored, as is the taburst stimulation.

Repetitive TMS is also being tested as a treatment for a variety of other disorders. In addition to the potential for altering interhemispheric imbalance, it has been proposed that high-frequency repetitive TMS may facilitate neuroplasticity.

**OBJECTIVE**

The objective of this evidence review is to evaluate whether the use of repetitive transcranial magnetic stimulation of the brain improves the net health outcome for individuals with various psychiatric or neurologic conditions.

**POLICY STATEMENT**

Repetitive transcranial magnetic stimulation (rTMS) of the brain may be considered medically necessary as a treatment of major depressive disorder when all of the following conditions (1-3) have been met:

1. Confirmed diagnosis of severe major depressive disorder (single or recurrent) documented by standardized rating scales that reliably measure depressive symptoms; and
2. Any one of the following (a, b, c, or d):
   1. Failure of 4 trials of psychopharmacologic agents including 2 different agent classes and 2 augmentation trials; or
   2. Inability to tolerate a therapeutic dose of medications as evidenced by 4 trials of psychopharmacologic agents with distinct side effects; or
   3. History of response to rTMS in a previous depressive episode (at least 3 months since the prior episode); or
   4. Is a candidate for electroconvulsive therapy; further, electroconvulsive therapy would not be clinically superior to rTMS (eg, in cases with psychosis, acute suicidal risk, catatonia or life-threatening inanition rTMS should NOT be used); and
3. Failure of a trial of a psychotherapy known to be effective in the treatment of major depressive disorder of an adequate frequency and duration, without significant improvement in depressive symptoms, as documented by standardized rating scales that reliably measure depressive symptoms.

Repetitive TMS for major depressive disorder that does not meet the criteria listed above is considered investigational.

Continued treatment with rTMS of the brain as maintenance therapy is considered investigational.

Repetitive TMS of the brain is considered investigational as a treatment of all other psychiatric and neurologic disorders, including but not limited to bipolar disorder, schizophrenia, obsessive-compulsive disorder, or migraine headaches.
POLICY GUIDELINES

Repetitive transcranial magnetic stimulation (TMS) should be performed using a U.S. Food and Drug Administration cleared device in appropriately selected patients over the age of 18 years, by physicians who are adequately trained and experienced in the specific techniques used. A treatment course should not exceed 5 days a week for 6 weeks (total of 30 sessions), followed by a 3-week taper of 3 TMS treatments in week 1, 2 TMS treatments the next week, and 1 TMS treatment in the last week.

Contraindications to repetitive TMS include:

1. Seizure disorder or any history of seizure with increased risk of future seizure; or
2. Presence of acute or chronic psychotic symptoms or disorders (e.g., schizophrenia, schizoaffective disorder) in the current depressive episode; or
3. Neurologic conditions that include epilepsy, cerebrovascular disease, dementia, increased intracranial pressure, having a history of repetitive or severe head trauma, or with primary or secondary tumors in the central nervous system; or
4. Presence of an implanted magnetic-sensitive medical device located 30 centimeters or less from the TMS magnetic coil or other implanted metal items, including but not limited to a cochlear implant, implanted cardioverter defibrillator, pacemaker, vagus nerve stimulator, or metal aneurysm clips or coils, staples, or stents.

The following should be present for the administration of repetitive TMS:

1. An attendant trained in basic cardiac life support and the management of complications such as seizures, as well as the use of the equipment must be present at all times; and
2. Adequate resuscitation equipment including, e.g., suction and oxygen; and
3. The facility must maintain awareness of response times of emergency services (either fire/ambulance or "code team"), which should be available within 5 minutes. These relationships are reviewed on at least a 1-year basis and include mock drills.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Devices for transcranial stimulation have been cleared for marketing by the U.S. Food and Drug Administration (FDA) for diagnostic uses (FDA Product Code: GWF). A number of devices subsequently received the FDA clearance for the treatment of major depressive disorder in adults who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode. Indications were expanded to include treating pain associated with certain migraine headaches in 2013, and obsessive-compulsive disorder in 2018.

In 2008, The NeoPulse, now known as NeuroStar TMS, was granted a de novo 510(k) classification by the FDA. 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.

In 2013, the Cerena™ TMS device (eNeura Therapeutics) was granted a de novo 510(k) classification by the FDA for the acute treatment of pain associated with a migraine headache with aura. Warnings, precautions, and contraindications include the following:

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
The device is only intended for 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.
- for medication overuse headaches.

The device has not been demonstrated as safe and/or effective:
- when treating cluster headache or a chronic migraine headache.
- when treating during the aura phase.
- in relieving the associated symptoms of a migraine (photophobia, phonophobia, and nausea).
- in pregnant women, children under the age of 18, and adults over the age of 65.

In 2014, eNeura Therapeutics received 510(k) marketing clearance for the SpringTMS for the treatment of migraine headaches. The device differs from the predicate Cerena™ TMS device with the addition of an LCD screen, a use authorization feature, a lithium battery pack, and a smaller size. The stimulation parameters are unchanged. The sTMS Mini (eNeura Therapeutics) received marketing clearance by the FDA in 2016. FDA product code: OKP.

In August 2018, the Deep TMS System (Brainsway) was granted a de novo 510(k) classification by the FDA as an adjunct for the treatment of adult patients with Obsessive-Compulsive Disorder. The new classification applies to this device and substantially equivalent devices of this generic type.

Table 1 lists some devices that are FDA cleared for major depressive disorder (Product Code: OBP), migraine headache pain (Product Code: OKP), and obsessive-compulsive disorder (Product Code: QCI).

Table 1. Repetitive TMS Devices Cleared by FDA for Major Depression, Migraine, or Obsessive-Compulsive Disorder

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>FDA Clearance No.</th>
<th>FDA Clearance Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurostar</td>
<td>Neuronetics</td>
<td>Major Depressive Disorder</td>
<td>K083538</td>
<td>12/16/2008</td>
</tr>
<tr>
<td>Brainsway Deep TMS System</td>
<td>Brainsway</td>
<td>Major Depressive Disorder</td>
<td>K122288</td>
<td>01/07/2013</td>
</tr>
<tr>
<td>Springtms Total Migraine System</td>
<td>Eneura</td>
<td>Migraine headache with aura</td>
<td>K140094</td>
<td>05/21/2014</td>
</tr>
<tr>
<td>Rapid Therapy System</td>
<td>Magstim</td>
<td>Major Depressive Disorder</td>
<td>K143531</td>
<td>05/08/2015</td>
</tr>
<tr>
<td>Magvita</td>
<td>Tonica Elektronik</td>
<td>Major Depressive Disorder</td>
<td>K150641</td>
<td>07/31/2015</td>
</tr>
<tr>
<td>Neurosoft</td>
<td>TeleEMG</td>
<td>Major Depressive Disorder</td>
<td>K160309</td>
<td>12/22/2016</td>
</tr>
<tr>
<td>Horizon</td>
<td>Magstim</td>
<td>Major Depressive Disorder</td>
<td>K171051</td>
<td>09/13/2017</td>
</tr>
<tr>
<td>Nexstim</td>
<td>Nexstim</td>
<td>Major Depressive Disorder</td>
<td>K171902</td>
<td>11/10/2017</td>
</tr>
<tr>
<td>Apollo</td>
<td>Mag &amp; More</td>
<td>Major Depressive Disorder</td>
<td>K180313</td>
<td>05/04/2018</td>
</tr>
</tbody>
</table>

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
The NeoPulse, now known as NeuroStar TMS, was granted a de novo 510(k) classification by the FDA in 2008. 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.

In 2014, the Cerena™ TMS device (eNeura Therapeutics) was granted a de novo 510(k) classification by the FDA for the acute treatment of pain associated with a migraine headache with aura. Warnings, precautions, and contraindications include the following:

- The device is only intended for 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.
  - for medication overuse headaches.
- The device has not been demonstrated as safe and/or effective:
  - when treating cluster headache or a chronic migraine headache.
  - when treating during the aura phase.
  - in relieving the associated symptoms of a migraine (photophobia, phonophobia, and nausea).
  - in pregnant women, children under the age of 18, and adults over the age of 65.

In 2014, eNeura Therapeutics received 510(k) marketing clearance for the SpringTMS for the treatment of migraine headaches. The device differs from the predicate Cerena™ TMS device with the addition of an LCD screen, a use authorization feature, a lithium battery pack, and a smaller size. The stimulation parameters are unchanged. The sTMS Mini (eNeura Therapeutics) received marketing clearance by the FDA in 2016. FDA product code: OKP.

In August 2018, the Deep TMS System (Brainsway) was granted a de novo 510(k) classification by the FDA as an adjunct for the treatment of adult patients with Obsessive-Compulsive Disorder. The new classification applies to this device and substantially equivalent devices of this generic type.

**RATIONALE**

**Summary of Evidence**

For individuals who have TRD who receive rTMS, the evidence includes a large number of sham-controlled randomized trials and meta-analyses of these trials. Relevant outcomes are symptoms, functional outcomes, and quality of life. The meta-analyses found a clinical benefit associated with rTMS for TRD with improved response rates and rates of remission compared with sham. The most recent meta-analyses have concluded that the effect of rTMS, on average depression scores, is smaller than the effect of electroconvulsive therapy (ECT) on TRD and that the mean improvement in depression scores with rTMS did not reach the minimal clinically important difference; however, clinically meaningful improvements were noted in a subgroup of studies using higher frequency pulses. One potential area of benefit for rTMS is in accelerating or enhancing the response to antidepressant medications, and there is some evidence that rTMS, when given in conjunction with the initiation of pharmacologic therapy, improves the response rate compared with pharmacologic therapy alone. The effect of rTMS appears to be less robust when it is given in combination with a stable dose of antidepressant medication. Meta-analyses have also found that the efficacy of rTMS decreases with longer follow-up, though some
studies have reported persistent response up to 6 months in some patients. There is limited evidence to compare the effects of these treatments on cognition, although the adverse events of rTMS appear to be minimal. While the most recent meta-analyses have reported that the effect of rTMS is smaller than the effect of ECT on TRD, because rTMS does not require general anesthesia or induce seizures, some individuals may decline ECT so the balance of incremental benefits and harms associated with rTMS may be reasonable compared with ECT. Based on the short-term benefit observed in randomized controlled trials (RCTs) and the lack of alternative treatments, aside from ECT in patients with TRD, rTMS may be considered a treatment option in patients with TRD who meet specific criteria. The evidence for thetaburst stimulation includes a large randomized trial showing noninferiority with another method of rTMS; no significant differences were noted in the number of adverse events. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have migraine headaches who receive rTMS, the evidence includes a sham-controlled RCT of 201 patients conducted for submission to the U.S. Food and Drug Administration for clearance in 2013. The trial results were limited by the 46% dropout rate and the use of a post hoc analysis. No recent studies have been identified with these devices. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have obsessive-compulsive disorder who receive rTMS, the evidence includes a number of small-to-moderate sized sham-controlled RCTs and a meta-analysis of these studies. The meta-analysis of 15 RCTs (total n=483 patients, range 18-65 patients) found a benefit of rTMS on patient-reported obsessive-compulsive disorder symptom severity at time points ranging from 2 to 6 weeks, but there was substantial variability in the stimulation parameters, including the cortical region that was stimulated and the frequency of stimulation. A more recent RCT compared deep rTMS to sham in 99 patients for 6 weeks, with an additional 4 weeks of follow-up as a secondary outcome. Using a modified ITT analysis (n=94), there was a larger mean change from baseline on the primary efficacy outcome; Yale-Brown Obsessive Compulsive Scale score in the active treatment group (-6.0 points) than the sham group (-2.8 points), translating to a moderate effect size of 0.69. At 6 weeks, the response rate was 38.1% in the active treatment group compared to 11.1% in the sham group (P=0.003), as measured by a 30% or greater decrease in the Yale-Brown Obsessive Compulsive Scale. The difference in the primary outcome measure between active and sham groups was not statistically significant in the ITT analysis. There was a benefit for rTMS on clinician-reported measures of improvement, but no significant difference between groups on patient-reported disability and impairment. Additional trials with sufficient sample size and follow-up duration are needed to confirm these results. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have psychiatric or neurological disorders other than depression, migraine, or obsessive-compulsive disorder (eg, amyotrophic lateral sclerosis, chronic pain, fibromyalgia, panic disorder, Parkinson disease, posttraumatic stress disorder, schizophrenia, stroke, substance use disorder and craving) who receive rTMS, the evidence includes numerous small-to-moderate sized RCTs and meta-analyses of these randomized trials. Relevant outcomes are symptoms, functional outcomes, and quality of life. The trials included in the meta-analyses are typically small and of low methodologic quality. In addition, stimulation parameters have not been established, and trial results are heterogeneous. There are no large, high-quality trials for any of these conditions demonstrating efficacy or the durability of any treatment effects. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Psychiatric Association

The American Psychiatric Association (2018) published consensus recommendations on repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression.59 The guidelines state, “Multiple randomized controlled trials and published literature have supported the safety and efficacy of rTMS antidepressant therapy.” The recommendations include information on the following variables: clinical environment, operator requirements, documentation, coils, cortical targets, coil positioning methods, determination of motor threshold, number of treatment sessions for acute treatment, and allowable psychotropic medications during TMS treatment.

The American Psychiatric Association's (2007, reaffirmed in 2012) guidelines on the treatment of patients with obsessive-compulsive disorder have indicated that "findings of the 4 published trials of repetitive TMS (rTMS) are inconsistent, perhaps because the studies..."
differed in design, stimulation sites, duration, and stimulation parameters. The available results and the technique's non-invasiveness and good tolerability should encourage future research, but the need for daily treatment may limit the use of TMS in practice.  

American Academy of Child and Adolescent Psychiatry

In 2013, the American Academy of Child and Adolescent Psychiatry published practice parameters on the assessment and treatment of children and adolescents with tic disorders. The Academy did not recommend rTMS, citing the limited evidence on the safety, ethics, and long-term impact on development.

National Institute for Health and Care Excellence

In 2015, the National Institute for Health and Care Excellence (NICE) provided revised guidance, stating that evidence on the short-term efficacy of rTMS for depression is adequate, although the clinical response is variable and some patients may not benefit.

In 2014, the NICE provided guidance on the use of rTMS for treating and preventing migraine. The guidance stated that evidence on the efficacy of TMS for the treatment of migraine was limited in quantity and for the prevention of migraine was limited in both quality and quantity. Evidence on its safety in the short- and medium-term was adequate, but there was uncertainty about the safety of long-term or frequent use of TMS.

American Academy of Neurology

In 2006, the American Academy of Neurology issued practice guidelines on the evaluation and treatment of depression, psychosis, and dementia in Parkinson disease. The guidelines found the evidence insufficient to support or refute the efficacy of TMS or electroconvulsive therapy in the treatment of depression associated with Parkinson disease (level U; data inadequate or conflicting given current knowledge, treatment is unproven).

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES


8. Berlim MT, Van den Eynde F, Daskalakis ZJ. Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. Depress Anxiety. Jul 2013; 30(7): 614-23. PMID 23349112


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

**POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 2012</td>
<td>New policy</td>
<td>Policy reviewed and rationale updated for non-FDA approved indications. No change in policy statement. New FDA approved device added.</td>
</tr>
<tr>
<td>March 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature review through October 30, 2014; references 15, 17, 25, 27, 36, 41, 48, 52, 53, and 55 added and some references removed; policy statements unchanged.</td>
</tr>
<tr>
<td>March 2015</td>
<td>Replace policy</td>
<td>Policy updated with literature review through October 30, 2014; references 15, 17, 25, 27, 36, 41, 48, 52, 53, and 55 added and some references removed; policy statements unchanged.</td>
</tr>
<tr>
<td>June 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review through November 9, 2015; references 17, 36, 43, 46, and 48 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>December 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through August 23, 2018; references 9, 10, 19, 21, 24, 29, 31, 35 and 37 added. Policy statements unchanged except &quot;not medically necessary&quot; revised to &quot;investigational&quot; to align with FDA 510(k) status.</td>
</tr>
<tr>
<td>December 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through August 26, 2019; references added. Policy statements unchanged.</td>
</tr>
<tr>
<td>October 2020</td>
<td>Replace policy</td>
<td>Policy updated with literature review through September 12, 2020; references added. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.