Medical Policy Manual

**Topic:** Transcranial Magnetic Stimulation as a Treatment of Depression and Other Disorders  
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**Section:** Medicine  
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**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

**DESCRIPTION**

Transcranial magnetic stimulation (TMS) is a noninvasive method of delivering electrical stimulation to 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 brain. In contrast to electroconvulsive therapy, transcranial magnetic stimulation does not require anesthesia and does not induce convulsions. Repetitive TMS (rTMS) is being evaluated as a treatment of depression and other psychiatric/neurologic brain disorders.

**Regulatory Status**

The Food and Drug Administration (FDA) granted 510(k) approval for the following devices:

- **NeuroStar®** (formerly known as NeoPulse®) TMS Therapy system (Neuronetics, Inc.) received de novo clearance for the treatment of major depressive disorder in adults who have failed a six-week course of one antidepressant medication.
- **Brainsway™ H-Coil Deep TMS System** (Brainsway, Ltd.) received FDA clearance for the treatment of depressive episodes in patients suffering from major depressive disorder who have failed to respond to antidepressant medications in their current episode of depression.
- Cerena™ TMS device (Eneura Therapeutics) received de novo marketing clearance for the acute treatment of pain associated with migraine headache with aura. Warnings, precautions, and contraindications include the following:
  
  o The device is only intended for use by patients experiencing the onset of pain associated with a migraine headache with aura.
  o The device should not be used on headaches due to underlying pathology or trauma.
  o The device should not be used for medication overuse headaches.
  o The device has not been demonstrated as safe or effective when treating cluster headache or chronic migraine headache.
  o The device has not been shown to be effective when treating during the aura phase.
  o The device has not been demonstrated as effective in relieving the associated symptoms of migraine (photophobia, phonophobia, and nausea).
  o 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.

MEDICAL POLICY CRITERIA

I. Transcranial magnetic stimulation (TMS) of the brain may be considered medically necessary as a treatment of major depressive disorder when all of the following criteria are met:

A. Confirmed diagnosis of severe major depressive disorder (single or recurrent) documented by standardized rating scales (see Policy Guidelines) that reliably measure depressive symptoms; AND

B. Any one of the following conditions is present:

1. Trials of at least four psychopharmacologic regimens, has been ineffective, not tolerated (as evidenced by distinct side effects), or is contraindicated (see Policy Guidelines); or

2. History of response to TMS in a previous depressive episode (at least 3 months since the prior episode); or

3. Is a candidate for electroconvulsive therapy (ECT) and ECT would not be clinically superior to TMS (e.g., in cases with psychosis, acute suicidal risk, catatonia, or life-threatening inanition TMS should not be utilized); AND

C. Failure of a trial of a psychotherapy (see Policy Guidelines) known to be effective in the treatment of major depressive disorder, conducted for a minimum duration of 6 weeks at least 1 time per week, without significant improvement in depressive symptoms, as documented by standardized rating scales (see Policy Guidelines) that reliably measure depressive symptoms.
II. Transcranial magnetic stimulation (TMS) of the brain is considered *investigational* as a treatment for all other indications, including but not limited to:

A. Alcohol dependence  
B. Alzheimer’s disease  
C. Attention deficit hyperactivity disorder (ADHD)  
D. Autism  
E. Bipolar mania  
F. Bulimia nervosa (BN)  
G. Depression (including major depressive disorder which does not meet criteria I. above)  
H. Dysphagia  
I. Epilepsy  
J. Fibromyalgia  
K. Migraine  
L. Obsessive compulsive disorder (OCD)  
M. Pain  
N. Panic Disorder  
O. Parkinson’s disease  
P. Posttraumatic stress disorder (PTSD)  
Q. Schizophrenia  
R. Spasticity  
S. Spinal cord injury  
T. Stroke rehabilitation  
U. Tinnitus  
V. Tourette’s syndrome
POLICY GUIDELINES

Depression Rating Scales

Assessment tools to diagnose severe major depressive disorder may include, but not limited to the following depression rating scales:

- Beck Depression Inventory (BDI)
- Inventory of Depressive Symptomatology Clinician-related (IDS-C)
- Quick Inventory of Depressive Symptomology Self-reported (QIDS-SR)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Patient Health Questionnaire (PHQ9)

Psychotherapy Methods

The following methods of psychotherapy are recommended by the American Psychiatric Association to treat major depressive disorder:[1]

- Cognitive behavioral therapy (CBT)
- Interpersonal therapy (IPT)
- Psychodynamic therapy
- Problem-solving therapy (in individual and group formats)

Contraindications

Contraindications to TMS include:

- Seizure disorder or any history of seizure with increased risk of future seizure; OR
- Presence of acute or chronic psychotic symptoms or disorders (such as schizophrenia, schizophreniform or schizoaffective disorder) in the current depressive episode; OR
- 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 (CNS); OR
- 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 (ICD), pacemaker, deep brain stimulator, vagus nerve stimulator, or metal aneurysm clips or coils, staples, or stents.

SCIENTIFIC EVIDENCE[2]

Well-designed randomized controlled trials comparing active transcranial magnetic stimulation (TMS) to sham devices are needed in order to establish safety and efficacy of this treatment for any condition.

Depression

BlueCross BlueShield Association (BCBSA) Technology Evaluation Center Assessment (TEC)
BCBSA TEC published three technology assessments on TMS for depression; with the most recent assessment published in 2013.\(^3\)\(^4\)

2013 TEC Assessment of TMS for Depression\(^5\)

The 2013 Assessment included 7 recent meta-analyses from 2010 or later, with the 4 largest meta-analyses including 24-34 trials. All of these meta-analyses evaluated endpoints at the completion of TMS treatment which was between 1-5 weeks. Despite the analyses conclusions that TMS is superior to sham as a short-term treatment of medication-resistant depression; conclusions reached in these studies are uncertain due to the following methodological limitations:

- All seven meta-analyses used the same two randomized trials\(^6\)\(^7\) which employed a “forced dropout strategy” for patients failing to improve after 3 weeks of active treatment. The incorporation of these studies into a pooled effects analysis may have biased results because randomization was not preserved; therefore, results may not be useful in reaching conclusions regarding treatment effects. Analysis which accounted for this potential confounding factor was not reported;
- Only one of the seven meta-analyses assessed the quality of trials used in pooled analyses and only one analysis addressed issues regarding publication bias;
- No evidence was reported regarding changes or augmentation of anti-depression medication.
- Equivocal efficacy in the 3 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;
- 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 (patients who have failed one 6-week course of antidepressant medication).

The 2013 Assessment concluded that, “Concerns about conclusions from the meta-analyses center on the potential for publication bias, and inclusion of the problematic 6-week results from 2 trials. It has not yet been demonstrated whether TMS improves health outcomes in the investigational setting.”

Meta-analyses and Systematic Reviews

- In 2014, the Washington State Health Care Authority conducted a Technology Assessment and updated review of the current literature comparing TMS to sham and ECT.\(^8\) The review included the AHRQ assessment noted below plus 3 additional RCTs. The WA TEC review came to the following conclusions:

  “Although the 3 RCTs published after the AHRQ report did not consistently detect statistically significant differences between rTMS and sham stimulation, the overall body of evidence is consistent with regard to direction of the results. A small quantity of data suggested that the durability of effect, i.e., the continued advantage of active rTMS over sham rTMS, may not last beyond 2 or 3 weeks after the end of treatment; rTMS may serve primarily to accelerate recovery (low-quality evidence).”

In addition the WA TEC assessment concluded that a review of 5 RCTs, “suggested that rTMS may be as effective as ECT under certain circumstances, but under other circumstances, ECT
may be superior; this evidence is based on low quality evidence because of unexplained inconsistency in study results.”

- A 2011 Agency for Healthcare Research and Quality (AHRQ) report, which was considered in the 2013 BCBSA TEC assessment, reported on nonpharmacologic interventions for treatment-resistant depression (TRD) in adults.\textsuperscript{[9]} Indirect evidence which compared nonpharmacologic including rTMS, vagus nerve stimulation (VNS), or psychotherapy, with a control or sham procedure in tier 1 populations (i.e., patients 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 3 times as likely to achieve a depressive response as patients receiving a sham procedure. Finally, rTMS was also more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving rTMS were more than 6 times as likely to achieve remission as those receiving the sham.

The authors of the AHRQ report identified three fair trials compared rTMS with a sham procedure and found no significant differences. However, too few patients were followed during the relapse prevention phases in 2 of the 3 studies, and patients in the third received a co-intervention providing insufficient evidence for a conclusion.

- A Cochrane review of 16 published trials, concluded that there was no strong evidence of benefit from TMS when used in the treatment of depression, finding no difference between TMS and sham TMS based on results of the Beck Depression Inventory or Hamilton Depression Rating Scale (HDRS).\textsuperscript{[10]}

- In 2013, Berlim and colleagues reported a meta-analysis on the effect of rTMS for accelerating and enhancing the clinical response to antidepressants.\textsuperscript{[11]} Data were obtained from 6 double-blind RCTs with a total of 392 patients. Response was defined as a 50% or greater reduction in the HDRS or the Montgomery-Asberg Depression Rating Scale (MADRS). At an average of 2.7 weeks after the start of the combined treatments, response rates were significantly higher with rTMS + antidepressant treatment compared to sham rTMS (43.3% vs 26.8%; odds ratio [OR] =2.50; p=.025); however, remission rates were not significantly different. At the end of the studies (average of 6.8 weeks), response and remission rates were significantly higher with combined high-frequency rTMS + antidepressant treatment compared to sham rTMS (response: 62% vs 46%, OR -1.9, p=0.49; remission: 53.8% vs 38.6%, OR 2.42, p=.007).

- Additional reviews of randomized controlled trials exhibited consistent results.\textsuperscript{[12-15]} Each analysis identified a number of limitations of the included studies such as small patient populations, short study time-lines, confounding co-therapies, and inconsistency with TMS treatment parameters. The meta-analyses concluded that TMS indicated some effect when compared to the sham groups, but
the clinical significance of this effect and its impact on health outcomes was not demonstrated. The above analyses concluded that additional, larger long-term studies were needed to better define optimal treatment parameters including frequency, positioning, and equipment for TMS.

Randomized Clinical Trials

The majority of additional randomized controlled trials (RCTs) that were not included in the meta-analyses noted above also had significant limitations which did not allow reliable conclusions to be made about the effectiveness of TMS as a treatment for depression. Limitations of individual studies and the body of the literature as a whole include one or more of the following:

- Standardized optimal treatment parameters for TMS have not been established. Studies varied with respect to frequency, location, intensity, and duration. Many studies did not mention repeat treatments using TMS after their intervention phase or in the follow-up assessments.[16-23]
- There were significant (greater than 10%) or unclear loss to follow-up and/or poorly defined intention-to-treat (ITT) analyses.[16-22,24,25]
- Use of co-therapies such as antidepressants, unequal distribution of co-therapies between treatment and sham groups, sham devices in which potential for some therapeutic effect was possible, and mental health counseling were allowed but not quantified in the results, potentially confounding the findings.[16-21,24,26-28]
- Follow-up of all study subjects was over a short period of time, less than 6 months, so durability of the results are unknown.[16-26,28-30]
- Study populations were small, less than 100 patients total, making results unreliable and difficult to apply to patients requiring treatment in the general population.[16-21,23-26,28-37]
- Statistical power calculations were inadequate or unclear, and/or the study failed to enroll a sufficient number of participants in order to have adequate statistical power to reliably detect differences between the treatment groups.[23]
- Randomization methods were not clearly stated or weak methods of randomization were used (e.g. one provider randomly assigned patients to groups using their own personal judgment).[17-19,23,24,26,29,30]
- Strict inclusion/exclusion criteria were used which were not representative of patients requiring treatment in the general population, for example, a mild to moderate level of depression or illness, no comorbidities (or only a few that were well controlled), and treatment resistance to standard therapies to name a few.[16-19,21,24,26,30]
- Studies used previously published unreliable data for new and/or further analyses.[38,39]

TMS Compared to Electroconvulsive Therapy for Treatment of Depression

Systematic Reviews

The current evidence is insufficient to determine whether TMS is better than or as effective as electroconvulsive therapy (ECT) for the treatment of depression:

- A 2013 systematic review by Berlim and colleagues identified 7 RCTs with a total of 294 patients that directly compared rTMS and ECT treatment for patients with major depression.[40] After an average of 15.2 sessions of high-frequency rTMS, 33.6% of patients were classified as remitters compared to 52% of patients who were classified as remitters following an average of 8.2 ECT
sessions. The pooled odds ratio was 0.46, indicating a significant difference (p=0.04) in outcome favoring ECT. There was no significant difference in dropout rates for the 2 treatments.

- The 2011 AHRQ report, noted above, found the available head-to-head literature concerning the efficacy of the nonpharmacologic interventions for tier 1 TRD was limited to 2 fair trials (both in major depressive disorder-only populations).\[9\] One compared electroconvulsive therapy (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 and there were no trials identified which directly compared rTMS to any other intervention for maintenance of remission or prevention of relapse.

The AHRQ authors concluded, “that comparative clinical research on nonpharmacologic interventions in a treatment-resistant depression (TRD) population is in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data was 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 comparative benefits,” reflecting low confidence that the evidence reflects the true effect and indicating that further research is likely to change the confidence in these findings. The finding of low strength is most notable in 2 cases: ECT and rTMS did not produce different clinical outcomes in TRD, and ECT produced better outcomes than pharmacotherapy. The AHRQ report further concluded, “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 delineate carefully the number of treatment failures following a treatment attempt of adequate dose and duration in the current episode.”

- Rosa et al. reported no significant difference between ECT and TMS in forty-two patients with treatment-resistant depression; however, response rates for both groups were low.\[41\] The number of remissions (score of seven or less on the HDRS) totaled three (20%) for ECT and two (10%) for TMS.

- The 2001 Cochrane Review found electroconvulsive therapy was more effective than TMS.\[10\]

**Maintenance Therapy**

No long-term RCTs were identified regarding the use of rTMS in patients with TRD. Additional data are needed to evaluate the use of rTMS in maintaining a response or remission of symptoms of depression.

**Conclusion**

Although evidence regarding TMS compared to sham demonstrated a statistically significant improvement in depression, the clinical significance of these findings to change health outcomes in patients with depression has not been demonstrated. In addition, the overall body of evidence regarding TMS versus sham studies, contain a variety of methodological limitations. Studies which compare TMS
with electroconvulsive therapy are few which limit the possibility of proper assessment or conclusion. Despite the weaknesses in the published clinical evidence, TMS has become a recognized standard of care for treatment resistant major depressive disorder.

**Schizophrenia**

**BlueCross BlueShield Association (BCBSA) Technology Evaluation Center Assessment (TEC)**

The 2011 TEC Assessment evaluated TMS as an adjunct treatment for schizophrenia.[42] 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 was unknown. The Assessment concluded that the available evidence is insufficient to demonstrate that TMS is effective as a treatment of schizophrenia.

**Meta-analyses**

- A 2015 Cochrane review included 41 studies with a total of 1473 participants.[43] 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.

- A 2013 meta-analysis included 17 RCTs (n=398) that evaluated low-frequency rTMS of the left temporoparietal cortex for the treatment of auditory hallucinations.[44] The mean effect size for severity of auditory hallucinations (all studies) was -0.42. The odds ratio for the response to treatment, defined as a 30% reduction or greater, was 2.94 (6 trials, n=181). No significant differences were found between active rTMS and sham for positive or negative symptoms.

- A 2012 meta-analysis included 17 randomized double blind sham-controlled trials (total n=337) of the effect of TMS on auditory hallucinations.[45] When measured at the end of treatment, the mean effect size of TMS directed at the left temporoparietal area was 0.40 (moderate) and the effect size of TMS directed at all brain regions was 0.33 (small). For the 5 trials that examined outcomes of TMS one month after treatment, the effect was no longer significant.

**Randomized Controlled Trials**

RCTs not included in the meta-analysis above include the following:

- 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.[46] Fifty-four patients with medication resistant auditory hallucinations were randomized to receive 20 sessions of left-
sided stimulation, priming, or sham TMS. 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 TMS with an H1 coil on auditory hallucinations.[47]

Conclusion

The evidence on TMS for the treatment of auditory hallucinations in schizophrenia consists of a number of 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 TMS does not produce a durable treatment effect in patients with schizophrenia.

Other Psychiatric Disorders

Cochrane Reviews

- The 2003 Cochrane review of TMS for the treatment of obsessive compulsive disorder (OCD) concluded that there was no strong evidence of benefit from TMS when used in the treatment of this disorder, finding no difference between TMS and sham TMS based on results of the Yale-Brown Obsessive Compulsive Scale (which is used to measure the severity of OCD) or the Hamilton Depression Rating Scale.[48] A meta-analysis was not possible due to the lack of information and poor data available from the three published trials on OCD.

- A 2014 Cochrane review identified 2 RCTs with a total of 40 patients that compared low frequency rTMS with sham rTMS.[49] The larger of the 2 studies was a randomized, double-blind, sham-controlled trial in 21 patients with panic disorder with comorbid major depression. Response was defined as a 40% or greater decrease on the Panic Disorder Severity Scale and a 50% or greater decrease on HAM-D. After 4 weeks of treatment, the response rate for panic was 50% with active rTMS and 8% with sham. The study had a high risk of attrition bias. The overall quality of evidence for the 2 studies was considered to be low, and the sample sizes were small, precluding any conclusions about the efficacy of rTMS for panic disorder.

Meta-analysis

A 2013 meta-analysis included 10 small randomized controlled trials totaling 282 patients with OCD.[50] Response rates of TMS augmentation therapy were 35% for active treatment and 13% for sham TMS. The pooled odds ratio (OR) was 3.39 and the number needed to treat (NNT) was 5. There was no reported evidence of publication bias. Exploratory subgroup analysis suggested that the two most promising stimulation parameters were low frequency-TMS and non-dorsolateral prefrontal cortex (DLPFC) regions (i.e., orbitofrontal cortex or supplementary motor area); however, additional studies are needed to evaluate low frequency TMS and non-DLPFC regions.

Other Randomized Controlled Trials

A number of RCTs explored the efficacy of TMS for a variety of mental health disorders other than depression, including, but not limited to, bipolar mania, obsessive-compulsive disorder (OCD), panic disorder, bulimia, alcohol dependence, posttraumatic stress disorder, autism, Alzheimer’s disease, and
ADHD. Many of these studies are preliminary (feasibility) studies and/or have serious methodological limitations that render outcomes unreliable. Some limitations of these studies include:

- Poorly defined or unmet endpoints[^48,51-57]
- Significant or unclear loss to follow-up and poorly defined intention-to-treat (ITT) analyses[^53,56,58-60]
- Lack of long-term follow up[^48,51-63]
- Small patient populations[^48,51-75]
- Lack of standardized optimal treatment parameters[^48,51-55,57-61,63,76]
- Use of co-therapies[^48,51-62]
- Strict inclusion/exclusion criteria which were not representative of patients requiring treatment in the general population[^48,51-55,58,61-63]

Conclusion

Current evidence is insufficient to determine the efficacy of TMS in patients with non-schizophrenic psychiatric disorders. Well-designed randomized clinical trials are needed which address the methodological limitations of current studies, noted above.

Epilepsy

In 2012, Sun et al. reported a randomized double-blind controlled trial of low frequency TMS to the epileptogenic zone for refractory partial epilepsy.[^77] Sixty patients were randomized into 2 groups; one group received 2 weeks of TMS at 90% of resting motor threshold and the other group received TMS at 20% of resting motor threshold. Outcomes were measured for 8 weeks after the end of treatment. With intent-to-treat analysis, high intensity TMS 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 TMS (from 8.6 at baseline to 8.4 per week at follow-up). High intensity TMS 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

Systematic Review

A 2012 systematic review included four studies on transcranial direct current stimulation (tDMS) and five on TMS for treatment of fibromyalgia pain[^78]. Four of the five TMS studies were double-blind randomized controlled trials, however the fifth included study was a case series of four patients 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. Results of four out of five of these studies reported significant decreases in pain and greater durability of pain reduction was observed overall, with stimulation of the primary motor cortex compared to the dorsolateral prefrontal cortex. However, all five TMS trials used in this analysis were limited by small sample size (n ≤ 40), continued use of concomitant medications and four had short-term follow-up (≥ 8 weeks) which preclude the ability to reach conclusions regarding the ability of TMS to effect pain reduction scores in patients suffering with fibromyalgia.

Other Randomized Controlled Trials (RCTs)
A 2013 RCT evaluated the effect of very low-intensity TMS in a randomized sham-controlled double-blinded trial of 54 patients with fibromyalgia.\[79\] TMS was performed once per week, for six weeks with 33 magnetic coils around the head. Authors reported a significant improvement in pain thresholds (+28%) across the 8 sessions and in the ability to perform daily activities (11%), perceived chronic pain (-39%) and sleep quality (75%). Fatigue, anxiety, depression, and severity of headaches were unaffected by treatment. Limitations of this study include small sample size and lack of long-term follow-up limiting conclusions regarding the benefit of TMS treatment for symptoms related to fibromyalgia.

**Conclusions**

Additional studies are needed to establish effective treatment parameters in a larger number of subjects and to evaluate the durability of tDMS or TMS treatment effect in patients with fibromyalgia.

**Parkinson’s Disease**

**Systematic Review**

- A 2015 meta-analysis included 20 sham-controlled RCTs with a total of 470 patients with Parkinson disease.\[80\] 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. The largest study (described below) included in the systematic review was an exploratory, multicenter, double-blind trial that randomized 106 patients to 8 weeks of 1-Hz rTMS, 10 Hz rTMS, or sham stimulation over the supplementary motor area.\[81\] At 9 weeks, all groups showed a similar amount of improvement. It cannot be determined from these results if the negative results of the largest trial are due to a lack of effect of rTMS on motor symptoms in general or to the location of stimulation. Additional study with a larger number of subjects and longer follow-up is needed to determine if high frequency rTMS over the primary motor cortex improves motor symptoms in patients with Parkinson disease.

- A systematic review from 2009 included 10 randomized controlled trials with a total of 275 patients with Parkinson’s disease.\[82\] 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 TMS 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 TMS the results were heterogeneous and did not significantly reduce the UPDRS. The analyzed studies varied in outcomes reported, TMS protocol, patient selection criteria, demographics, stages of Parkinson’s disease and duration of follow-up, which ranged from immediate to 16 weeks after treatment

**Other Randomized Controlled Trials (RCTs)**

- A 2013 exploratory multicenter double-blind trial randomized 106 patients to 8 weeks of 1 Hz TMS, 10 Hz TMS, or sham stimulation over the supplementary motor area.\[81\] 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. There was no
significant improvement in other outcome measures.

- In 2012, Benninger et al. reported a randomized double-blind sham-controlled trial of brief (6 sec) very high frequency (50 Hz) TMS over the motor cortex in 26 patients with mild to moderate Parkinson’s disease.\(^{[83]}\) Eight sessions of 50 Hz TMS 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 patients with Parkinson’s disease to 12 brief sessions (6 min) of high frequency (5-Hz) TMS or sham TMS over the leg area of the motor cortex followed by treadmill training.\(^{[84]}\) Blinded evaluation showed a significant effect of TMS 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 TMS groups.

**Conclusions**

The current evidence is mixed regarding the treatment benefits of TMS in patients with Parkinson’s disease. Additional well-designed, RCTs, which control for treatment effect and include a larger number of subjects and longer follow-up, is needed to determine if TMS improves motor symptoms in patients with Parkinson’s disease.

**Stroke Rehabilitation**

**Meta-analyses**

- A 2015 meta-analysis included 4 RCTs on rTMS over the right pars triangularis for patients (N=137) with aphasia after stroke.\(^{[85]}\) All of 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 patients is needed to determine with greater certainty the effect of this treatment on aphasia after stroke.

- A 2014 meta-analysis assessed the effect of rTMS on recovery of hand function and excitability of the motor cortex after stroke.\(^{[86]}\) Eight RCTs with a total of 273 participants were included in the review. The quality of the studies was rated moderate to high, although the size of the studies was small. There was variability in the time since stroke (5 days to 10 years), in the frequency of rTMS applied (1 Hx to 25 Hx for 1 sec to 25 mins per day), and the stimulation sites (primary motor cortex or premotor cortex of the unaffected hemisphere). Meta-analysis found a positive effect on finger motor ability (4 studies, n=79, standardized mean difference of 0.58) and hand function (3 studies, n=74, standardized mean difference of -0.82), but no significant change in motor evoked potential (n=43) or motor threshold (n=62).

- A recent 2013 Cochrane review included 19 trials with a total of 588 participants on the effect of TMS for improving function after stroke.\(^{[87]}\) The 2 largest trials included in the review showed that TMS was not associated with a significant improvement in the Barthel Index score. Four trials
(n=73) found no significant effect for motor function. Subgroup analysis for different stimulation frequencies or duration of illness also did not show a significant benefit of rTMS when compared to sham rTMS or no treatment. The review concluded that current evidence does not support the routine use of TMS for the treatment of stroke.

- Hsu et al. reported a meta-analysis on the effect of TMS on upper limb motor function in patients with stroke in 2012.[88] Eighteen randomized-controlled trials with a total of 392 patients 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) TMS over the unaffected hemisphere, 5 applied high frequency (5 Hz) TMS 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 TMS on motor outcome, with a greater effect size of TMS in patients 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 TMS (mean effect size, 0.69) compared to high frequency TMS (effect size, 0.41). Effect size of 0.5 or greater was considered to be clinically meaningful.

Other Randomized Controlled Trials (RCTs)

In 2012, Seniow et al. reported a randomized double-blind sham-controlled pilot study of low frequency TMS (1 Hz at 90% of resting motor threshold for 30 min) to the contralesional motor cortex combined with physiotherapy in patients with moderate upper extremity hemiparesis following stroke.[89] Power analysis indicated that a sample size of 129 patients would be required to detect changes in functional motor ability, but only 40 patients 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 TMS when measured either immediately after the 3-week intervention or at 3-month follow-up.

Conclusions

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

Other Medical Indications

Systematic reviews and randomized controlled trials have been published exploring the efficacy of TMS for a variety of central nervous system-related disorders such as migraine headaches, central pain related to spinal cord injury, tinnitus, dysphagia, blepharospasm, amyotrophic lateral sclerosis (ALS), chronic pain, substance abuse, cravings and Alzheimer’s disease.[76,90-134] In addition, symptom management in breast cancer has been examined as well.[135] All of these studies had one or more significant methodological limitations, including but not limited to small patient populations, short follow-up times, heterogeneous treatment parameters, continued use of concurrent therapies, and/or significant loss to follow-up. Generally, the authors agreed that larger, long-term randomized controlled trials are needed, along with better defined optimal treatment parameters for administering TMS.

Clinical Practice Guidelines

Movement Disorder Society (MDS)
The MDS published an evidence-based review of treatments for motor (published in 2012) and non-motor (published in 2011) symptoms of Parkinson’s disease. The review found insufficient evidence to make adequate conclusions on the efficacy of repetitive transcranial magnetic stimulation (TMS) for the treatment of depression in Parkinson’s disease. In a 2012 update, MDS did note that evidence regarding TMS treatment of depression is growing; however, data was still found to be insufficient for the recommendation of TMS as a treatment in Parkinson’s patients with depression.

In 2008, the society also conducted a literature review describing current management practices for tic disorder and noted that studies results regarding the use of TMS as a treatment for tics varied.

American Psychiatric Association (APA)

In 2010, and reaffirmed in 2015, the American Psychiatric Association published an evidence-based guideline on treatment of patients with major depressive disorder. The guideline concluded that the evidence on transcranial magnetic stimulation (TMS) consists of studies with methodological limitations and inconsistent findings. For example, the guideline noted that “a substantial number of studies of TMS have been conducted, but most have had small sample sizes, and the studies overall have yielded heterogeneous results. Further complicating the interpretation of the TMS literature is the variability in stimulation intensities (relative to the motor threshold), stimulus parameters (e.g., pulses/second, pulses/session), anatomical localization of stimulation, and number of TMS sessions in the treatment course.” The guideline also concluded that, based on the available evidence, TMS appears to be safe and well tolerated. However, the evidence is less consistent concerning the efficacy of TMS treatment. The guideline states that TMS “has shown small to moderate benefits in most [i.e. four] but not all [i.e. two] clinical trials and recent meta-analyses.” Given the evidence, the guideline lists TMS as a treatment option for patients who do not respond adequately to pharmacotherapy; however the guideline does not include a strong recommendation for this treatment.

The APA made the following comment regarding the duration of psychotherapeutic treatment of major depression:

“Onset of benefit from psychotherapy tends to be a bit more gradual than that from medication, but no treatment should continue unmodified if there has been no symptomatic improvement after 1 month. Generally, 4–8 weeks of treatment are needed before concluding that a patient is partially responsive or unresponsive to a specific intervention.”

Summary

The current evidence regarding the benefits of transcranial magnetic stimulation (TMS) as a treatment for major depressive disorder contains methodological limitations including, but not limited to, small study populations, short duration of follow-up and significant drop-out rates. Despite the weaknesses in the published clinical evidence, TMS has become a recognized standard of care for treatment resistant major depressive disorder. Therefore, TMS may be considered medically necessary as a treatment of major depressive disorder when criteria are met.

The current evidence is insufficient to permit conclusions regarding the safety and long-term benefits transcranial magnetic stimulation (TMS) for the treatment of all other indications. In addition, there are no clinical practice guidelines from U.S. professional associations that recommend the use of TMS for
conditions other than treatment resistant, major depressive disorder. Therefore, TMS is considered investigational as a treatment of all other indications.

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**CROSS REFERENCES**

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