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NOTE: This policy has been revised. The revised policy will be effective September 1, 2024. To view the revised policy, click here.

Medical Policy Manual Medicine, Policy No. 148

Transcranial Magnetic Stimulation as a Treatment of Depression and Other Disorders

Effective: July 1, 2024

Next Review: February 2025
Last Review: June 2024

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.

MEDICAL POLICY CRITERIA

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

   A. As initial treatment of a depressive episode (up to 36 treatment sessions, including tapering) when all of the following criteria are met (1. - 4.):

1. Confirmed diagnosis of severe major depressive disorder (single or recurrent) when both of the following criteria are met (a. - b.):
    a. Diagnosis is confirmed by standardized rating scales (see Policy Guidelines) that reliably measure depressive symptoms; and
    b. Documentation is submitted of both the rating scale that was used and the score.
2. Patient is age 18 years or older
3. One of the following conditions is present:
    a. Symptoms are ongoing despite treatment with the following psychopharmacologic regimens, and each has been ineffective, not tolerated (as evidenced by distinct side effects), or is contraindicated (see Policy Guidelines):
        i. Either of the following:
            a.) At least 3 antidepressant medications from at least 2 different classes in separate trials; or
            b.) 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; and
        ii. At least four weeks' duration for one or more of the antidepressant agents (unless none of the agents was tolerated).
    b. History of response to TMS in a previous depressive episode (at least 3 months since the prior episode); or
    c. Both of the following criteria are met (i. - ii.):
        i. Patient is a candidate for electroconvulsive therapy (ECT); and
        ii. The patient does not have psychosis, acute suicidal risk, catatonia, significantly impaired essential function, or other condition for which ECT would be clinically superior to TMS.
4. Failure of a trial of a psychotherapy (see Policy Guidelines) known to be effective in the treatment of major depressive disorder, when both of the following criteria are met (a. - b.):
    a. Documentation is submitted showing that psychotherapy was conducted for a minimum duration of 6 weeks at least 1 time per week; and
    b. No significant improvement in depressive symptoms has occurred, as documented in the clinical records.

B. Extension of initial therapy when both of the following criteria are met (1. - 2.):
1. The TMS is demonstrating meaningful improvements as documented by a 50% or greater improvement in standardized rating scales (see Policy Guidelines) that reliably measure depressive symptoms in the member's clinical status; and
2. There is reasonable expectation that continued treatment will produce improvement.

II. Transcranial magnetic stimulation (TMS) of the brain is considered **not medically necessary** as a treatment for major depressive disorder when Criterion I. above is not met.

III. Transcranial magnetic stimulation (TMS) of the brain is considered **investigational** as a treatment for all other indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEPRESSION RATING SCALES

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

- Beck Depression Inventory (BDI): scores range from 0 to 63, higher scores represent more severe depression
- Inventory of Depressive Symptomatology Clinician-related (IDS-C): scores range from 0 to 84, higher scores represent more severe depression
- Quick Inventory of Depressive Symptomology Self-reported (QIDS-SR): scores range from 0 to 27, higher scores represent more severe depression
- Montgomery-Asberg Depression Rating Scale (MADRS): scores range from 0 to 60, higher scores represent more severe depression
- Patient Health Questionnaire (PHQ9): scores range from 0 to 27, higher scores represent more severe depression

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
- Significantly impaired essential function, defined as functions necessary to sustain life, such as feeding and hydrating oneself; 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.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Confirmed diagnosis of severe major depressive disorder (single or recurrent) documented by standardized rating scales, including:
    - Standardized rating scale(s) used
    - Score
- Documentation of psychotherapy history, including:
    - Duration
    - Cadence
    - Depressive symptom response documented by standardized rating scales
- Psychopharmacologic regimen history with documented response

CROSS REFERENCES

1. Spravato, esketamine, Medication Policy Manual, Policy No. dru605

BACKGROUND

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; e.g., 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 (e.g., 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 thetaburst 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.

Regulatory Status

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

- Brainsway™ H-Coil Deep TMS System (Brainsway, Ltd.) received FDA clearance (2013) for the treatment of depressive episodes in adult patients suffering from major depressive disorder who have failed to respond to antidepressant medications in their current episode of depression.

- The Deep TMS System (Brainsway) was granted a de novo 510(k) classification by FDA (DEN170078) in August 2018. The new classification applies to this device and substantially equivalent devices of this generic type. The Brainsway Deep TMS system is cleared for treatment of adult patients with Obsessive-Compulsive Disorder (approved in 2019). FDA product code: QCI.

- Cerena™ TMS device (Eneura Therapeutics) received de novo marketing clearance for the acute treatment of pain associated with migraine headache with aura in 2013. 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.

- MagVita TMS Therapy System® (approved 2015) and MagVita TMS Therapy System w/Theta Burst Stimulation (approved 2018) are indicated for the treatment of Major Depressive Disorder in adult patients who failed to receive satisfactory improvement from prior antidepressant medication in the current episode.

- NeuroStar® (formerly known as NeoPulse®) TMS Therapy system (Neuronetics, Inc.) received de novo clearance in 2008 for the treatment of major depressive disorder in adults who have failed a six-week course of one antidepressant medication. NeuroStar Advanced Therapy System (approved in 2022) is indicated as an adjunct for the treatment of adult patients who are suffering from Obsessive-Compulsive Disorder (OCD).

- Rapid^2 Therapy System from Magstim Company Limited (approved 2015) is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to

achieve satisfactory improvement from prior antidepressant medication in the current episode.

- SpringTMS® received FDA clearance for the treatment of migraines, with aura.
- Neurosoft TMS (TeleEMG) was approved by the FDA in 2016 for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.
- Apollo TMS Therapy System (Mag & More, approved in 2018) is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.
- Nexstim Navigated Brain Therapy (NBT®) System 2 (approved in 2017) is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.
- ALTMS Magnetic Stimulation Therapy System (also Blossom TMS Therapy System, approved in 2022) is indicated for the treatment of Major Depressive Disorder in adult patients, who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.

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.

EVIDENCE SUMMARY

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

MAJOR DEPRESSIVE DISORDER

Systematic Reviews and Technology Assessments

A systematic review conducted by Voigt (2021) focused on theta burst stimulation for treatment-resistant depression (TRD).[2] The reviewers included eight RCTs comparing theta burst stimulation to sham treatment and one comparing theta burst stimulation to conventional rTMS. As measured by the HAM-D, theta burst stimulation was superior to sham on response (RR 2.4; 95% CI 1.27 to 4.55; p=0.007; I^2 = 40%). There was no statistically significant difference between theta burst stimulation and conventional rTMS (RR 1.02; 95% CI 0.85 to 1.23; p=0.80; I^2 = 0%). There was no difference between theta burst stimulation and rTMS in the incidence of adverse events.

Chu (2020) published an SR on theta-burst stimulation for major depression. A total of 10 studies met inclusion criteria. Six, including 294 participants, were RCTs, and four, including 297 participants, were uncontrolled. According to the meta-analysis, the overall effect size of response rate was 0.38 (95% confidence interval [CI] 0.29 to 0.48) and the overall effect size of remission rate was 0.20 (95% CI 0.13 to 0.29).

In 2019, the Canadian Agency for Drugs and Technologies in Health (CADTH) published an updated review of rTMS for depression, previously published in 2015.[3] The report addressed the clinical safety and effectiveness of TMS for treatment-resistant depression and the cost-effectiveness. This summary will focus on the safety and effectiveness review. The review includes three SRs (the Health Quality Ontario SR described below and two more recent SRs) and five RCTs on the safety and effectiveness of rTMS. Two of the SRs included only sham comparators, while the third included pharmacological, ECT, and sham comparators. One SR reported separately on unilateral and bilateral stimulation, although both resulted in greater rates of response and remission (with weighted mean differences [WMDs] of 3.36 and 2.67 for unilateral and bilateral, respectively). The second and third SRs did not do separate analyses of unilateral and bilateral rTMS. The second reported a difference in Montgomery-Asberg Depression Rating Scale (MADRS) score of -3.6 points (95% credible interval [CrI], -7.6 to 0.3) between rTMS and sham and the third reported a WMD in HDRS scores between rTMS and sham of 2.31 points (95% CI 1.19 to 3.43, $p<0.001$) in favor of rTMS. In the analysis of rTMS versus ECT in the third SR, the WMD in HDRS scores was 5.97 (95% CI 10.94 to 11.0) in favor of ECT, with a 72% higher response rate and 44% higher remission rate. The review concluded that the effect of rTMS would be considered clinically relevant in two systematic reviews, but not in the third. Additionally, the review stated that based on one SR, the benefit of ECT versus rTMS would be considered clinically relevant.

Hung (2020) performed an SR evaluating the use of deep TMS for treatment-resistant depression.[4] A total of 15 studies met inclusion criteria, including three RCTs and 12 uncontrolled studies. Results of the meta-analysis including all 15 studies indicated that dTMS significantly improved the depressive (Hedges' $g=-1.323$, 95% CI -1.651 to -0.995, $p<0.001$) and anxiety symptoms (Hedges' $g=-1.282$, 95% CI -1.514 to -1.051, $p<0.001$) in patients with treatment-resistant depression. A subgroup analysis was performed of RCTs versus uncontrolled studies that indicated there was a larger effect size in the uncontrolled studies (-1.461 for uncontrolled studies vs -0.756 for RCTs).

In 2019, Voigt published an SR that reviewed the efficacy of repetitive TMS (rTMS) in non-treatment resistant patients with major depressive disorder.[5] Ten studies were included in the analysis. The quality of these studies was assessed with GRADE and CEBM. Only one study was a double-blind RCT (quality rating 1B). This RCT compared medication resistant patients (two or more medication trials) with non-medication resistant patients (one unsuccessful medication trial). The likelihood of responding to rTMS was four times higher in the group with only one unsuccessful medication trial before rTMS compared to the group that received two or more unsuccessful trials ($p=0.021$). Of the remainder of the studies, four were RCTs. They were all single-center RCTs conducted in China and all had a quality rating of 1B. Two addressed treatment of the first episode of depression. One reported significantly greater numbers of early improvers in rTMS plus antidepressant compared to sham plus antidepressant at two weeks ($p=0.031$) but not four weeks ($p=0.586$). The other reported that the rate of relapse/recurrence at 12 months was significantly lower in rTMS plus antidepressant compared to antidepressant alone ($p=0.033$). Two RCTs addressed treatment naïve patients. One reported significantly greater response and remission rates in active versus sham rTMS (both in combination with antidepressant; $p<0.05$). The other reported a significantly greater number of patients achieving a ≥50% reduction in HAMD-17 score in the active versus sham rTMS (both in combination with antidepressant; $p<0.05$). Limitations of this analysis were heterogeneity of the included studies and a lack of risk of bias assessment.

Martin (2017) published an SR that evaluated the cognitive effects of rTMS used for the treatment of depression. Eighteen studies were included in the analysis.[6] Using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials, the authors determined that the majority of studies had a low risk of bias across most standard criteria, but had an unclear risk of bias for allocation concealment and selective reporting of results. One study, which was not randomized, had a high risk of selection bias. Measures of attention and working memory, processing speed, executive function, and learning and memory were examined. Significant differences were found between rTMS and sham for the Trail Making Test Parts A and B, measures of attention/working memory and processing speed. A lack of significant differences was found for the remainder of measures analyzed.

Kedzior (2017) published an SR assessing cognitive outcomes following high-frequency rTMS versus electroconvulsive therapy (ECT).[7] Due to high heterogeneity with respect to cognitive assessment, no meta-analyses were performed. Cognitive functioning was assessed in six studies including 111 high-frequency rTMS-treated and 94 ECT-treated patients. All but one study reported similar acute cognitive impairments were reported following ECT and high-frequency rTMS. Three studies reported outcomes that favored ECT over high-frequency rTMS based on acute mood outcomes. The review concluded that more studies are needed to be able to reliably compare the effects of these treatments on cognitive outcomes.

In 2016, the Health Quality Ontario published a meta-analysis of left DLPFC rTMS for treatment-resistant depression (TRD).[8] Reviewers included 23 RCTs (n=1156 patients) that compared rTMS with sham and six RCTs (n=266 patients) that compared rTMS with ECT. In 16 studies, patients received rTMS in addition to antidepressant medication. Seven studies used intensities of less than 100% motor threshold and the definition of remission in the included studies varied (from ≤7 to ≤10 on the HAM-D). A meta-analysis showed a statistically significant improvement in depression scores when compared with sham, with a weighted mean difference (WMD) of 2.31. However, this was smaller than the prespecified clinically important difference of 3.5 points on the HAM-D, and the effect size was small (0.33; 95% confidence interval [CI], 0.17 to 0.5; $p<0.001$). Subgroup analysis showed a larger and clinically significant treatment effect in the rTMS studies using 20 Hz with shorter train duration compared with other rTMS techniques (WMD=4.96; 95% CI 1.15 to 8.76; $p=0.011$). Secondary analyses showed rTMS demonstrated statistically greater rate of response among 20 studies (pooled relative risk, 1.72; 95% CI 1.13 to 2.62; $p=0.11$) as well as statistically greater rate of remission among 13 studies (pooled relative risk=2.20; 95% CI 1.44 to 3.38, $p<0.001$).

For the six trials that compared rTMS with ECT, the WMD of 5.97 was both statistically and clinically significant in favor of ECT. The relative risk for remission and response rates favor ECT but was not statistically significant. Remission and relapse rates at the six-month follow-up were reported in two studies including 40 and 46 subjects, comparing rTMS and ECT. While one study reported slightly higher remission rate for ECT (27.3%) compared with rTMS (16.7%), the other study did not find significant difference between ECT and rTMS for mean depression scores at three or six months, but did note relapses were less frequent for ECT. Statistical comparisons were either not significant or not available, limiting the interpretation of these findings. The authors concluded there is little data to evaluate the long-term effects of rTMS and that ECT was more effective in improving depression.

Kedzior (2016) published a SR that evaluated cognitive function i.e. memory, attention, and psychomotor coordination after dTMS, using the H-coil system for patients with major

psychiatric disorders.[9] Thirteen studies were included, with most being of poor quality. Patients had either unipolar or bipolar depression or schizophrenia and showed short-term improvements. Although short-term cognitive function improved, more long-term sham-controlled studies are needed beyond the daily stimulation phase.

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.[10] The review included the AHRQ assessment noted below plus three additional RCTs. The WA TEC review came to the following conclusions:

> Although the three 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 two or three 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 five 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.”

Randomized Controlled Trials

Zangen (2023) explored whether Deep TMS targeting the medial prefrontal cortex (MPFC) is noninferior to targeting the lateral prefrontal cortex (LPFC) and whether electrophysiological or clinical markers for patient selection can be identified.[11] The present prospective, multicenter, randomized study enrolled 169 patients with MDD for whom antidepressants failed in the current episode. Patients were randomized to receive 24 Deep TMS sessions over 6 weeks, using either the H1 coil or the H7 coil. The primary efficacy endpoint was the change from baseline to week 6 in Hamilton Depression Rating Scale scores. Clinical efficacy and safety profiles were similar and not significantly different between groups, with response rates of 60.9% for the H1 coil and 64.2% for the H7 coil. Moreover, brain activity measured by EEG during the first treatment session correlated with clinical outcomes in a coil-specific manner. This study provides a treatment option for MDD, using the H7 coil, and initial guidance to differentiate between patients likely to respond to LPFC versus MPFC stimulation targets. This study needs validation by other future studies.

The STAR*D study and recent update by Rush (2020) has demonstrated that patients with a major depressive episode who have failed to respond to their initial pharmacologic treatment show less and less response and remission rates with subsequent medication trials.[12, 13] Rush stated that after non-efficacy with an initial failed SSRI trial, only *21%* of patients achieved remission and *58%* of patients achieve no meaningful benefit with a second step switch to another antidepressant. Over four levels of treatment, 1/3 of patients will not respond. In the Deep TMS pivotal trial, patients were shown to have a remission rate of *32.6%* vs 14.6% sham and a response rate of 38.4% vs. 21.4% sham after the initial 4 weeks (20 sessions).[14] Patients who failed 1 or 2 medications had a remission rate of *36.6%* vs 16.7% while patients who failed 3+ medications had a remission rate of *28.9%* vs. 12.2% in the sham treatment. Additionally, approximately 64% of the acute phase (initial 20 sessions) non-responders, achieved remission during the continuation phase (24 sessions over 12 weeks).

Blumberger (2018) published a multicenter, randomized noninferiority trial (THREE-D) comparing 10 Hz rTMS with intermittent theta burst stimulation (iTBS).[15] Between 2013 and 2016, 414 patients with treatment-resistant major depressive disorder were enrolled and randomized to four to six weeks of MRI-guided rTMS (n=205) or iTBS (n=209). Treatment resistance was defined as failure to tolerate two or more antidepressant trials of adequate dose and duration or no clinical response to an adequate dose of an antidepressant. Patients who failed more than three antidepressant trials of adequate dosage were excluded from the study. Patients could alter their medication through the trial. Treatment with rTMS (37 minutes) and iTBS (3 minutes) was delivered five times a week for four to six weeks. The primary outcome measure was the 17-item HAM (HAM-17), for which scores for patients treated with rTMS improved by 10.1 points and scores for patients treated with iTBS improved by 10.2 points, indicating noninferiority of iTBS (adjusted difference, 0.103; lower 95% CI -1.16; p=0.001). Treatment with iTBS resulted in a higher self-rated intensity of pain (mean score, 3.8; SD=2.0) than treatment with rTMS (mean score, 3.4; SD=2.0; p=0.011). Headache was the most common treatment-related adverse event for both groups (rTMS 131/204 [64%]; iTBS 136/208 [65%]). Serious adverse events were noted in patients treated with rTMS (n=1; myocardial infarction) and iTBS (n=3; agitation, worsening suicidal ideation, worsening depression); there was no significant difference in the number of adverse events in the two groups. The study was limited by absence of a treatment group with placebo.

Several RCTs not discussed above or included in the above systematic reviews 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 six months, so durability of the results is unknown.[16-26, 28-31]
- 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, 28-30, 32-39]
- 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.[40, 41]

Adolescents

There are currently no TMS devices with FDA approval for use in adolescents, but research in this population is ongoing.

Zheng (2023) published a systematic review of randomized controlled trials (RCTs) to explore the therapeutic effects and safety of active low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) versus sham LF-rTMS in children and adolescent patients with first-episode and drug-naïve (FEDN) major depressive disorder (MDD).[42] A systematic search of the literature yielded 442 references, of which 3 RCTs (130 children and adolescents with FEDN MDD, 50.8% male, and mean age range from 14.5 to 17.5 years) met the inclusion criteria. Among the two RCTs (66.7%, 2/3) examining the effects of LF-rTMS on study-defined response and remission and cognitive function, active LF-rTMS was more efficacious than sham LF-rTMS in terms of study-defined response rate and cognitive function (all $p < 0.05$) but not regarding study-defined remission rate (all $p > 0.05$). The authors reported that LF-rTMS could benefit children and adolescents with FEDN MDD in a relatively safe manner, although further studies are warranted.

Majumder (2021) performed a systematic review of the safety and efficacy of rTMS in adolescents and children (ages 10 and over) with major depressive disorder.[43] A total of 18 publications, including case reports, met inclusion criteria. Most studies included treatment-resistant depression, defining it as one, two or several failed antidepressant trials depending on the study. The multi-subject trials allowed comorbid anxiety disorder, dysthymia, attention deficit hyperactivity disorder (ADHD) but excluded schizophrenia, bipolar disorder, substance use disorder, post-traumatic stress disorder (PTSD), intellectual disability, pervasive developmental disorders, and eating disorders. There was heterogeneity in inclusion criteria, number of rTMS sessions, and various other parameters. No meta-analysis was completed due to heterogeneity. Overall, the included studies indicated that in children and adolescents rTMS is safe but did not show that it is superior to placebo as a stand-alone treatment for resistant depression. The results were more promising for rTMS as an add-on treatment.

The only RCT included in the above systematic review was performed by Croarkin (2021), which TMS for adolescents with treatment-resistant depression.[44] Individuals aged 12 to 21 years with treatment-resistant depression (defined as an antidepressant treatment record level of 1 to 4 in a current episode of depression) were randomized to receive active NeuroStar TMS monotherapy (n=48) or sham TMS (n=55). Treatment was delivered daily for 30 days. At the end of treatment, there was no statistically significant difference in improvement in the least-squares mean (SE) HAM-D-24 between groups (active -11.1 [2.03]; sham -10.6 [2.00]; p= 0.8; difference [95% CI], - 0.5 [-4.2 to 3.3]). There were also no statistically significant differences between groups in response rates (active 41.7%; sham 36.4%; p=0.6) or remission rates (active 29.2%; sham 29.0%; p=0.95).

Durability of rTMS

<u>Systematic Reviews</u>

Kedzior (2015) examined the durability of the antidepressant effect of high-frequency rTMS on the left DLPFC in the absence of maintenance treatment.[45] Included were 16 double-blind, sham-controlled randomized trials (total n=495 patients). The range of follow-up was 1 to 16 weeks, but most studies only reported follow-up to two weeks. The overall effect size was small with a standardized mean difference (SMD; Cohen's d) of -0.48, and the effect sizes were lower in RCTs with 8 to 16 weeks of follow-up (d=-0.42) than with 1 to 4 weeks of follow-up (d=-0.54). The effect size was larger when an antidepressant medication was initiated concurrently with rTMS (five RCTs, d=-.56) than when patients were on a stable dose of medication (nine RCTs, d=-0.43) or were unmedicated (two RCTs, d=-0.26).

Observational Studies

Dunner (2014) reported a one-year follow-up with maintenance therapy from a large multicenter observational study (42 sites) of rTMS for patients with TRD.[46] A total of 257 patients agreed to participate in the follow-up study of 307 who were initially treated with rTMS. Of them, 205 completed the 12-month follow-up, and 120 patients had met the Inventory of Depressive Symptoms-Self Report response or remission criteria at the end of treatment. Ninety-three (36.2%) of the 257 patients who enrolled in the follow-up study received additional rTMS (mean, 16.2 sessions). Seventy-five (62.5%) of the 120 patients who met response or remission criteria at the end of the initial treatment phase (including a two-month taper phase) continued to meet response criteria through a one-year follow-up.

A variety of tapering schedules are being studied. For example, Richieri (2013) used propensity-adjusted analysis of observational data and found that patients who had rTMS tapered over 20 weeks (from three times per week to once a month) had a significantly reduced relapse rate than patients who had no additional treatment (37.8% vs 81.8%).[47] Connolly (2012) reported that in the first 100 cases treated at their institution, the response rate was 50.6% and the remission rate was 24.7%.[48] At six months after the initial rTMS treatment, 26 (62%) of 42 patients who received tapered maintenance therapy (from two sessions per week for the first three weeks to monthly) maintained their response. In another study, Janicak (2010) evaluated patients who met criteria for a partial response during either a sham-controlled or an open-label phase of a prior study were tapered from rTMS and simultaneously started on maintenance antidepressant monotherapy.[27] During the 24-week follow-up, 10 of 99 patients relapsed, 38 had symptom worsening, and of these 32 (84%) had symptomatic benefit with adjunctive rTMS.

Section Summary

There are a large number of sham-controlled randomized trials and meta-analyses of these RCTs evaluating the use of rTMS for depression. The meta-analyses found a clinical benefit associated with rTMS for TRD, with improved response rates and remission rates compared with sham. 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, while the effect of rTMS is less robust when it is given in combination with a stable dose of antidepressant medication. 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 found that the effect of rTMS is smaller than the effect of ECT on TRD, given that rTMS does not require general anesthesia or induce seizures and some individuals may not elect ECT, the balance of incremental benefits and harms associated with rTMS may be reasonable compared with ECT.

BIPOLAR DISORDER

Systematic Review

Konstantinou et al (2022) conducted a systematic review of 31 RCTs of rTMS for the treatment of bipolar disorder; meta-analysis was not performed.[49] Most included studies were in the setting of bipolar depression (n=24). Only 8 studies had a low risk of bias. Overall, rTMS seems safe and well-tolerated but efficacy results are mixed and there is no consensus about the optimal rTMS regimen. The authors noted limitations of the available literature including heterogeneity among studies, differences in sham treatments, and small sample sizes. They also stated that adequately powered sham-controlled studies are needed to verify the efficacy of rTMS in patients with bipolar disorder.

Tee (2020) conducted a systematic review of sham-controlled RCTs of rTMS for bipolar disorder.[50] A total of 11 RCTs met inclusion criteria, of which seven included only patients with bipolar depression, three included only patients with bipolar mania, and one included both unipolar and bipolar depression. Of the 345 included bipolar patients, 257 were treated for bipolar depression, 85 for mania, and 2 for mixed episodes. Risk of bias was assessed with the Cochrane Risk of Bias Tool. Of the studies of bipolar depression, one study was classified as good quality, two were classified as fair quality, and five were classified as poor quality. Of the studies of bipolar mania, one study was classified as fair quality and two were classified as poor quality. Results of the meta-analysis showed a statistically significant improvement in depressive symptoms in rTMS-treated versus sham-treated patients (standardized mean difference = 0.302, 95% CI 0.055 to 0.548, p=0.016). There was no statistically significant heterogeneity. There was also a statistically significant difference between groups in favor of rTMS for remission rate (risk difference = 0.14, $p<0.05$). There were no significant differences between groups for patients treated for bipolar mania. No serious adverse events were reported.

Randomized Controlled Trials

Torres (2023) published a randomized sham-controlled trial where 16 patients received active Intermittent theta burst stimulation (iTBS) to the Left Dorsolateral Prefrontal Cortex (DLPF) and 15 patients received sham stimulation across four weeks.[51] No significant improvements were observed in any cognitive variables in the active relative to the sham group; however, there was a trend for increased left hippocampal volume in the former. Left hippocampal volume increases were associated with improvements in nonverbal memory in the active group. Larger studies are required to determine the effects of iTBS for bipolar disorder.

Tavares (2017) published a randomized sham-controlled trial that examined the safety and efficacy of deep (H1-coil) TMS (dTMS) for treatment-resistant bipolar depression patients.[52] Fifty patients were randomized to 20 sessions of active or sham dTMS over the left dorsolateral prefrontal cortex. Two patients in the sham and five patients in the active group dropped out during the study. Assessments using the 17-item Hamilton Depression Rating Scale (HDRS-17) were completed at baseline, week four (end of treatment), and week eight. Patients were also assessed using the dTMS adverse effects questionnaire and the Young Mania Rating Scale, which would identify treatment-emergent mania switch. Changes in HDRS-17 from baseline (25.32 and 25.8 in sham and dTMS groups, respectively) were statistically superior in the active versus sham dTMS group at the end of treatment (difference at four weeks favoring dTMS=4.88; 95% CI 0.43 to 9.32, p=0.03) but not at

follow-up (difference favoring dTMS=2.76; 95% CI 1.68 to 7.2, p=0.22). Response and remission rates were not significantly different between groups. No incidences of treatment-emergent mania were reported.

McGirr (2016) performed a meta-analysis to assess the efficacy of TMS for bipolar depression.[53] The analysis included randomized, double-blind, sham-controlled trials of rTMS involving five or more sessions that randomized patients with bipolar depression to both active and sham rTMS arms. Many of the studies did not include enough patients with bipolar depression to analyze them separately within the study. Data from a total of 19 studies were included. Study quality was not evaluated. There was high methodological heterogeneity, but there was no statistical evidence of heterogeneity. A funnel plot revealed an asymmetrical distribution. According to the meta-analysis, significantly more patients who received active rTMS achieved clinical response at study end compared to those who received sham rTMS (47/106, 44.3%, vs. 19/75, 25.3%; RD=0.18, 95% CI: 0.06 to 0.30, p<0.01).

Fitzgerald (2016) published a two arm parallel design RCT evaluating rTMS for patients with refractory bipolar depression.[54] Forty-nine patients participated in the study and received rTMS or sham stimulation. The authors concluded there was no difference in depression between the groups. The study was limited in size.

BIPOLAR DEPRESSION

Randomized Controlled Trials

Nahas (2003) performed an RCT and carried out the following left prefrontal rTMS study to determine the safety, feasibility, and potential efficacy of using TMS to treat the depressive symptoms of bipolar affective disorder (BPAD).[55] They enrolled 23 depressed BPAD patients (12 BPI depressed state, nine BPII depressed state, two BPI mixed state). Patients were randomly assigned to receive either daily left prefrontal rTMS (5 Hz, 110% motor threshold, 8 sec on, 22 sec off, over 20 min) or placebo each weekday morning for 2 weeks. The authors failed to find a statistically significant difference between the two groups in the number of antidepressant responders (>50% decline in HRSD or HRSD <10 - 4 active and 4 sham) or the mean HRSD change from baseline over the 2 weeks (t = -0.22, p = 0.83). The authors concluded that further studies are needed to fully investigate the potential role, if any, of TMS in BPAD depression.

Myczkowski (2018) performed an RCT to evaluate the cognitive effects of H1-coil (deep) transcranial magnetic stimulation (TMS) in patients with treatment-resistant bipolar depression.[56] Fourty-three patients were randomized to receive 20 sessions of active (55 trains, 18 Hz, 120% resting motor threshold intensity) or sham rTMS within a double-blind, sham-controlled trial. : Cognitive improvement was shown for all cognitive domains. It occurred regardless of intervention group and depression improvement. For the language domain, greater improvement was observed in the sham group over time. No correlations between depression (at baseline or during treatment) and cognitive improvement were found. The authors comment that Putative pro-cognitive effects of rTMS in BD were not observed and thus should be further investigated.

Zengin (2022) performed an RCT to is to investigate the efficacy and safety of Transcranial magnetic stimulation (TMS) treatment, a non-invasive brain stimulation technique, on depressive symptoms in treatment-resistant bipolar depression (TRBD).[57] The study included 29 patients between the ages of 18-65, with bipolar disorder depressive episode. Patients were divided into two groups double-blind-randomly, 20 sessions of TMS and 20 sessions of sham TMS were applied crossover. In both groups, the severity of depression was decreased significantly according to HAM-D and BDI scores after the procedure. As well as active stimulation, some positive placebo effects were observed with sham stimulation. But the decreases seen in HAM-D and BDI scores and response to the treatment were higher during the weeks when the groups received active stimulation (respectively p=0.000, p=0.001, p=0.005). The authors concluded that TMS treatment is an effective and safe treatment for patients with treatment-resistant bipolar depression.

Mallik (2023) published an RCT for to study the effect of novel continuous theta burst stimulation (cTBS) targeting right dorsolateral prefrontal cortex in a randomized rater blinded placebo control design.[58] Nineteen patients aged 18 to 59 years (baseline Hamilton Depression Rating Scale [HAM-D] 17 severity score >18) were randomly allocated to active cTBS (n = 11) and sham cTBS (n = 9) groups using block randomization method. They received 15 cTBS sessions (burst of 3 pulses delivered at 50 Hz, repeated every 200 ms at 5 Hz, 600 pulses per session), 3 sessions per day (total of 1800 pulses) for 5 days in a week at 80% resting motor threshold. On repeated measures analysis of variance, a significant within-group time effect (from pretreatment to 2 weeks after TBS) for HAM-D ($F = 15.091$, $P < 0.001$), Beck Depression Inventory ($F = 22.376$, $P < 0.001$), Hamilton Anxiety Rating Scale ($F = 18.290$, $P < 0.001$), Changes in Sexual Functioning Questionnaire ($F = 9.281$, $P = 0.001$), and World Health Organization's abbreviated quality of life assessment ($F = 24.008$, $P < 0.001$). The authors concluded that although safe and well tolerated, the therapeutic efficacy of intensive intermittent TBS in acute-phase bipolar depression is inconclusive.

POST TRAUMATIC STRESS DISORDER AND ANXIETY

Systematic Reviews

Cui (2019) included 21 studies (n=1481 patients) in a meta-analysis of rTMS plus drug therapy compared to drug therapy alone for the treatment of generalized anxiety disorder.[59] Results of the analysis showed that rTMS improved anxiety symptoms as measured by the Hamilton Anxiety Scale, (standardized mean difference = −0.68, 95% CI −0.89 to −0.46). The conclusions that could be drawn from the body of evidence were limited by significant heterogeneity across studies, and the authors concluded that additional high-quality studies are needed to confirm the results.

An SR by Cirillo (2019) evaluated the safety and efficacy of TMS as a treatment for anxiety and trauma-related disorders.[60] The authors identified 17 studies that met inclusion criteria. Nine were for post-traumatic stress disorder (PTSD) (six double-blind, randomized, sham-controlled, one open-label, and two retrospective), four were for generalized anxiety disorder (two double-blind, randomized, sham-controlled, and two uncontrolled open-label), two were for specific phobias (one double-blind, randomized, sham-controlled, and single-blind, randomized, sham-controlled), and two were for panic disorder (both double-blind, randomized, sham-controlled). According to the meta-analysis including all nine PTSD

studies, the overall effect size for PTSD was -0.88 (95% CI -1.42 to -0.34), favoring TMS. According to the meta-analysis for generalized anxiety disorder, which included all four studies meeting inclusion criteria, the effect size for generalized anxiety disorder was −2.06 (95%CI −2.64 to −1.48), favoring TMS. No meta-analyses were performed for panic disorder and specific phobia due to an insufficient number of studies and patients.

Trevizol (2016) published a SR to evaluate the effects of rTMS on PTSD.[61] The five studies included showed rTMS statistically superior to sham stimulation (standard mean difference [SMD] =0.74; 95% CI 0.06 to 1.42), although heterogeneity of the trials was high. Despite improvements, the authors concluded this SR was limited in size and additional RCTs are needed to determine clinical impact.

Randomized Control Trials

Isserles (2021) reported a multisite randomized sham-controlled trial of deep TMS combined with exposure therapy for the treatment of PTSD.[62] A total of 125 patients were randomly assigned to receive deep TMS or sham during 12 sessions administered over four weeks. The primary endpoint was change in five-week Clinician-Administered PTSD Scale for DSM-5 score. While both groups improved significantly, the improvement in the sham group was significantly greater than the improvement in the active treatment group (20.52 vs. 16.32; p=0.027). This remained true at the nine-week follow-up (p=0.024).

SCHIZOPHRENIA

Systematic Reviews and Technology Assessments

Marzouk (2019) published an SR evaluating the use of TMS for positive symptoms in schizophrenia.[63] Thirty studies met the inclusion criteria, of which 25 investigated auditory verbal hallucinations. Twelve studies reported significant beneficial effects of TMS while 18 reported no significant beneficial effects. The SR concluded that further research with larger sample sizes is needed.

A 2019 SR published by Limori evaluated the effect of rTMS on cognitive function when used for depression, schizophrenia, and Alzheimer’s disease.[64] A total of 31 studies met inclusion and exclusion criteria, of which 15 were conducted in patients with depression, 11 in patients with schizophrenia, and 5 in patients with Alzheimer's disease. Six studies reported positive effects of rTMS on executive function while the rest reported no significant cognitive effects. A small number of studies also reported positive effects on verbal memory, working memory, and attention. No studies reported adverse cognitive effects. Conclusions were limited by heterogeneity between studies in terms of cognitive measures applied, stimulation parameters, and participants.

He (2017) published a meta-analysis of the effects of 1-Hz (low frequency) and 10-Hz rTMS (high frequency) for auditory hallucinations and negative symptoms of schizophrenia, respectively.[65] For 1-Hz rTMS, 13 studies were included. Compared with sham, the rTMS group showed greater improvement in auditory hallucinations (SMD = -0.29; 95% CI -0.57 to -0.01). However, significant heterogeneity between the studies was found (p=0.06). In the seven studies included for 10-Hz rTMS, the overall effect size for improvement in negative symptoms was -0.41 (95% CI -1.16 to -0.35); again, there was significant heterogeneity between studies (p<0.001). The study was further limited by the small number of articles included and by the unavailability of original data for some studies.

Dollfus (2016) published a SR to evaluate the impact of the placebo effect in studies involving rTMS on visual hallucinations for patients with schizophrenia.[66] Twenty-one articles with 303 patients were reviewed. The authors concluded that the placebo in rTMS studies cause bias and that the design or such studies should be carefully evaluated.

A 2015 Cochrane SR included 41 studies with a total of 1473 participants.[67] Based on very low-quality evidence, there was a significant benefit of temporoparietal TMS compared to sham for global state (seven RCTs) and positive symptoms (five 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 2011 BCBSA TEC Assessment evaluated TMS as an adjunct treatment for schizophrenia.[68] Five meta-analyses were reviewed, along with 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.

Randomized Controlled Trials

Several additional small, single center RCTs of rTMS for the treatment of schizophrenia have been published since the systematic reviews described above.[69-72] These studies were limited by their small sample sizes (28 to 50), very high loss to follow-up, and inadequate duration of followup. Due to these limitations, these studies do not provide sufficient evidence to draw conclusions about the effectiveness of the technology in patients with schizophrenia.

Section Summary

The evidence on TMS for the treatment of auditory hallucinations in schizophrenia consists of a number of small RCTs. 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.

OBSESSIVE COMPULSIVE DISORDER

Systematic Reviews

Pellegrini (2022) attempts to explain some of this heterogeneity in trails for testing the efficacy of r-TMS as a treatment for OCD by comparing the efficacy of r-TMS in patients with or without resistance to treatment with selective serotonin reuptake inhibitors (SSRI), defined using standardized criteria.[73] Twenty-five independent comparisons (23 studies) were included. Overall, r-TMS showed a medium-sized reduction of Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores (Hedge's g: -0.47; 95%CI - 0.67 to -0.27) with moderate heterogeneity (I2 = 39.8%). Subgroup analysis found that those studies including patients non-resistant to SSRI (stage 1) (g: -0.65; 95%CI -1.05 to -0.25, k = 7) or with low SSRI-resistance

(stage 2) (g:-0.47; 95%CI -0.86 to -0.09, k = 6) produced statistically significant results with low heterogeneity, while studies including more highly resistant patients at stage 3 (g: -0.39; 95%CI: -0.90 to 0.11, k = 4) and stage 4 (g: -0.36; 95%CI: -0.75 to 0.03, k = 8) did not. The authors conclude that r-TMS is an effective treatment for OCD, but largely for those not resistant to SSRI or failing to respond to only one SSRI trial. As a consequence, r-TMS may be best implemented earlier in the care pathway.

Fitzsimmons (2022) reported results of a systematic review and pairwise/network meta-analysis of randomized, sham-controlled studies of rTMS for obsessive compulsive disorder (OCD).[74] A total of 21 studies including 662 participants met inclusion criteria. Studies were generally small and there was heterogeneity in study protocols. Overall, rTMS for OCD was found to be efficacious across all protocols according to the pairwise meta-analysis (Hedges' g=-0.502 [95%CI -0.708 to -0.296]). rTMS remained efficacious in analyses where stimulation protocols were clustered only by anatomical location, including both dorsolateral prefrontal cortex (dlPFC) stimulation and medial frontal cortex stimulation, and in analyses of each unique combination of frequency and location separately, including low frequency (LF) pre-supplementary motor area (preSMA) stimulation, high frequency (HF) bilateral dlPFC stimulation, and LF right dlPFC stimulation.

Suhas (2021) conducted a network meta-analysis [NMA] to compare the efficacy of all interventions in SRI-resistant OCD from published RCTs from all modalities of treatments; pharmacological, psychological, neuromodulation, neurosurgery including deep brain stimulation.[75] 55 RCTs examining 19 treatments or placebo involving 2011 participants were included in the NMA. Ondansetron [Standardized mean difference -2.01 (95% CI -3.19, -0.83)], deep TMS [- 1.95 (-3.25, -0.65)], therapist administered Cognitive Behavioral Therapy [CBT-TA] [-1.46 (-2.93, 0.01)] and aripiprazole [-1.36 (-2.56, -0.17)] were ranked as the best four treatments on using the Surface Under the Cumulative Ranking [SUCRA] percentage values (85.4%, 83.2%, 80.3%, 67.9% respectively). The authors concluded that deep TMS, ondansetron, CBT, and aripiprazole may be considered a first-line intervention for SRI-resistant OCD in adults. The small number of subjects in individual studies, higher confidence interval limits, and wider prediction interval for most agents warrant a cautious interpretation.

Pereyra (2021) conducted a systematic review and meta-analysis of rTMS in the treatment of OCD.[76] All RCTs in the analysis (n=26) had a low risk of bias. A random effects model was used to compare pre- and post-stimulation YBOCS scores, with effect sizes reported as Hedges' g. The analysis found that rTMS had a significant effect on YBOCS scores compared to sham (effect size, 0.64; 95% CI, 0.39 to 0.89; p<.0001). Raw mean difference in standardized mean difference for the primary outcome (YBOCS score) between treatments was 4.04 (95% CI, 2.54 to 5.54; p<.001). The effect size was still significant when 2 dominant trials were removed. Effect sizes with rTMS appeared to be significant until 4 weeks after treatment, and low- and high-frequency rTMS had similar efficacy to each other. The authors performed several subgroup analyses (cortical target, stimulation frequency, total pulses per session, total duration of treatment) but none of the effect sizes were significant between rTMS and sham.

Liang (2021) conducted a systematic review and meta-analysis of different TMS modalities for the treatment of OCD.[77] Three of the five protocols assessed were significantly more efficacious than sham TMS, and all treatment strategies were similar to sham TMS regarding tolerability. Transcranial magnetic stimulation was not more effective than sham TMS, but there was direct evidence from only one RCT for this comparison (Carmi, 2019, discussed in

the next section).[78] The overall quality of the evidence was rated very low for efficacy and low for tolerability, and the reviewers concluded that high quality RCTs with low selection and performance bias are needed to further verify the efficacy of specific rTMS strategies for OCD treatment.

Zhou (2017) published an SR that analyzed 20 sham-controlled studies with 791 patients examining the effect of rTMS on obsessive-compulsive disorder (OCD).[79] Treatments targeted the bilateral DLPFC, left DLPFC, right DLPFC, supplementary motor area (SMA), and the orbitofrontal cortex. The majority of studies did not use intention to treat analyses and only three studies assessed the effectiveness of the blinding procedures used. Results of a meta-analysis indicated a large effect size for therapeutic effect (g=0.71; 95%CI 0.55 to 0.87; p<0.001). Significant improvements over sham treatment were seen for rTMS targeting the supplementary motor area, left dorsolateral prefrontal cortex (DLPFC), bilateral DLFPC, and right DLPFC, excluding the orbitofrontal cortex. High-frequency and low-frequency treatments were significantly better than sham treatment, with no differences found between frequencies.

A systematic review by Trevizol (2016) included 15 RCTs (total n=483) that compared active with sham rTMS for obsessive-compulsive disorder (OCD).[80] All studies were sham-controlled and double-blinded. Sample sizes in the trials ranged from 18 to 65 patients. Mean age of participants was 31.9 (SD = 7.6) years. The duration of the studies was between one and six weeks. Seven studies used low-frequency stimulation and eight studies used high-frequency stimulation. The cortical regions varied among the studies, targeting the supplementary motor area, orbitofrontal cortex, or left, right, or bilateral DLPFC. The researchers calculated the YBOCS score. Response rates were not reported. The pooled mean difference between groups on the YBOCS was 2.94 (95% CI 1.26 to 4.62), translating to a small to moderate effect size for active stimulation of 0.45 (95% CI 0.20 to 0.71). Individual adverse effects were not assessed due to a lack of reporting in the primary studies, but there was no difference between groups in the dropout rate. Intervention protocols were heterogeneous across the studies, but regression analysis did not identify any treatment protocol or other variables as predictors of TMS response.

Randomized Controlled Trials

Roth (2021) published the efficacy of Deep transcranial magnetic stimulation (dTMS) with the H7-coil was for obsessive-compulsive disorder (OCD) based on multicenter sham-controlled studies.[81] The primary outcome measure was response, defined by at least a 30% reduction in the Yale Brown Obsessive Compulsive Scale (YBOCS) score from baseline to endpoint. Secondary outcome measures included first response, defined as the first time the YBOCS score has met response criteria, and at least one-month sustained response. Twenty-two clinical sites with H7-coils provided data on details of treatment and outcome (YBOCS) measures from a total of 219 patients. First response was achieved in average after 18.5 sessions (SD = 9.4) or 31.6 days (SD = 25.2). Onset of sustained one-month response was achieved in average after 20 sessions (SD = 9.8) or 32.1 days (SD = 20.5). Average YBOCS scores demonstrated continuous reduction with increasing numbers of dTMS sessions. The authors reported that the majority of OCD patients benefitted from dTMS, and the onset of improvement usually occurs within 20 sessions.

A more recent RCT, Carmi (2019) was addressed in the 2021 Liang systematic review, above.[78] The trial was submitted to FDA as part of the de novo classification request, to establish a reasonable assurance of safety and effectiveness of the deep TMS device for

OCD.[78] Adults ages 22 to 68 years with a diagnosis of OCD as a primary disorder, who were receiving treatment in an outpatient setting, and have a YBOCS score >20 were included. In addition, patients were either in maintenance treatment with a therapeutic dosage of a serotonin reuptake inhibitor (SRI) for at least two months before randomization or, were in maintenance treatment on cognitive-behavioral therapy (CBT) and had failed to respond adequately to at least one past trial of an SRI. A total of 99 patients were randomized to active treatment or sham. The primary outcome was the difference between groups in the mean change from baseline to six weeks on the YBOCS. Secondary outcomes included the response rate (defined as a 30% or greater improvement from baseline on the YBOCS), the Clinical Global Impression of Improvement (CGI-I), the Clinical Global Impression of Severity (CGI-S), and the Sheehan Disability Scale, a patient-reported measure of disability and impairment. Results at 10 weeks were also reported as secondary outcomes.

The primary efficacy analysis used a modified intention to treat analysis (n=94), excluding five patients who were found to not meet eligibility criteria following randomization. There was a greater decrease from baseline 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 six weeks, the response rate was 38.1% in the active treatment group compared to 11.1% in the sham group (p=0.003). The FDA review provides data from the ITT analysis of the mean change in YBOCS score (n=99). In the ITT data set, the YBOCS score decreased by -6.0 points (95% CI -3.8 to -8.2) in the active group and by -4.1 points (95% CI -1.9 to -6.2) in the sham group. Although the decreases were both statistically significant from baseline, the difference of 1.9 points between the treatment arms was not statistically significant (p=0.0988). Results on the secondary outcomes were mixed. More patients in the active treatment group were considered improved based on the Clinical Global Impression of Improvement (CGI-I) and the Clinical Global Impression of Severity (CGI-S) at six weeks, but there was no significant difference between groups on the Sheehan Disability Scale. The number of adverse events and dropouts were similar between groups (73% vs. 69% for adverse events and 12.5% vs. 12.0% for dropouts, for TMS and sham, respectively).

Additional small, single center RCTs of rTMS for the treatment of OCD have been published since the systematic reviews described above.[82] These studies were limited by their small sample sizes (under 50), very high loss to follow-up, and inadequate duration of followup.

OTHER PSYCHIATRIC DISORDERS

Systematic Reviews

Westwood (2021) published an SR and meta-analysis of noninvasive brain stimulation for the treatment of attention-deficit/hyperactivity disorder (ADHD).[83] A total of 18 studies met inclusion criteria, of which four addressed rTMS and 14 addressed tDCS. The meta-analysis showed no statistically significant improvements following rTMS or tDCS in any measures.

A 2020 SR on noninvasive brain stimulation for alcohol craving published by Mostafavi identified 34 eligible studies, of which 23 addressed rTMS and 11 addressed tDCS.[84] Twenty-seven of the studies included a control group. According to the meta-analysis, the pooled standardized mean differences in alcohol cravings based on tDCS or rTMS treatment were not statistically significant (- 0.13 [-0.34 to 0.08] and - 0.43 [-1.02 to 0.17], respectively).

A 2018 SR published by Barahona-Corrêa assess the use of rTMS for the treatment of Autism Spectrum Disorder (ASD).[85] A total of 23 studies met inclusion criteria, including four case-

reports, seven non-controlled clinical trials, and 12 controlled clinical trials. The controlled trials compared the effects of real TMS with waiting-list controls (n=6) or sham-treatment (n=6). Four of the controlled trials were not randomized. Meta-analyses indicated moderate, statistically significant effects on repetitive and stereotyped behaviors, social behavior, and number of errors in executive function tasks. However, most studies had a moderate to high risk of bias and outcomes were not reported long-term.

A 2014 Cochrane review identified two RCTs with a total of 40 patients that compared low frequency rTMS with sham rTMS for the treatment of panic disorder.[86] The larger of the two 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 four 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 two studies was considered to be low, and the sample sizes were small, precluding any conclusions about the efficacy of rTMS for panic disorder.

Additional SRs have been published exploring the efficacy of TMS for a variety of psychiatric disorders like borderline personality disorder and addiction.[87-89] All of these SRs had one or more significant methodological limitations, including but not limited to small patient populations, short follow-up times, continued use of concurrent therapies, and/or significant loss to follow-up in the included studies, heterogeneous treatment parameters between studies, and limited management of study bias and conflict of interest. Generally, the authors agreed that larger, long-term RCTs are needed, along with better defined optimal treatment parameters for administering TMS.

Randomized Controlled Trials

A number of additional RCTs explored the efficacy of TMS for a variety of mental health disorders other than depression, including, but not limited to, bipolar mania, panic disorder, alcohol dependence, 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[90-95]
- Significant or unclear loss to follow-up and poorly defined intention-to-treat (ITT) analyses[92, 94, 96-98]
- Lack of long-term follow up[90-104]
- Small patient populations[90-100, 105-115]
- Lack of standardized optimal treatment parameters[90-93, 95-99, 105, 116-118]
- Use of co-therapies[90-100]
- Strict inclusion/exclusion criteria which were not representative of patients requiring treatment in the general population[90-93, 96, 99, 100, 105]

Section Summary

Current evidence is insufficient to determine the efficacy of TMS in patients with the psychiatric disorders discussed here. Well-designed RCTs are needed which address the methodological limitations of current studies, noted above.

ALZHEIMER’S DISEASE AND DEMENTIA

Teselink (2021) performed an SR and meta-analysis of non-invasive brain stimulation for Alzheimer's disease and mild cognitive impairment.[119] A total of 19 studies measuring cognition and nine measuring neuropsychiatric symptoms met inclusion criteria. There was no evidence of publication bias. Overall, noninvasive stimulation was found to significantly improve global cognition (p=0.001) and neuropsychiatric symptoms (p=0.019) compared to sham stimulation. According to subgroup analyses, these effects were driven by TMS treatment in Alzheimer's disease and there was no significant effect of tDCS or in dementia patients. A meta-regression analysis showed Meta-regression showed that age was significantly associated with global cognition response (p=0.02). There was substantial heterogeneity across all subgroup analyses and meta-regressions (all $I^2 > 50\%$).

Wang (2020) published an SR and meta-analysis of rTMS and tDCS for the behavioral and psychological symptoms of dementia.[120] A total of 10 studies were identified. Seven of the studies included patients with Alzheimer's disease. The meta-analysis included both forms of stimulation and the results indicated that stimulation resulted in a statistically significant improvement in the behavioral and psychological symptoms of dementia immediately following stimulation (SMD, 0.31; 95% CI 0.10 to 0.52; p=0.005). The improvement was not statistically significant at the last follow-up visit for stimulation overall (0.15; 95% CI - 0.11 to 0.41; p=0.25), but was statistically significant in the subgroup analysis for rTMS (0.57; 95% CI 0.18 to 0.96; p=0.004). The subgroup analysis for Alzheimer's disease patients did not indicate any significant differences from the group overall.

Vacas (2018) published an SR and meta-analysis of rTMS and tDCS for the behavioral and psychological symptoms of dementia.[121] Three RCTs and two open-label clinical trials of rTMS were identified as well as two RCTs of tDCS. A meta-analysis with four RCTs did not show significant efficacy of noninvasive brain stimulation techniques, but a meta-analysis of the rTMS RCTs alone showed a statistically significant positive effect on behavioral and psychological symptoms of dementia (overall effect = -0.58; 95% CI -1.02 to -0.14; $I^2 = 0\%$). The adverse effects reported were mild and not clinically relevant.

A 2017 SR published by Cheng analyzed studies that used rTMS for patients with mild to moderate Alzheimer's disease.[122] Seven RCTs (including 107 active and 87 sham rTMS patients) were included in a meta-analysis analyzing a primary outcome of cognitive function as measured by the Mini-Mental State Examination or the Alzheimer's Disease Assessment Scale-cognitive subscale. Active rTMS was found to be significantly more effective than sham for improving cognition.

CEREBRAL PALSY

Systematic Reviews

No SRs were identified.

Randomized Control Trials

Gupta (2016) published a RCT that evaluated motor function, after rTMS for cerebral palsy (CP) patients.[123] Forty-one spastic CP children who completed the study and were randomly assigned to receive physical therapy (n=12) alone, 5hz rTMS followed by physical therapy (n=15), or 10hz rTMS, (n=14) followed by physical therapy for 20 days. The gross motor function measure (GMFM) test was applied at baseline and after 20 treatments. Although the study showed improved motor function for the rTMS plus physical therapy groups, the authors

concluded the results should not be interpreted as a final outcome, especially with previous studies showing lack of progress from this treatment. Larger studies evaluating long-term effects are needed.

EPILEPSY

Systematic Reviews

A meta-analysis conducted by Mishra and colleagues (2020) included seven RCTs that compared rTMS with sham or placebo controls in patients with epilepsy.[124] Two of the included studies showed statistically significant reductions in the seizure rate from baseline, three trials failed to show any statistically significant difference in seizure frequency, and two had unclear results due to inadequate power. In a meta-regression, when adjusted for other potential variables such as the type of coil used, stimulation frequency, and the total duration of the active intervention, seizure frequency worsened by 2.00 ± 0.98 (p=0.042) for each week of lengthening of the posttreatment follow-up period. These results suggested that rTMS exerted only a short-term effect. The reviewers concluded that although the procedure may be a therapeutic alternative for patients with drug-resistant epilepsy, further RCTs using standardized protocols and with adequate sample sizes and duration are still needed.

Walton (2021) published an update to a Cochrane SR that included eight RCTs to evaluate the effects of rTMS on health outcomes for patients with drug-resistant epilepsy.[125] All studies were randomized and seven were blinded. However, a meta-analysis could not be conducted due to differences in the design, interventions, and outcomes of the studies. Therefore, a qualitative synthesis was performed. For the outcome of seizure rate, two studies showed a significant reduction and six studies did not. Of the four studies evaluating the mean number of epileptic discharges, three showed a statistically significant reduction in discharges. Adverse effects were uncommon and mild, involving headache, dizziness, and tinnitus. There were no significant changes in medication use. The authors noted low quality of evidence and that more studies are needed to evaluate reduction in seizure activity, quality of life, and adverse outcomes.

Pereira (2016) published an update to a 2007 SR that evaluated the safety of rTMS for patients with epilepsy and how well the procedure was tolerated.[126] Sixteen new studies were identified totaling 48, for this SR. The authors concluded the risk of increased seizure activity with rTMS was small and adverse events for patients with epilepsy were similar to healthy patients. They also questioned data control, stated results should be interpreted with caution and more studies are needed.

Randomized Control Trials

No RCTs were identified since the publication of the above SRs.

FIBROMYALGIA

Systematic Review

Su (2021) conducted a meta-analysis of 18 RCTs (n=643) with rTMS in patients with fibromyalgia.[127] Reduction in disease influence according to the Fibromyalgia Impact Questionnaire showed a significant effect of rTMS (SMD, -0.7; 95% CI -1.173 to -0.228). The effect of rTMS on disease influence, pain, depression, and anxiety lasted for at least 2 weeks after the last session. Older patients were most likely to experience reduced

Fibromyalgia Impact Questionnaire scores. The authors concluded that larger RCTs are needed to confirm these findings.

Sun (2022) performed a systematic review and meta-analysis of the effectiveness of rTMS for fibromyalgia.[128] A total of 14 studies, including 433 participants, met inclusion criteria. The mean study quality was rated 8.5/10 on the PEDro scale. The analysis found that rTMS resulted in a greater improvement than sham treatment in the Numerical Pain Rating Scale (NPRS) (standardized mean difference = -0.49; 95% CI -0.86 to 0.13; p=0.0008) and the Fibromyalgia Impact Questionnaire (FIQ) (standardized mean difference = -0.50, 95% CI -0.75 to - 0.25; p=0.0001). No significant differences between groups were identified for the Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS) anxiety score, Pain Catastrophizing Scale (PCS), or Fatigue Severity Scale (FSS).

In 2017, Saltychev and Laimi published a meta-analysis of rTMS for the treatment of patients with fibromyalgia.[129] The meta-analysis included seven sham-controlled double-blinded RCTs with low risk of bias. The sample size of the trials ranged from 18 to 54. Five of the studies provided high-frequency stimulation to the left primary motor cortex, the remaining two were to the right DLPFC or left DLPFC. The number of sessions ranged from 10 to 24, and follow-up ranged from immediately after treatment to three months after treatment. In the pooled analysis, pain severity decreased after the last simulation by 1.2 points (95% CI -1.7 to -0.8) on a 10-point numeric rating scale, while pain severity measured at one week to one month after the last simulation decreased by 0.7 points (95% CI -1.0 to -0.3 points). Both were statistically significant but not considered to be clinically significant, with a minimal clinically important difference of 1.5 points.

Kninik (2016) published a SR that determined the effects repetitive transcranial magnetic stimulation (rTMS) versus a sham stimulation had on fibromyalgia, depression and/or quality of life.[130] The SR included five RCTs of moderate quality. The authors concluded that rTMS had a superior effect on quality of life after 30 days, but more studies are needed to determine why and how rTMS impacts health outcomes and what treatment protocols are appropriate.

A 2012 SR included four studies on transcranial direct current stimulation (tDMS) and five on TMS for treatment of fibromyalgia pain.[131] Four of the five TMS studies were double-blind RCTs, 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.

Randomized Controlled Trials

No sham-controlled RCTs were identified since the publication of the above SRs that evaluated the safety and efficacy of TMS for fibromyalgia.

Section Summary

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.

HEADACHES/MIGRAINES

Systematic Reviews and Technology Assessments

Saltychev (2022) conducted a systematic review and meta-analysis of 8 RCTs from 2004-2021 that studied that compared rTMS to sham stimulation in patients with migraine (n=339).[132] All RCTs used high-frequency rTMS to the left dorsolateral prefrontal cortex and all studies except 1 included patients with chronic migraine. The treatment duration was three to 12 sessions over three to eight days. All studies except 1 had a low risk of bias and the risk of publication bias was nonsignificant. Results for the frequency of migraine days per month and the intensity of migraine pain both favored rTMS; however, the authors stated that the difference in migraine pain intensity was clinically insignificant.

A 2020 the Canadian Agency for Drugs and Technologies in Health (CADTH) rapid response report evaluated the use of non-invasive nerve stimulation for migraine pain.[133] The six included publications assessed a variety of stimulation methods, including but not limited to TMS, tDCS, and trigeminal nerve stimulation. The review concluded that the evidence is limited in quality and quantity. Based on the limited evidence identified, the review concluded that there is a lack of evidence of the effectiveness of non-invasive nerve stimulation for migraine pain.

Feng (2019) performed an SR of non-invasive brain stimulation (rTMS and transcranial direct current stimulation [tDCS]) for the treatment of migraine.[134] Nine RCTs met inclusion criteria, of which five used rTMS and four used tDCS. Several studies overlapped with the WA HCA technology assessment below. Results of a meta-analysis of outcomes following excitatory stimulation of the primary motor cortex of migraine patients showed a significant reduction in headache intensity (Hedges' g = -0.94; 95% CI -1.28 to -0.59; $p<0.001$, I^2 =18.39%) and frequency (Hedges' g=-0.88; 95% CI -1.38 to -0.38; p=0.001, I^2 = 57.15%). Stimulation of the dorsolateral prefrontal cortex also showed a significant effect on headache intensity (Hedges' g=-1.14; 95% CI -2.21 to -0.07; p=0.04, I^2 =61.86%), but did not significantly alter the frequency of headaches.

In 2017, the Washington State Health Care Authority (WA HCA) published a technology assessment of treatments for chronic migraine and chronic tension-type headache. [134, 135] The authors identified two small RCTs that evaluated the efficacy of TMS for the treatment of chronic migraine using a sham control. One RCT was considered to be at moderately low risk of bias and the other moderately high risk of bias due to multiple methodological concerns. One of the RCTs found that at four weeks post-treatment, TMS resulted in statistically significant improvement in outcomes compared to sham (low quality of evidence). With regard to safety, this study reported no statistical difference between the TMS and sham group in frequency of study withdrawal due to adverse events, but more TMS-treated patients experienced discomfort compared to sham. In the other RCT, eight weeks-results were reported. At this time-point, no statistical differences were reported between TMS and sham for reduction in migraine attacks or reduction in migraine days and no differences were reported in the frequency of minor adverse events or study withdrawal due to adverse events. The assessment authors concluded that the data in the second RCT was of insufficient quality to draw conclusions.

A 2019 SR published by Stilling evaluated the use of TMS and tDCS for the treatment of headache.[136] A total of 34 studies met inclusion criteria, including 16 rTMS, 6 TMS, and 12 tDCS studies. The quality of the studies was assessed using GRADE and ranged from very low to high. rTMS was found to be the most promising, but few studies reported changes from active treatment greater than sham.

Lan (2017) performed a meta-analysis that included five RCTs and 313 migraine patients.[137] Only one study was identified that assessed the efficacy of TMS on migraine with aura. This study found a significant effect of TMS after the first attack. The remaining four RCTs assessed the effect of TMS on chronic migraine. These studies were found to have statistically significant heterogeneity. The analysis showed no significant effect of TMS on chronic migraine.

Randomized Control Trials

A 2019 RCT published by Granato evaluated the effects of high-frequency rTMS in patients with chronic migraine and medication overuse headache.[138] Of the 26 patients enrolled, 14 completed the study. Half of these received high-frequency rTMS and half received sham treatment. Outcome measures were changes in headache days (HD), headache hours (HH) and symptomatic drug intake (SDI). These were recorded for 30 days before the beginning of stimulation and during the three following months. There were reductions in all measures in both groups but no significant differences between groups.

Leung (2015) published an RCT that evaluated how rTMS improved headaches for military patients with mild traumatic brain injury (MTBI).[139] Twenty-four patients received rTMS or sham rTMS at the left motor cortex (LMC). Patients were evaluated one week and one-month post treatment. Although the authors concluded rTMS is an effective treatment for MTBI headaches, this study did not evaluate whether the outcomes were sustained long-term.

Rapinesi (2016) published an RCT that evaluated the impact of dTMS on chronic migraines (CM).[140] Fourteen treatment-resistant patients were randomized to receive add-on high-frequency dTMS (n=7) or standard abortive or preventive antimigraine treatment (n=7). Twelve sessions were received over one-month time. Depression symptoms were evaluated during treatment and one month later. Although the authors concluded add-on dTMS is effective in decreasing the intensity and frequency of migraines, this study was limited in size and did not evaluate long-term effects.

PAIN

Systematic Reviews

Che (2021) reported the results of a systematic review of rTMS over the DLPFC for the treatment of chronic and provoked pain.[141] A total of 26 studies met inclusion criteria. A publication bias was identified in the studies of provoked pain but not for chronic pain conditions. Overall, no significant effect was found for TMS across chronic pain conditions. However, there was a significant short-term analgesia effect in neuropathic pain conditions (SMD = -0.87). There was an overall pain reduction identified in the midterm (SMD = -0.53, 24.6 days average) and long-term (SMD = -0.63, three months average) post DLPFC stimulation across pain conditions, but not within specific chronic pain conditions.

A 2019 SR by Ramger analyzed the efficacy of non-invasive brain stimulation for the treatment of central post-stroke pain.[142] Six studies met inclusion criteria. These included one RCT of direct current stimulation and five studies of TMS (three within-subject randomized cross-over studies, one case series, and one prospective cohort). Only one of the cross-over studies was rated as “good/excellent” quality, while the remainder of included studies were rated as “fair” or “poor”. Four studies reported significant decreases in VAS ($p<0.05$). Overall, the authors concluded that there may be a beneficial effect of non-invasive brain stimulation for central post-stroke pain, but that the evidence is limited.

An SR published by Hamid (2019) evaluated the efficacy of TMS for chronic pain. Twelve RCTs met inclusion criteria.[143] Risk of bias was assessed for the included studies and ranged from low to high. Limitations of the studies include that not all clearly specify sham blinding, inconsistent reporting of the type of control, and heterogeneity in treatment protocols. A meta-analysis demonstrated a statistically significant improvement in pain measured by the pain VAS associated with rTMS ($p<0.001$).

Randomized Control Trials

Attal (2021) conducted a multicenter sham-controlled randomized trial of rTMS for neuropathic pain.[144] A total of 152 patients were randomized to receive rTMS to the primary motor cortex (M1; n=49), rTMS to the dorsolateral prefrontal cortex (DLPFC; n=52), or sham rTMS (n=48). The primary end point was the comparison between active M1-rTMS, active DLPCF-rTMS and sham-rTMS for the change over the 25 weeks (Group × Time interaction) in average pain intensity (from 0 no pain to 10 maximal pain) on the Brief Pain Inventory in patients who received at least one rTMS session (modified intention-to-treat population). Compared to sham, M1-rTMS significantly improved pain intensity, pain relief, sensory dimension of pain, self-reported pain intensity and fatigue, Patient and Clinician Global Impression of Change (PGIC and CGIC). DLPFC-rTMS did not result in outcomes that were significantly different than sham. rTMS to either brain region resulted in no differences from sham for quality of pain, mood, sleep, or quality of life. The most commonly reported side effect was headache, which did not occur at significantly different rates between groups.

Ambriz-Tututi (2016) published a RCT that evaluated the impact of rTMS on patients with chronic low back pain.[145] Eighty-two patients received rTMS, sham stimulation, or physical therapy (PT) for one week and were evaluated with the visual analogue scale (VAS), Short Form McGill pain questionnaire (SF-MPQ), and the Short Form 36 Health Survey. The authors concluded long-term reduction of pain in the rTMS group, but there was no apparent long-term outcome documented.

Malavera (2016) published a randomized, double-blinded, parallel group, single-center RCT to evaluate the impact of rTMS on phantom limb pain (PLP), for land mine victims.[146] Fifty-four patients received rTMS (n=27) or sham stimulation (n=27) five days a week for two weeks and were evaluated 15 and 30 days after treatments. The rTMS group showed significant PLP improvement up to 15 days after treatment, but as the authors noted the study was limited in size and may not have included enough assessment data, nor were the long-term effects evaluated.

Additional studies are not discussed here due to methodological limitations, including low patient numbers and lack of long-term follow-up.[147]

PARKINSON’S DISEASE

Systematic Reviews

Li (2022) conducted a meta-analysis of 32 sham-controlled RCTs of rTMS in patients with Parkinson disease and motor dysfunction (n=1048 patients).[148] Motor dysfunction was assessed using the United Parkinson's Disease Rating Scale part III score. Overall, rTMS had a significant effect on motor symptoms compared to sham (SMD, 0.64; 95% CI, 0.47 to 0.80; p<.0001; I2=64%). High-frequency rTMS to the primary motor cortex was the most effective intervention. Significant benefit of rTMS was also demonstrated for akinesia, rigidity, and tremor.

2022 systematic review and meta-analysis by Cheng evaluated the efficacy of TBS on motor and nonmotor symptoms of Parkinson's disease.[149] A total of eight studies met inclusion criteria. Of these, two evaluated only in the "off" medicine status (under the anti-Parkinsonism medicine withdrawal status for at least 12 hours), two evaluated only in the "on" anti-Parkinsonism medicine state, and four assessed both the "on" and "off" medicine states. According to the meta-analysis, TBS significantly improved the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) score compared to sham in the "off" medicine state (SMD = -0.37; 95% CI -0.65 to -0.09; p<0.01; I^2 = 19%) but not the "on" medicine state (SMD = -0.06; 95% CI -0.37 to 0.25; p=0.69; I^2 = 0%). Statistically significant effects were also reported for improved slowing of gait in the "off" medicine status (SMD = -0.37; 95% CI -0.71 to -0.03; p = 0.03; I^2 = 0%) and therapeutic effect on PD depression (mean difference = -2.93; 95% CI -5.52 to -0.33; p=0.03). The authors concluded that large, high-quality RCTs are needed to confirm these findings.

Jiang (2020) performed a systematic review and meta-analysis of the effect of rTMS on cognitive function in Parkinson's disease patients.[150] A total of 14 studies (173 participants) met inclusion criteria. Significant effects of rTMS were identified for the mini-mental state examination (MMSE) for the global cognitive outcome, and executive function. No significant effects were identified for the rest of the cognitive domains (memory, attention, and language ability).

A 2019 SR by Kim evaluated the effect of non-invasive brain stimulation (NIBS), including repetitive transcranial magnetic stimulation and transcranial direct current stimulation, for freezing of gait in parkinsonism.[151] Seven studies met inclusion criteria. A meta-analysis was performed on the data from the 102 included patients. It showed a significant improvement in freezing of gait questionnaire scores (SMD=0.28; 95% CI 0.01 to 0.55) and turning time (SMD = 0.30; 95% CI 0.02 to 0.58). The effect size was greater when only Parkinson's disease patients were included.

Qin (2018) published a meta-analysis of RCTs examining high-frequency rTMS for Parkinson's disease (PD).[152] The primary outcome measure was changes in depressive symptoms in Parkinson's disease patients and the secondary outcome was changes in motor symptoms. Nine RCTs, with data from 332 participants, were analyzed. Results were reported as mean difference (MD) or standard mean difference (SMD). For the primary outcome, changes in depressive symptoms, rTMS was not better than sham-rTMS (SMD =-0.33, 95% CI -0.83 to 0.17) or selective serotonin re-uptake inhibitors (SSRIs) (SMD =0.07, 95% CI -0.52 to 0.18). The changes in motor symptoms were greater, both compared to sham-rTMS (MD =-2.80, 95% CI -5.45 to -0.15) and SSRIs (MD =-2.70, 95% CI -4.51 to -0.90).

Wagle (2016) published a SR that evaluated how rTMS improved motor symptoms in patients with Parkinson's disease.[153] Twenty-one clinical trials with an active and control

arm were reviewed. The authors concluded that rTMS can improve motor function as an adjunct therapy, but had insufficient data to evaluate specific clinical conditions related to Parkinson's disease i.e. dyskinesia, bradykinesia, and gait. Larger studies are needed to evaluate clinical features that will have a positive long-term response.

A 2015 SR included 20 sham-controlled RCTs with a total of 470 patients with PD.[154] 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 SR was an exploratory, multicenter, double-blind trial that randomized 106 patients to eight weeks of 1-Hz rTMS, 10 Hz rTMS, or sham stimulation over the supplementary motor area.[155] At nine 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 SR from 2009 included 10 RCTs with a total of 275 patients with PD.[156] Seven of the studies were double-blind, one was not blinded and two 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

Randomized Controlled Trials

He (2021) conducted a randomized sham-controlled study on the effect of iTBS on mild cognitive impairment in Parkinson's disease.[157] A total of 35 PD patients were randomly assigned to receive iTBS (n=20) or sham (n=15) over the left dorsolateral prefrontal cortex for 10 consecutive weekdays. Statistically significant differences in improvement in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Montreal Cognitive Assessment (MoCA) were reported immediately post-intervention for both the iTBS and sham groups and at the three-month follow-up for only the iTBS group ($p<0.05$).

Cohen (2018) reported a double-blind, randomized, sham-controlled study to assess repetitive deep TMS for PD.[158] Forty-eight patients were randomized to sham or real repetitive deep TMS to the primary motor cortex and prefrontal cortex. The primary outcome measures were the total and motor scores of the Unified Parkinson's Disease Rating Scale, and secondary measures were rating of depression and quantitative motor tasks. Both groups improved significantly over the trial period. There was no significant effect of treatment. Side effects were reported to be more common in the repetitive deep TMS group. These effects were transient and reported to be tolerable.

Makkos (2016) published a double-blinded placebo-controlled RCT to determine if rTMS can improve depression for patients with PD.[159] Forty-six patients with mild to moderate depression received rTMS (n=23) or sham stimulation (n=23) for 10 days. Patients were evaluated by the Montgomery-Åsberg Depression Rating Scale at baseline, one day into treatment and 30 days after treatment. The authors concluded results were promising for the rTMS group, but rTMS trials should further evaluate the effects of rTMS on PD patients with severe depression.

A 2013 exploratory multicenter double-blind trial randomized 106 patients to eight weeks of 1 Hz TMS, 10 Hz TMS, or sham stimulation over the supplementary motor area.[155] At nine 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 reported a double-blind sham-controlled RCT of brief (six sec) very high frequency (50 Hz) TMS over the motor cortex in 26 patients with mild to moderate Parkinson's disease.[160] 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 one 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.

In another study from 2012, Yang randomized 20 patients with Parkinson's disease to 12 brief sessions (six min) of high frequency (5-Hz) TMS or sham TMS over the leg area of the motor cortex followed by treadmill training.[161] 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.

Section Summary

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

Systematic Reviews

Qiao (2022) performed a meta-analysis of RCTs that assessed the effect of rTMS in 433 patients with post-stroke dysphagia.55, Twelve trials that used dysphagia severity rating scales (Dysphagia Grade and Penetration Aspiration Scale) were included. The specific controls used in each study were not specified. Study characteristics included duration of treatment of 1 to 10 days, stimulation frequency of 1 to 10 Hz, and duration of stimulation of 5 to 20 minutes. The analysis favored rTMS (SMD, -0.67; 95% CI -0.88 to -0.45; p<.001; I2=42%). Subgroup analyses identified treatment duration >5 days and rTMS during the subacute phase after stroke as potential situations with greater clinical benefit, but there was no difference in efficacy according to stimulation frequency, location, or duration of each stimulation. The authors noted that publication bias was present and there may be limited clinical applicability of the dysphagia rating scales.

Xie (2021) published an SR and network meta-analysis of rTMS for lower extremity motor function recovery in stroke patients.[162] A total of 18 RCTs met inclusion criteria. The meta-analysis indicated high-frequency rTMS was superior to sham in promoting lower extremity motor function recovery. Based on the five relevant studies, the meta-analysis also indicated that high-frequency rTMS resulted in higher amplitudes of motor evoked potentials than low-frequency rTMS or sham stimulation.

Dionísio (2018) published an SR on the efficacy of rTMS for recovery of nonmotor functions following stroke.[163] A total of 38 studies met the inclusion criteria on the topics of aphasia, dysphagia, neglect, and visual extinction. No meta-analysis was completed. Most of the included studies had small patient numbers. The authors concluded that the variability that was present in terms of patient selection, treatment protocols, and outcome measures, limits the conclusions that can be drawn.

Zhang (2017) published an SR and meta-analysis evaluating the effects of rTMS on upper-limb motor function after stroke.[164] A search for studies published before October 2016 was performed, yielding 34 RCTs with a total of 904 participants (range, 6 to 108 participants). Pooled estimates found improvement with rTMS for both short-term (SMD=0.43; $p<0.001$) and long-term (SMD=0.49; $p<0.001$) manual dexterity. Of the 28 studies reporting on adverse events, 25 studies noted none. Mild adverse events, such as headache and increased anxiety were reported in three studies. The review was limited by variation in TMS protocols between studies.

Sebastianelli (2017) published an SR including 67 studies on the use of low-frequency rTMS of the unaffected hemisphere in stroke patients.[165] No meta-analyses were included. The SR concluded that rTMS applied to the unaffected hemisphere following stroke appears to be safe and has potential to be a useful adjuvant strategy for neurorehabilitation but that further research is needed.

McIntyre (2017) published an SR on the use of rTMS for spasticity post-stroke. Ten studies met the inclusion criteria, two of which were RCTs.[166] The RCTs were rated on the Physiotherapy Evidence Database with scores of eight to nine. Meta-analyses were conducted separately for the uncontrolled studies and the RCTs. Whereas the uncontrolled pre-post studies found significant improvements in spasticity, the RCTs did not.

A 2017 SR published by Fan included 12 studies total examining the effect of noninvasive brain stimulation in the recovery of unilateral neglect in poststroke patients.[167] Eleven RCTs were included in the meta-analysis. Techniques of noninvasive brain stimulation included transcranial direct current stimulation, theta-burst TMS, and rTMS. The quality of included RCTs was good to excellent, with PEDro scores of eight or nine in seven studies and six to eight in the remainder. A moderate degree of heterogeneity was identified in rTMS and cTBS studies. The meta-analysis showed a significant effect of rTMS immediately following treatment and at follow-up.

In 2016, Graef reported a meta-analysis of rTMS combined with upper-limb training for improving function after stroke.[168] Included were 11 sham-controlled randomized trials with 199 patients that evaluated upper-limb motor/functional status and spasticity; eight RCTs with sufficient data were included in the meta-analysis. These studies were considered to have a low-to-moderate risk of bias. In the overall analysis, there was no benefit of rTMS on upper-limb function or spasticity (SMD=0.03; 95% CI -0.25 to 0.32).

Liao (2016) published a SR that evaluated the impact of rTMS on dysphagia in stroke patients.[169] Six RCTs with a total of 163 patients were reviewed. The authors concluded that patients had improved, four weeks after treatment with low or high frequency rTMS. High frequency rTMS may be more beneficial than low frequency rTMS. This SR did not include long-term outcomes.

A 2015 meta-analysis by Li included four RCTs on rTMS over the right pars triangularis for patients (n=137) with aphasia after stroke.[170] 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 by Le assessed the effect of rTMS on recovery of hand function and excitability of the motor cortex after stroke.[171] 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 (five days to 10 years), in the frequency of rTMS applied (1 Hx to 25 Hx for one 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 (four studies, n=79, standardized mean difference of 0.58) and hand function (three 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 2013 Cochrane review included 19 trials with a total of 588 participants on the effect of TMS for improving function after stroke.[172] The two 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.

Randomized Controlled Trials

Zhong (2023) published an RCT to evaluate the effect of high-frequency cerebellar rTMS on poststroke dysphagia.[173] This was a randomized, sham-controlled, double-blind trial. A total of eighty-four study participants were randomly assigned into the cerebellum and control groups. The cerebellum group received bilateral 10Hz rTMS treatment of the pharyngeal motor area of the cerebellum. The control group was administered with sham rTMS of the pharyngeal motor area of the cerebellum. All patients underwent the same conventional swallowing rehabilitation training after the intervention 5 days a week for a total of 10 days. The interaction between time and intervention had a significant effect on PAS ($P<0.001$) and Fiberoptic Endoscopic Dysphagia Severity Scale (FEDSS) ($P<0.001$). Compared to the control group, the cerebellum group exhibited significantly improved clinical swallowing function scores (PAS: $P=0.007$, FEDSS: $P=0.002$). Bilateral cerebellar rTMS is a potential new neurorehabilitation technique for post-stroke dysphagia. The authors comment on the need for more studies investigating the therapeutic mechanism for cerebellar rTMA.

Wang (2020) conducted an RCT to determine the efficacy of high-frequency TMS over the contralesional motor cortex for motor recovery in severe hemiplegic stroke patients. Patients with ischemic or hemorrhagic stroke in the territory of the middle cerebral artery were

randomized to receive 10 Hz rTMS (n=15), 1 Hz rTMS (n=15) or sham (n=15). Treatment was applied over the contralesional motor cortex (M1) prior to physiotherapy daily for two weeks. Clinical efficacy was assessed by the FMA score (a standardized motor impairment scale) and the Barthel Index (BI; a measure of daily life ability). According to a repeated-measures mixed analysis of variance, all patients had a significant recovery from impairment and improvement in activities of daily living postintervention compared to pre-treatment. There were no statistically significant differences between the 1 Hz rTMS group and the sham group. The 10 Hz rTMS group FMA and BI scores were significantly higher than the 1 Hz rTMS group and the sham group ($p<0.05$ and $p<0.005$, respectively). Neurophysiological measures and muscle activation were also improved in all groups, but significantly greater in the 10 Hz rTMS group ($p<0.05$ for both).

An RCT published by Ren (2019) assessed the use of rTMS over the right pars triangularis of the posterior inferior frontal gyrus (pIFG) and the right posterior superior temporal gyrus (pSMG) for the treatment of poststroke global aphasia. A total of 45 patients were randomized to receive one of three treatments: rTMS over the right triangular part of the pIFG, rTMS over the right pSTG, or sham stimulation. Outcomes reported were aphasia quotient (AQ) scores obtained from the Chinese version of the Western Aphasia Battery (WAB), spontaneous speech, auditory comprehension, and repetition. These were measured at baseline and immediately after three weeks (15 days) of experimental treatment. There were statistically significant increases in the right pSTG rTMS group compared to sham for auditory comprehension, repetition, and AQ ($p<0.05$). There were statistically significant increases in the pIFG rTMS group compared with sham for repetition, spontaneous speech, and AQ ($p<0.05$).

Choi (2018) examined the effects of high frequency rTMS on hemiplegic shoulder pain in patients with chronic stroke.[174] A total of 24 chronic stroke patients with chronic hemiplegic shoulder pain were randomly assigned to receive real rTMS (10 sessions of high-frequency stimulation) or sham rTMS. Pain was evaluated using the Numeric Rating Scale (NRS) at one day and one, two, and four weeks after treatment. Additional measures were changes the Motricity Index (MI-UL) and modified Brunnstrom Classification (MBC), which were used to evaluate changes in upper-limb motor function. There was a significant improvement in the NRS score at all time points in the real rTMS but not sham group. No significant changes were observed in the measures of upper-limb motor function.

Forogh (2017) performed a randomized double-blind sham-controlled trial on TMS for stroke recovery.[175] Twenty-six patients were evaluated. Patients received five days of low-frequency rTMS or sham rTMS. Follow-up was conducted at 12 weeks. Static postural stability, balance, muscle strength, and motor recovery were assessed. Significant differences between real and sham treatment groups were observed for static postural stability, balance, and muscle strength. There was significant improvement in muscle recovery compared to baseline in the real rTMS group. However, the groups were different in this measure at baseline, and they were not significantly different at three or 12 weeks.

Huang (2017) reported results of an RCT on the use of rTMS for the recovery of lower extremities after stroke.[176] Thirty-eight subacute stroke patients with significant leg disabilities received real or sham rTMS followed by 45 minutes of physical therapy for three weeks. Real rTMS consisted of 15 minutes of 1-Hz treatment over the contralesional motor cortex representing the quadriceps muscle. Recovery in ambulation, balance, motor functions, and activities of daily living were assessed. No significant differences between

groups were identified.

Guan (2017) performed a prospective, double-blind, randomized, sham-controlled study to assess the effectiveness of rTMS on motor recovery after stroke.[177] Forty-two were assessed and found eligible for the study and following dropout during the study, 27 were included in the final analysis. Patients were randomized to receive real or sham high-frequency rTMS treatment. Treatment consisted of 10 consecutive days of 5 Hz rTMS applied to the ipsilesional M1. Motor functional scores, including the National Institutes of Health Stroke Scale (NIHSS), Barthel Index (BI), Fugl-Meyer Assessment Upper Limb/Lower Limb (FMA-UL/LL), modified Rank Score (mRS), and the resting motor threshold (RMT) of the hemiplegic limb, were assessed. At one month following treatment, there were significant differences in score improvement from baseline in HIHSS, BI, and FMA-UL. At three months, six months, and one year the only score for which a significant difference in improvement was seen was FMA-UL, representing a lasting improvement in upper extremities function.

Additional RCTs of the efficacy of TMS for post-stroke recover have been published that are preliminary (feasibility) studies and/or have serious methodological limitations, such as very small patient populations or lack of a sham control, that render outcomes unreliable.

Section Summary

Evidence consists of a number of RCTs and SRs 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.

TINNITUS

Systematic Reviews

The Washington HTA published a technology assessment in 2020 that reviewed non-invasive, non-pharmacological treatments for tinnitus. The authors identified a total of 10 parallel-assignment RCTs and 9 crossover RCTs from 19 publications describing results of rTMS stimulation interventions compared to sham stimulation. Intervention protocols were heterogeneous. Most of the 18 RCTs reporting measures of tinnitus distress or disability did not report a significant difference between active and sham rTMS. No significant differences between groups were reported for depression, anxiety, and sleep outcomes in the five RCTs reporting on psychological measures or quality of life in the one reporting RCT. A total of 14 studies reported on adverse events. In five, no adverse events were reported and in three, results were not reported by group. Of the six studies that reported differences by group, three reported similar incidence between groups, two reported higher incidence of adverse events in the active rTMS group and one reported a higher incidence of adverse events in the sham rTMS group.

Randomized Control Trials

In 2017, Sahlsten published a prospective randomized placebo-controlled study to investigate the effects of rTMS using electric field navigation for tinnitus.[179] Thirty-nine patients were randomized to receive 10 sessions of 1 Hz rTMS or placebo targeted to the region of the left auditory cortex corresponding to tonotopic representation of tinnitus pitch. Primary outcomes were tinnitus intensity represented by the visual analogue scores (VAS 0-100), annoyance and distress, and the Tinnitus Handicap Inventory (THI). These were evaluated immediately

following treatment and one, three, and six months later. All measures tested decreased significantly in both groups. No significant differences between groups were reported.

Landgrebe (2017) reported a multicenter randomized, sham-controlled trial that investigated the efficacy and safety of rTMS for chronic tinnitus.[180] A total of 163 patients were randomized to receive real or sham rTMS. Treatment consisted of 10 sessions of 1 Hz to the left temporal cortex. Tinnitus questionnaire scores were taken at baseline and at the end of treatment. The primary outcome was change in this score and secondary outcome measures were depression and quality of life. There were no significant differences in any measures between groups at the end of the trial.

Lehner (2016) published a two-arm parallel group RCT that evaluated 74 patients who received ten sessions of triple-site stimulation (n=25), single-site stimulation (n=24) or placebo (n=25).[181] Patients answered a tinnitus questionnaire day one and 12 and at follow-up three and six months later. The authors concluded rTMS reduces tinnitus severity in both groups the single and triple site groups, with no differences between them. Larger RCTs are needed to determine long-term effects, objective outcomes and appropriate treatment protocols.

OTHER MEDICAL INDICATIONS

SRs and RCTs have been published exploring the efficacy of TMS for a variety of central nervous system-related disorders such as central pain related to spinal cord injury, dysphagia, blepharospasm, amyotrophic lateral sclerosis (ALS), multiple sclerosis, chronic pain, substance abuse, burning mouth syndrome, phantom limb sensations, cravings, traumatic brain injury, concussion, symptom management in breast cancer and Alzheimer's disease.[182-249] 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 RCTs are needed, along with better defined optimal treatment parameters for administering TMS.

PRACTICE GUIDELINE SUMMARY

MOVEMENT DISORDER SOCIETY

The Movement Disorder Society (MDS) published an evidence-based review of treatments for motor (updated in 2018) and non-motor (updated in 2019) symptoms of Parkinson's disease.[250, 251] The reviews found insufficient evidence to make adequate conclusions on the efficacy of rTMS for the treatment of motor symptoms or depression in Parkinson's disease. The MDS did note that evidence regarding TMS treatment of depression in the general population is growing; therefore, it concludes that the practice implication is "possibly useful."

In 2008, the society also conducted a literature review describing current management practices for tic disorder and noted that study results regarding the use of TMS as a treatment for tics varied.[252]

AMERICAN PSYCHIATRIC ASSOCIATION

In 2018, the American Psychiatric Association published consensus recommendations on rTMS for the treatment of depression.[253] 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 APA's guidelines on the treatment of patients with obsessive-compulsive disorder (2007, reaffirmed in 2012) state that "findings of the four 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 NEUROLOGY

The American Academy of Neurology published an evidence-based practice guideline in 2016 on the treatment of restless legs syndrome (RLS) in adults.[254] It stated, "For patients or clinicians wanting to use nonpharmacologic approaches to treat RLS…clinicians may consider prescribing near-infrared spectroscopy (NIRS) or repetitive transcranial magnetic stimulation (rTMS) (where available) (Level C)." This recommendation is based on one Class II study.

DEPARTMENT OF VETERANS AFFAIRS/DEPARTMENT OF DEFENSE

The 2022 Veteran's Affairs/Department of Defense guideline for management of major depressive disorder recommends offering rTMS to patients who have experienced partial response or no response to an adequate trial of 2 or more pharmacologic treatments (strength of recommendation: weak).[255] Recommended options for the second treatment attempt after the initial therapy tried include switching to another antidepressant or adding augmentation therapy with a second-generation antipsychotic. The recommendation for rTMS was graded as weak due to limitations of the available literature including small study effects, high rates of discontinuation, lack of allocation concealment, and the practical limitations of the need for daily treatment and lack of widespread access to facilities that offer this therapy. The guideline also concluded that there is limited evidence to recommend for or against theta-burst stimulation for treatment of depression.

In 2019, the Department of Veterans Affairs (VA)/Department of Defense (DoD) published an update to its 2010 evidence-based clinical practice guideline for the management of stroke rehabilitation.[256] The guideline includes the following recommendation regarding TMS:

> There is insufficient evidence to recommend for or against repetitive transcranial magnetic stimulation to improve upper or lower extremity motor function. (Recommendation rating: Neither For Nor Against; Reviewed, New-added)

A clinical practice guideline on the primary care management of headache published in 2020 by the VA/DoD states that there is insufficient evidence to recommend for or against Transcranial magnetic stimulation for headache (Recommendation rating: Neither For nor Against; Reviewed, New-added).[257]

A clinical practice guideline on management and rehabilitation of post-acute mild traumatic brain injury published in 2021 by the VA/DoD recommends against the use of rTMS for the treatment of symptoms attributed to mild traumatic brain injury (Recommendation rating: Weak Against; Reviewed, New-added).[258]

SUMMARY

It appears that transcranial magnetic stimulation (TMS) may improve depression for some people with major depressive disorder. Despite the weaknesses in the published clinical evidence and limited guideline support, TMS has become a recognized standard of care for treatment resistant major depressive disorder. Therefore, TMS may be considered medically necessary for up to 36 sessions as a treatment of major depressive disorder when policy criteria are met. Additional sessions may be considered medically necessary when continuation criteria are met.

Transcranial magnetic stimulation (TMS) is not clinically indicated for major depressive disorder except in the clinical scenarios addressed in the criteria. Therefore, TMS is considered not medically necessary when Criterion I. is not met.

There is not enough research to show that transcranial magnetic stimulation (TMS) improves health outcomes for any condition other than major depressive disorder. Therefore, TMS is considered investigational as a treatment of all other conditions.

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CODES

Codes	Number	Description
CPT	0858T	Externally applied transcranial magnetic stimulation with concomitant measurement of evoked cortical potentials with automated report
	0889T	Personalized target development for accelerated, repetitive high-dose functional connectivity MRI–guided theta-burst stimulation derived from a structural and resting-state functional MRI, including data preparation and transmission, generation of the target, motor threshold–starting location, neuronavigation files and target report, review and interpretation
	0890T	Accelerated, repetitive high-dose functional connectivity MRI–guided theta-burst stimulation, including target assessment, initial motor threshold determination, neuronavigation, delivery and management, initial treatment day
	0891T	Accelerated, repetitive high-dose functional connectivity MRI–guided theta-burst stimulation, including neuronavigation, delivery and management, subsequent treatment day
	0892T	Accelerated, repetitive high-dose functional connectivity MRI–guided theta-burst stimulation, including neuronavigation, delivery and management, subsequent

Codes	Number	Description
		motor threshold redetermination with delivery and management, per treatment day
	90867	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management
	90868	;subsequent delivery and management, per session
	90869	;subsequent motor threshold re-determination with delivery and management
HCPCS	None	

Date of Origin: *April 2002*