

Transcranial Magnetic Stimulation as a Treatment of Depression and Other Disorders

Effective: May 1, 2018

Next Review: February 2019

Last Review: April 2018

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 all of the following criteria are met (A-C):
 - A. Confirmed diagnosis of severe major depressive disorder (single or recurrent) documented by standardized rating scales (see Policy Guidelines) that reliably measure depressive symptoms; AND
 - B. One of the following conditions is present:

1. Trials of at least four psychopharmacologic regimens, has been ineffective, not tolerated (as evidenced by distinct side effects), or is contraindicated (see Policy Guidelines); OR
 2. History of response to TMS in a previous depressive episode (at least 3 months since the prior episode); OR
 3. Is a candidate for electroconvulsive therapy (ECT) and ECT would not be clinically superior to TMS (e.g., in cases with psychosis, acute suicidal risk, catatonia, or significantly impaired essential function, TMS should not be utilized); AND
- C. Failure of a trial of a psychotherapy (see Policy Guidelines) known to be effective in the treatment of major depressive disorder, conducted for a minimum duration of six weeks at least one time per week, without significant improvement in depressive symptoms, as documented by standardized rating scales (see Policy Guidelines) that reliably measure depressive symptoms.
- II. Transcranial magnetic stimulation (TMS) of the brain is considered **investigational** as a treatment for all other indications, including but not limited to:
- A. Alcohol dependence
 - B. Alzheimer's disease
 - C. Attention deficit hyperactivity disorder (ADHD)
 - D. Autism
 - E. Bipolar mania
 - F. Bulimia nervosa (BN)
 - G. Depression (including major depressive disorder which does not meet criteria I. above)
 - H. Dysphagia
 - I. Epilepsy
 - J. Fibromyalgia
 - K. Migraine
 - L. Obsessive compulsive disorder (OCD)
 - M. Pain
 - N. Panic Disorder
 - O. Parkinson's disease
 - P. Posttraumatic stress disorder (PTSD)
 - Q. Schizophrenia
 - R. Spasticity
 - S. Spinal cord injury
 - T. Stroke rehabilitation
 - U. Tinnitus

V. Tourette's syndrome

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

POLICY GUIDELINES

SUBMISSION OF 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
- Psychotherapy history documenting duration, cadence and depressive symptom response documented by standardized rating scales
- Psychopharmacologic regimen history with documented response

DEPRESSION RATING SCALES

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

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

PSYCHOTHERAPY METHODS

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

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

CONTRAINDICATIONS

Contraindications to TMS include:

- Seizure disorder or any history of seizure with increased risk of future seizure; OR
- Presence of acute or chronic psychotic symptoms or disorders (such as schizophrenia, schizophreniform or schizoaffective disorder) in the current depressive episode; OR
- Neurologic conditions that include epilepsy, cerebrovascular disease, dementia, increased intracranial pressure, having a history of repetitive or severe head trauma, or with primary or secondary tumors in the central nervous system (CNS); OR

- 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.

CROSS REFERENCES

1. [Dopamine Transporter Single-Photon Emission Computed Tomography \(DAT-SPECT\)](#), Radiology, Policy No. 57

BACKGROUND

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 for the treatment of depressive episodes in patients suffering from major depressive disorder who have failed to respond to antidepressant medications in their current episode of depression.
- Cerena™ TMS device (Eneura Therapeutics) received de novo marketing clearance for the acute treatment of pain associated with migraine headache with aura. Warnings, precautions, and contraindications include the following:
 - 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® is 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 for the treatment of major depressive disorder in adults who have failed a six-week course of one antidepressant medication.
- Rapid² Therapy System from Magstim Company Limited 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) is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.

The 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.

DEPRESSION

TMS Compared to Sham

Systematic Reviews and Technology Assessments

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.^[2] 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.

In 2016, the Health Quality Ontario published a meta-analysis of left DLPFC rTMS for treatment-resistant depression (TRD).^[3] 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, $p < 0.001$). This publication also analyzed trials comparing rTMS with ECT, discussed in the section below.

McGirr (2016) performed a meta-analysis to assess the efficacy of TMS for bipolar depression.^[4] 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: 0.06-0.30, $p<0.01$).

Nordenskjöld (2016) published a SR that evaluated ethical and economic factors involving deep transcranial magnetic stimulation (dTMS) using the Hesel-coil (H-coil), an enhanced form of rTMS for patients with depression.^[5] One RCT was identified, which lacked evidence to support dTMS for depression. At this time, the authors stated dTMS should be limited to clinical trials.

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.^[6] 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.

BlueCross BlueShield Association (BCBSA) Technology Evaluation Center (TEC) published three technology assessments on TMS for depression; with the most recent assessment published in 2013.^[7-9]

The 2013 Assessment included seven meta-analyses from 2010 or later, with the four largest meta-analyses including 24-34 trials.^[9] All of these meta-analyses evaluated endpoints at the completion of TMS treatment which was between one and five weeks. Despite the analyses' conclusions that TMS is superior to sham as a short-term treatment of medication-resistant depression; conclusions reached in these studies are uncertain due to the following methodological limitations:

- All seven meta-analyses used the same two randomized trials^[10,11] which employed a “forced dropout strategy” for patients failing to improve after three weeks of active treatment. The incorporation of these studies into a pooled effects analysis may have biased results because randomization was not preserved; therefore, results may not be useful in reaching conclusions regarding treatment effects. Analysis which accounted for this potential confounding factor was not reported;
- Only one of the seven meta-analyses assessed the quality of trials used in pooled analyses and only one analysis addressed issues regarding publication bias;
- No evidence was reported regarding changes or augmentation of anti-depression medication.
- Equivocal efficacy in the three largest sham-controlled trial of TMS;
- Uncertain clinical significance of the short-term anti-depressant effects found in meta-analyses, which are also at high risk of bias due to the inclusion of numerous small trials;

- Limited evidence beyond the acute period of treatment; and
- Lack of comparison with standard therapy (a second course of antidepressant therapy) in the population for whom TMS is indicated (patients who have failed one six-week course of antidepressant medication).

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

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.^[12] 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.”

A 2011 Agency for Healthcare Research and Quality (AHRQ) report, which was considered in the 2013 BCBSA TEC assessment, reported on nonpharmacologic interventions for TRD in adults.^[13] Indirect evidence which compared nonpharmacologic including rTMS, vagus nerve stimulation (VNS), or psychotherapy, with a control or sham procedure in tier 1 populations (i.e., patients had two or more prior treatment failures with medications). The number of these trials with the same or similar control group was very small, so they could not pool them quantitatively. They assessed the potential benefits of nonpharmacologic interventions versus controls by calculating mean changes in depressive severity, relative risks of response, and relative risks of remission.

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

The authors of the AHRQ report identified three fair trials compared rTMS with a sham procedure and found no significant differences. However, too few patients were followed

during the relapse prevention phases in two of the three studies, and patients in the third received a co-intervention providing insufficient evidence for a conclusion.

A Cochrane SR included 16 RCTs. The authors concluded that there was no strong evidence of benefit from TMS when used in the treatment of depression, finding no difference between TMS and sham TMS based on results of the Beck Depression Inventory or Hamilton Depression Rating Scale (HDRS).^[14]

Berlim (2013) reported a SR on the effect of rTMS for accelerating and enhancing the clinical response to antidepressants.^[15] Data were obtained from six double-blind RCTs with a total of 392 patients. Response was defined as a 50% or greater reduction in the HDRS or the Montgomery-Asberg Depression Rating Scale (MADRS). At an average of 2.7 weeks after the start of the combined treatments, response rates were significantly higher with rTMS + antidepressant treatment compared to sham rTMS (43.3% vs 26.8%; odds ratio [OR] =2.50; $p=.025$); however, remission rates were not significantly different. At the end of the studies (average of 6.8 weeks), response and remission rates were significantly higher with combined high-frequency rTMS + antidepressant treatment compared to sham rTMS (response: 62% vs 46%, OR =1.9, $p=0.49$; remission: 53.8% vs 38.6%, OR 2.42, $p=.007$).

Additional reviews of RCTs exhibited consistent results.^[16-19] Each analysis identified a number of limitations of the included studies such as small patient populations, short study time-lines, confounding co-therapies, and inconsistency with TMS treatment parameters. The meta-analyses concluded that TMS indicated some effect when compared to the sham groups, but the clinical significance of this effect and its impact on health outcomes was not demonstrated. The above analyses concluded that additional, larger long-term studies were needed to better define optimal treatment parameters including frequency, positioning, and equipment for TMS.

Randomized Controlled Trials

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.^[20] 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.

Fitzgerald (2016) published a two arm parallel design RCT evaluating rTMS for patients with refractory bipolar depression.^[21] 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.

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.^[22-29]
- There were significant (greater than 10%) or unclear loss to follow-up and/or poorly defined intention-to-treat (ITT) analyses.^[22-28,30,31]
- 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.^[22-27,30,32-34]
- Follow-up of all study subjects was over a short period of time, less than six months, so durability of the results is unknown.^[22-32,34-37]
- Study populations were small, less than 100 patients total, making results unreliable and difficult to apply to patients requiring treatment in the general population.^[22-27,29-32,34-36,38-45]
- 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.^[29]
- 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).^[23-25,29,30,32,35,36]
- 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.^[22-25,27,30,32,36]
- Studies used previously published unreliable data for new and/or further analyses.^[46,47]

TMS Compared to Electroconvulsive Therapy

Systematic Reviews and Technology Assessments

Kedzior (2017) published an SR assessing cognitive outcomes following high-frequency rTMS versus electroconvulsive therapy (ECT).^[48] 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.

Sehatzadeh (2016) published a Health Quality Ontario technology assessment evaluating the impact on health outcomes when patients with refractory unipolar depression received rTMS.^[3] Twenty-nine RCTs were identified, of which 27 compared rTMS to sham and six compared rTMS to ECT. 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 are shown in Table 1 which favor ECT but was not statistically significant. Remission and relapse rates at the 6-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.

Berlim (2013) identified seven RCTs with a total of 294 patients that directly compared rTMS and ECT treatment for patients with major depression.^[49] After an average of 15.2 sessions of high-frequency rTMS, 33.6% of patients were classified as remitters compared to 52% of patients who were classified as remitters following an average of 8.2 ECT sessions. The pooled odds ratio was 0.46, indicating a significant difference ($p=0.04$) in outcome favoring ECT. There was no significant difference in dropout rates for the two treatments

The 2011 AHRQ report, noted above, found the available head-to-head literature concerning the efficacy of the nonpharmacologic interventions for tier one TRD was limited to two fair trials (both in major depressive disorder-only populations).^[13] One compared electroconvulsive therapy (ECT) and rTMS, and the other compared ECT and ECT plus rTMS. They showed, with low strength of evidence, no differences between treatment options for depressive severity, response rates, and remission rates. No trial involved a direct comparison of psychotherapy with another nonpharmacologic intervention and there were no trials identified which directly compared rTMS to any other intervention for maintenance of remission or prevention of relapse.

The AHRQ authors concluded, “that comparative clinical research on nonpharmacologic interventions in a TRD population is in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data was substantially hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence is for ECT and rTMS; however, even for the few comparisons of treatments that are supported by some evidence, the strength of evidence is low for comparative benefits,” reflecting low confidence that the evidence reflects the true effect and indicating that further research is likely to change the confidence in these findings. The finding of low strength is most notable in two cases: ECT and rTMS did not produce different clinical outcomes in TRD, and ECT produced better outcomes than pharmacotherapy.

The AHRQ report further concluded, “no trials directly compared the likelihood of maintaining remission for nonpharmacologic interventions. The few trials addressing adverse events, subpopulations, subtypes, and health-related outcomes provided low or insufficient evidence of differences between nonpharmacologic interventions. The most urgent next steps for research are to apply a consistent definition of TRD, to conduct more head-to-head clinical trials comparing nonpharmacologic interventions with themselves and with pharmacologic treatments, and to delineate carefully the number of treatment failures following a treatment attempt of adequate dose and duration in the current episode.”

Rosa (2006) reported no significant difference between ECT and TMS in forty-two patients with treatment-resistant depression; however, response rates for both groups were low.^[50] The number of remissions (score of seven or less on the HDRS) totaled three (20%) for ECT and two (10%) for TMS.

The 2001 Cochrane Review found electroconvulsive therapy was more effective than TMS.^[14]

Randomized Controlled Trials

No RCTs were identified, after the above SRs.

Section Summary

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

POST TRAUMATIC STRESS DISORDER

Systematic Review

Trevizol (2016) published a SR to evaluate the effects of rTMS on post-traumatic stress disorder (PTSD).^[51] The five studies included showed rTMS statistically superior to sham stimulation (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

No RCTs were identified.

SCHIZOPHRENIA

Systematic Reviews and Technology Assessments

Dollfus (2016) published a SR to evaluate the impact of the placebo effect in studies involving rTMS on visual hallucinations for patients with schizophrenia.^[52] Twenty-one articles with 303 patients were reviewed. The authors concluded that the placebo in rTMS studies cause bias and that the design of such studies should be carefully evaluated.

A 2015 Cochrane SR included 41 studies with a total of 1473 participants.^[53] 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 2013 SR included 17 RCTs (n=398) that evaluated low-frequency rTMS of the left temporoparietal cortex for the treatment of auditory hallucinations.^[54] The mean effect size for severity of auditory hallucinations (all studies) was -0.42. The odds ratio for the response to

treatment, defined as a 30% reduction or greater, was 2.94 (6 trials, n=181). No significant differences were found between active rTMS and sham for positive or negative symptoms.

A 2012 SR included 17 double blind sham RCTs (total n=337) of the effect of TMS on auditory hallucinations.^[55] When measured at the end of treatment, the mean effect size of TMS directed at the left temporoparietal area was 0.40 (moderate) and the effect size of TMS directed at all brain regions was 0.33 (small). For the five trials that examined outcomes of TMS one month after treatment, the effect was no longer significant.

A 2011 BCBSA TEC Assessment evaluated TMS as an adjunct treatment for schizophrenia.^[56] 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

Li (2016) published a RCT evaluating the efficacy of rTMS in patients with Schizophrenia.^[57] Forty-seven patients received rTMS over the left dorsolateral prefrontal cortex (n=25) or sham stimulation (n= 22). Patients were evaluated at baseline, four weeks and eight weeks, using the Scale for the Assessment of Negative Symptoms (SANS). No significant differences were seen at two weeks, but at eight weeks the SANS score improved significantly in the rTMS group vs. the control group. The authors concluded there is a delayed positive effect in symptoms, for schizophrenia patients receiving rTMS. This study was limited in size and did not include follow-up past eight weeks.

Hasan (2016) published a multi-center sham-controlled RCT that evaluated rTMS impact on cognitive function i.e. working memory, attention, and verbal learning in patients with schizophrenia.^[58] 156 schizophrenia patients with mainly negative symptoms received 10-Hz rTMS (n=77) or sham stimulation (n=79) for 15 sessions over three weeks. Assessments occurred two weeks prior to treatment and at days 21, 45, and 105. Data did not show statistically significant positive cognitive changes for the rTMS group. The authors concluded more multi-center RCTs are needed.

Koops (2016) published a double-blinded RCT that evaluated how Theta-burst (TB) rTMS impacted auditory verbal hallucinations (AVH) in schizophrenic patients refractory to medications.^[59] Seventy-one patients received TB rTMS or sham stimulation for six visits. Evaluation occurred at baseline, after six treatments, within one week and at a follow-up one month later using the Psychotic Symptom Rating Scale (PSYRATS) and the Auditory Hallucinations Rating Scale (AHRs). No difference in outcomes was seen by either group.

Blumberger examined the efficacy of priming stimulation (6 Hz) prior to low frequency stimulation (1 Hz) of Heschl's gyrus within the left temporoparietal cortex.^[60] Fifty-four patients with medication resistant auditory hallucinations were randomized to receive 20 sessions of left-sided stimulation, priming, or sham TMS. Response rates on the Psychotic Symptoms Rating Scale did not differ between the three treatment groups.

A small (n=18) double-blind sham-controlled RCT from 2012 found no significant effect of deep TMS with an H1 coil on auditory hallucinations.^[61]

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.

OTHER PSYCHIATRIC DISORDERS

Systematic Reviews

Zhou (2017) published an SR that analyzed 20 sham-controlled studies with 791 patients examining the effect of rTMS on obsessive compulsive disorder (OCD).^[62] Results of a meta-analysis indicated a large effect size for therapeutic effect ($g=0.71$; 95%CI, 0.55-0.87; $P<0.001$). Significant improvements over sham treatment were seen for rTMS targeting the supplementary motor area, left dorsolateral prefrontal cortex (DLPFC), bilateral DLPFC, 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 2017 SR published by Cheng analyzed studies that used rTMS for patients with mild to moderate Alzheimer's disease.^[63] 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.

A 2014 Cochrane review identified two RCTs with a total of 40 patients that compared low frequency rTMS with sham rTMS.^[64] 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.

A 2013 SR included 10 small RCTs totaling 282 patients with OCD.^[65] Response rates of TMS augmentation therapy were 35% for active treatment and 13% for sham TMS. The pooled odds ratio (OR) was 3.39 and the number needed to treat (NNT) was five. There was no reported evidence of publication bias. Exploratory subgroup analysis suggested that the two most promising stimulation parameters were low frequency-TMS and non-dorsolateral prefrontal cortex (DLPFC) regions (i.e., orbitofrontal cortex or supplementary motor area); however, additional studies are needed to evaluate low frequency TMS and non-DLPFC regions.

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, obsessive- OCD, panic disorder, alcohol dependence, Alzheimer's disease, and ADHD. Many of these studies

are preliminary (feasibility) studies and/or have serious methodological limitations that render outcomes unreliable. Some limitations of these studies include:

- Poorly defined or unmet endpoints^[66-73]
- Significant or unclear loss to follow-up and poorly defined intention-to-treat (ITT) analyses^[68,72,74-76]
- Lack of long-term follow up^[66-83]
- Small patient populations^[66-79,84-94]
- Lack of standardized optimal treatment parameters^[66-71,73-77,79,95]
- Use of co-therapies^[66-78]
- Strict inclusion/exclusion criteria which were not representative of patients requiring treatment in the general population^[66-71,74,77-79]

Section Summary

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

BULIMIA

Systematic Reviews

No SRs were identified.

Randomized Control Trials

Gay (2016) published a double-blind randomized trial that evaluated the safety and efficacy of rTMS, for patients with bulimia nervosa.^[96] Forty-seven woman with bulimia nervosa received ten sessions of high frequency rTMS or sham stimulation to the left dorsolateral prefrontal cortex (DLPFC). Follow-up occurred at 15 days post treatment and no improvements in binge symptoms were seen, within the rTMS group. The authors noted additional studies need to evaluate the methodology applied and consider rTMS to different target areas.

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.^[97] 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

Chen (2016) published a Cochrane SR that included seven RCTs to evaluate the effects of rTMS on health outcomes for patients with drug-resistant epilepsy.^[98] Five of the RCTs were randomized and 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 five 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.^[99] 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

Seynaeve (2015) published a single-center randomized sham-controlled crossover clinical trial that determined if rTMS could reduce seizure activity in patients with epilepsy.^[100] Eleven patients were enrolled and received either a figure-eight, round or sham coil. Fifteen thousand stimulations were received/day for ten weekdays; then patients were observed for the next ten weeks. The study concluded rTMS was not effective in reducing seizure activity and could actually increase seizure activity.

Sun (2012) reported a double-blind RCT of low frequency TMS to the epileptogenic zone for refractory partial epilepsy.^[101] Sixty patients were randomized into two groups; one group received two weeks of TMS at 90% of resting motor threshold and the other group received TMS at 20% of resting motor threshold. Outcomes were measured for eight weeks after the end of treatment. With intent-to-treat analysis, high intensity TMS resulted in a significant decrease in seizures when compared to baseline (from 8.9 per week at baseline to 1.8 per week at follow-up) and when compared to low intensity TMS (from 8.6 at baseline to 8.4 per week at follow-up). High intensity TMS also decreased interictal discharges (from 75.1 to 33.6 per hour) and improved ratings on the Symptom Checklist-90. These initial results are promising, but require substantiation in additional trials.

FIBROMYALGIA

Systematic Review

In 2017, Saltychev and Laimi published a meta-analysis of rTMS for the treatment of patients with fibromyalgia.^[102] 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.^[103] 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.^[104] 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 ($n \leq 40$), 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

A 2013 RCT evaluated the effect of very low-intensity TMS in a sham-controlled double-blinded RCT of 54 patients with fibromyalgia.^[105] TMS was performed once per week, for six weeks with 33 magnetic coils around the head. Authors reported a significant improvement in pain thresholds (+28%) across the eight sessions and in the ability to perform daily activities (11%), perceived chronic pain (-39%) and sleep quality (75%). Fatigue, anxiety, depression, and severity of headaches were unaffected by treatment. Limitations of this study include small sample size and lack of long-term follow-up limiting conclusions regarding the benefit of TMS treatment for symptoms related to fibromyalgia.

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

Lan (2017) performed a meta-analysis that included five RCTs and 313 migraine patients.^[106] 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

Leung (2015) published a RCT that evaluated how rTMS improved headaches for military patients with mild traumatic brain injury (MTBI).^[107] 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 long-term sustained impact.

Rapinesi (2016) published a RCT that evaluated the impact of dTMS on chronic migraines (CM).^[108] 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

Gao (2017) published an SR that evaluated two RCTs and four cross-over RCTs. A total of 127 patients with neuropathic pain following a spinal cord injury were treated with rTMS or sham rTMS. Patients who received rTMS had pain relief that was numerically better but not statistically significant than sham-treated patients. The authors noted that more studies are needed to confirm the health outcome impact of rTMS for neuropathic pain.

Randomized Control Trials

Ambriz-Tututi (2016) published a RCT that evaluated the impact of rTMS on patients with chronic low back pain.^[109] 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.^[110] 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.^[111]

PARKINSON'S DISEASE

Systematic Reviews

Qin (2018) published a meta-analysis of RCTs examining high-frequency rTMS for Parkinson's disease (PD).^[112] 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.^[113] 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.^[114] 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.^[115] 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.^[116] 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

Cohen (2018) reported a double-blind, randomized, sham-controlled study to assess repetitive deep TMS for PD.^[117] 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.^[118] 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.^[115] 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.^[119] 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.^[120] 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

Sebastianelli (2017) published an SR including 67 studies on the use of low-frequency rTMS of the unaffected hemisphere in stroke patients.^[121] 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.^[122] 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.^[123] 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.^[124] 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.^[125] 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.^[126] 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.^[127] 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 (4 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.^[128] 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.

Hsu reported a meta-analysis on the effect of TMS on upper limb motor function in patients with stroke in 2012.^[129] Eighteen RCTs with a total of 392 patients were included in the meta-analysis. Most of the studies were double blind (n=11) or single blind (n=3). Eight studies applied low frequency (1 Hz) TMS over the unaffected hemisphere, five applied high frequency (5 Hz) TMS over the affected hemisphere, and two used both low- and high-frequency stimulation. Outcomes included kinematic motion analyses (five trials), hand grip (two trials), and the Wolf Motor Function Test (two trials). Meta-analysis of results showed a moderate effect size (0.55) for TMS on motor outcome, with a greater effect size of TMS in patients with subcortical stroke (mean effect size, 0.73) compared to non-specified lesion sites (mean effect size, 0.45), and for studies applying low frequency TMS (mean effect size, 0.69) compared to high frequency TMS (effect size, 0.41). Effect size of 0.5 or greater was considered to be clinically meaningful.

Randomized Controlled Trials

Choi (2018) examined the effects of high frequency rTMS on hemiplegic shoulder pain in patients with chronic stroke.^[130] 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.^[131] 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.^[132] 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.^[133] 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.

Park (2016) published a single-blind RCT with a blind observer.^[134] Thirty-five stroke patients received bilateral rTMS, unilateral rTMS, or sham stimulation for two weeks. Patients were evaluated at baseline, after the intervention and at a three-week follow-up. Although the authors stated bilateral rTMS is an effective additional treatment for dysphagia, this study was limited in size and did not evaluate long-term outcomes.

Du (2016) published a RCT that evaluated the impact of low or high frequency rTMS on dysphagia for post-stroke patients.^[135] Patients received five sessions of sham, 3-Hz ipsilesional, or 1-Hz contralesional rTMS. Evaluation occurred at baseline, and at the first, second and third month after treatment. The authors concluded high and low frequency rTMS appear to improve swallowing function in the early stroke phase.

In 2012, Seniow reported a randomized double-blind sham-controlled pilot study of low frequency TMS (1 Hz at 90% of resting motor threshold for 30 min) to the contralesional motor cortex combined with physiotherapy in patients with moderate upper extremity hemiparesis following stroke.^[136] Power analysis indicated that a sample size of 129 patients would be required to detect changes in functional motor ability, but only 40 patients met eligibility criteria over the four years of the study. Blinded analysis showed no significant difference in hand function or level of neurological deficit between active or sham TMS when measured either immediately after the three-week intervention or at 3-month follow-up.

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

No SRs were identified.

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.^[137] 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.^[138] 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).^[139] 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 migraine headaches, central pain related to spinal cord injury, tinnitus, dysphagia, blepharospasm, amyotrophic lateral sclerosis (ALS), chronic pain, substance abuse, cravings and Alzheimer's disease.^[95,140-188] In addition, symptom management in breast cancer has been examined as well.^[189] 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 rRCTs are needed, along with better defined optimal treatment parameters for administering TMS.

Umezaki (2015) published a single-blind RCT to evaluate the impact of rTMS on burning mouth syndrome (BMS).^[190] Patients received rTMS (n=12) or sham TMS nine(n=8). Patients were assessed until two months after treatment. The authors concluded the BMS pain improved two weeks into treatment, but more studies are needed to refine and improve TMS for BMS.

PRACTICE GUIDELINE SUMMARY

MOVEMENT DISORDER SOCIETY

The Movement Disorder Society (MDS) published an evidence-based review of treatments for motor (published in 2012) and non-motor (published in 2011) symptoms of Parkinson's disease.^[191,192] The review found insufficient evidence to make adequate conclusions on the efficacy of rTMS for the treatment of depression in Parkinson's disease. In a 2012 update, MDS did note that evidence regarding TMS treatment of depression is growing;^[193] however, data was still found to be insufficient for the recommendation of TMS as a treatment in Parkinson's patients with depression.

In 2008, the society also conducted a literature review describing current management practices for tic disorder and noted that study results regarding the use of TMS as a treatment for tics varied.^[194]

AMERICAN PSYCHIATRIC ASSOCIATION

In 2010, and reaffirmed in 2015, the American Psychiatric Association (APA) published an evidence-based guideline on treatment of patients with major depressive disorder.^[1] The guideline concluded that the evidence on TMS consists of studies with methodological limitations and inconsistent findings. For example, the guideline noted that “a substantial number of studies of TMS have been conducted, but most have had small sample sizes, and the studies overall have yielded heterogeneous results. Further complicating the interpretation of the TMS literature is the variability in stimulation intensities (relative to the motor threshold), stimulus parameters (e.g., pulses/second, pulses/session), anatomical localization of stimulation, and number of TMS sessions in the treatment course.” The guideline also concluded that, based on the available evidence, TMS appears to be safe and well tolerated. However, the evidence is less consistent concerning the efficacy of TMS treatment. The guideline states that TMS “has shown small to moderate benefits in most [i.e. four] but not all [i.e. two] clinical trials and recent meta-analyses.” Given the evidence, the guideline lists TMS as a treatment option for patients who do not respond adequately to pharmacotherapy; however, the guideline does not include a strong recommendation for this treatment.

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

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

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.^[195] 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.

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 as a treatment of major depressive disorder when policy criteria are met.

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

REFERENCES

1. Practice guideline for the treatment of patients with major depressive disorder, third edition. [cited 3/7/2018]; Available from: <https://www.guidelines.gov/summaries/summary/24158/practice-guideline-for-the-treatment-of-patients-with-major-depressive-disorder-third-edition?q=transcranial+magnetic+stimulation>
2. Martin, DM, McClintock, SM, Forster, JJ, Lo, TY, Loo, CK. Cognitive enhancing effects of rTMS administered to the prefrontal cortex in patients with depression: A systematic review and meta-analysis of individual task effects. *Depression and anxiety*. 2017 Nov;34(11):1029-39. PMID: 28543994
3. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Ontario health technology assessment series*. 2016;16(5):1-66. PMID: 27099642
4. McGirr, A, Karmani, S, Arsappa, R, et al. Clinical efficacy and safety of repetitive transcranial magnetic stimulation in acute bipolar depression. *World Psychiatry*. 2016;15(1):85-6. PMID: PMC4780310
5. Nordenskjold, A, Martensson, B, Pettersson, A, Heintz, E, Landen, M. Effects of Hesel-coil deep transcranial magnetic stimulation for depression - a systematic review. *Nordic journal of psychiatry*. 2016 Oct;70(7):492-7. PMID: 27093104
6. Kedzior, KK, Gierke, L, Gellersen, HM, Berlim, MT. Cognitive functioning and deep transcranial magnetic stimulation (DTMS) in major psychiatric disorders: A systematic review. *Journal of psychiatric research*. 2016 Apr;75:107-15. PMID: 26828370
7. TEC Assessment "Transcranial magnetic stimulation for depression." BlueCross BlueShield Association Technology Evaluation Center, Vol. 26, Tab 3.
8. TEC Assessment 2009. "Transcranial magnetic stimulation for depression." BlueCross BlueShield Association Technology Evaluation Center, Vol. 24, Tab 5.
9. TEC Assessment 2013. "Transcranial Magnetic Stimulation for Depression." BlueCross BlueShield Association Technology Evaluation Center, Vol. 28, Tab 9.
10. George, MS, Lisanby, SH, Avery, D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry*. 2010 May;67(5):507-16. PMID: 20439832
11. O'Reardon, JP, Solvason, HB, Janicak, PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. 2007 Dec 1;62(11):1208-16. PMID: 17573044
12. Washington State Health Care Authority, Health Technology Assessment: Nonpharmacologic Treatments for Treatment-Resistant Depression. [cited 3/7/2018]; Available from: [http://www.hca.wa.gov/assets/program/trd_final_findings_decision_052014\[1\].pdf](http://www.hca.wa.gov/assets/program/trd_final_findings_decision_052014[1].pdf)
13. Gaynes, BN, Lux, LJ, Lloyd, SW, et al. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. *AHRQ Comparative Effectiveness Reviews*. 2011. PMID: 22091472

14. Rodriguez-Martin, JLR, Barbanoj-Rodriguez, MJ, Schlaepfer, TE, et al. Transcranial magnetic stimulation for treating depression (Cochrane Review). *The Cochrane Library*. 2001(4). PMID: No PMID Entry
15. Berlim, MT, Van den Eynde, F, Daskalakis, ZJ. High-frequency repetitive transcranial magnetic stimulation accelerates and enhances the clinical response to antidepressants in major depression: a meta-analysis of randomized, double-blind, and sham-controlled trials. *J Clin Psychiatry*. 2013 Feb;74(2):e122-9. PMID: 23473357
16. Burt, T, Lisanby, SH, Sackeim, HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int J Neuropsychopharmacol*. 2002 Mar;5(1):73-103. PMID: 12057034
17. Holtzheimer, PE, 3rd, Russo, J, Avery, DH. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacol Bull*. 2001 Autumn;35(4):149-69. PMID: 12397863
18. Martin, JL, Barbanoj, MJ, Schlaepfer, TE, Thompson, E, Perez, V, Kulisevsky, J. Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis. *Br J Psychiatry*. 2003 Jun;182:480-91. PMID: 12777338
19. Couturier, JL. Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: a systematic review and meta-analysis. *J Psychiatry Neurosci*. 2005 Mar;30(2):83-90. PMID: 15798783
20. Tavares, DF, Myczkowski, ML, Alberto, RL, et al. Treatment of Bipolar Depression with Deep TMS: Results from a Double-Blind, Randomized, Parallel Group, Sham-Controlled Clinical Trial. England, 2017. p. 2593-601.
21. Fitzgerald, PB, Hoy, KE, Elliot, D, McQueen, S, Wambeek, LE, Daskalakis, ZJ. A negative double-blind controlled trial of sequential bilateral rTMS in the treatment of bipolar depression. *J Affect Disord*. 2016 Jul 01;198:158-62. PMID: 27016659
22. Fregni, F, Santos, CM, Myczkowski, ML, et al. Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2004 Aug;75(8):1171-4. PMID: 15258224
23. Poulet, E, Brunelin, J, Boeue, C, et al. Repetitive transcranial magnetic stimulation does not potentiate antidepressant treatment. *Eur Psychiatry*. 2004 Sep;19(6):382-3. PMID: 15363481
24. Fitzgerald, PB, Benitez, J, de Castella, A, Daskalakis, ZJ, Brown, TL, Kulkarni, J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry*. 2006 Jan;163(1):88-94. PMID: 16390894
25. Isenberg, K, Downs, D, Pierce, K, et al. Low frequency rTMS stimulation of the right frontal cortex is as effective as high frequency rTMS stimulation of the left frontal cortex for antidepressant-free, treatment-resistant depressed patients. *Ann Clin Psychiatry*. 2005 Jul-Sep;17(3):153-9. PMID: 16433057
26. Avery, DH, Holtzheimer, PE, 3rd, Fawaz, W, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biol Psychiatry*. 2006 Jan 15;59(2):187-94. PMID: 16139808
27. Rossini, D, Magri, L, Lucca, A, Giordani, S, Smeraldi, E, Zanardi, R. Does rTMS hasten the response to escitalopram, sertraline, or venlafaxine in patients with major depressive disorder? A double-blind, randomized, sham-controlled trial. *J Clin Psychiatry*. 2005 Dec;66(12):1569-75. PMID: 16401159

28. Avery, DH, Isenberg, KE, Sampson, SM, et al. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. *J Clin Psychiatry*. 2008 Mar;69(3):441-51. PMID: 18294022
29. Myczkowski, ML, Dias, AM, Luvisotto, T, et al. Effects of repetitive transcranial magnetic stimulation on clinical, social, and cognitive performance in postpartum depression. *Neuropsychiatric disease and treatment*. 2012;8:491-500. PMID: 23118543
30. Anderson, IM, Delvai, NA, Ashim, B, et al. Adjunctive fast repetitive transcranial magnetic stimulation in depression. *Br J Psychiatry*. 2007 Jun;190:533-4. PMID: 17541116
31. Mogg, A, Pluck, G, Eranti, SV, et al. A randomized controlled trial with 4-month follow-up of adjunctive repetitive transcranial magnetic stimulation of the left prefrontal cortex for depression. *Psychol Med*. 2008 Mar;38(3):323-33. PMID: 17935639
32. Fitzgerald, PB, Hoy, K, McQueen, S, et al. Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol*. 2008 Feb;28(1):52-8. PMID: 18204341
33. Janicak, PG, Nahas, Z, Lisanby, SH, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. *Brain Stimul*. 2010 Oct;3(4):187-99. PMID: 20965447
34. Ullrich, H, Kranaster, L, Sigges, E, Andrich, J, Sartorius, A. Ultra-high-frequency left prefrontal transcranial magnetic stimulation as augmentation in severely ill patients with depression: a naturalistic sham-controlled, double-blind, randomized trial. *Neuropsychobiology*. 2012;66(3):141-8. PMID: 22948250
35. Dang, T, Avery, DH, Russo, J. Within-session mood changes from TMS in depressed patients. *J Neuropsychiatry Clin Neurosci*. 2007 Fall;19(4):458-63. PMID: 18070851
36. Jorge, RE, Moser, DJ, Acion, L, Robinson, RG. Treatment of vascular depression using repetitive transcranial magnetic stimulation. *Arch Gen Psychiatry*. 2008 Mar;65(3):268-76. PMID: 18316673
37. Wang, YM, Li, N, Yang, LL, et al. Randomized controlled trial of repetitive transcranial magnetic stimulation combined with paroxetine for the treatment of patients with first-episode major depressive disorder. *Psychiatry Res*. 2017 Aug;254:18-23. PMID: 28441583
38. Triggs, WJ, Ricciuti, N, Ward, HE, et al. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: a randomized, sham-controlled trial. *Psychiatry Res*. 2010 Aug 15;178(3):467-74. PMID: 20643486
39. Levkovitz, Y, Harel, EV, Roth, Y, et al. Deep transcranial magnetic stimulation over the prefrontal cortex: evaluation of antidepressant and cognitive effects in depressive patients. *Brain Stimul*. 2009 Oct;2(4):188-200. PMID: 20633419
40. Sobis, J, Jarzab, M, Hese, RT, et al. Therapeutic efficacy assessment of weak variable magnetic fields with low value of induction in patients with drug-resistant depression. *J Affect Disord*. 2010 Jun;123(1-3):321-6. PMID: 19896204
41. Hoepfner, J, Padberg, F, Domes, G, et al. Influence of repetitive transcranial magnetic stimulation on psychomotor symptoms in major depression. *Eur Arch Psychiatry Clin Neurosci*. 2010 Apr;260(3):197-202. PMID: 19680706
42. Bares, M, Kopecek, M, Novak, T, et al. Low frequency (1-Hz), right prefrontal repetitive transcranial magnetic stimulation (rTMS) compared with venlafaxine ER in the treatment of resistant depression: a double-blind, single-centre, randomized study. *J Affect Disord*. 2009 Nov;118(1-3):94-100. PMID: 19249105

43. Ray, S, Nizamie, SH, Akhtar, S, Praharaj, SK, Mishra, BR, Zia-ul-Haq, M. Efficacy of adjunctive high frequency repetitive transcranial magnetic stimulation of left prefrontal cortex in depression: a randomized sham controlled study. *J Affect Disord.* 2011 Jan;128(1-2):153-9. PMID: 20621361
44. Anderson, BS, Kavanagh, K, Borckardt, JJ, et al. Decreasing procedural pain over time of left prefrontal rTMS for depression: initial results from the open-label phase of a multi-site trial (OPT-TMS). *Brain Stimul.* 2009 Apr;2(2):88-92. PMID: 20161310
45. Dolberg, OT, Dannon, PN, Schreiber, S, Grunhaus, L. Transcranial magnetic stimulation in patients with bipolar depression: a double blind, controlled study. *Bipolar Disord.* 2002;4 Suppl 1:94-5. PMID: 12479689
46. Janicak, PG, O'Reardon, JP, Sampson, SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *J Clin Psychiatry.* 2008 Feb;69(2):222-32. PMID: 18232722
47. Lisanby, SH, Husain, MM, Rosenquist, PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology.* 2009 Jan;34(2):522-34. PMID: 18704101
48. Kedzior, KK, Schuchinsky, M, Gerkensmeier, I, Loo, C. Challenges in comparing the acute cognitive outcomes of high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) vs. electroconvulsive therapy (ECT) in major depression: A systematic review. *Journal of psychiatric research.* 2017 Aug;91:14-7. PMID: 28288306
49. Berlim, MT, Van den Eynde, F, Daskalakis, ZJ. Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. *Depression and anxiety.* 2013 Jul;30(7):614-23. PMID: 23349112
50. Rosa, MA, Gattaz, WF, Pascual-Leone, A, et al. Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. *Int J Neuropsychopharmacol.* 2006 Dec;9(6):667-76. PMID: 16923322
51. Trevizol, AP, Barros, MD, Silva, PO, Osuch, E, Cordeiro, Q, Shiozawa, P. Transcranial magnetic stimulation for posttraumatic stress disorder: an updated systematic review and meta-analysis. *Trends in psychiatry and psychotherapy.* 2016 Jan-Mar;38(1):50-5. PMID: 27074341
52. Dollfus, S, Lecardeur, L, Morello, R, Etard, O. Placebo Response in Repetitive Transcranial Magnetic Stimulation Trials of Treatment of Auditory Hallucinations in Schizophrenia: A Meta-Analysis. *Schizophr Bull.* 2016;42:301-8. PMID: 26089351
53. Dougall, N, Maayan, N, Soares-Weiser, K, McDermott, LM, McIntosh, A. Transcranial magnetic stimulation (TMS) for schizophrenia. *Cochrane Database Syst Rev.* 2015;8:CD006081. PMID: 26289586
54. Zhang, Y, Liang, W, Yang, S, Dai, P, Shen, L, Wang, C. Repetitive transcranial magnetic stimulation for hallucination in schizophrenia spectrum disorders: A meta-analysis. *Neural Regen Res.* 2013;8:2666-76. PMID: 25206578
55. Slotema, CW, Aleman, A, Daskalakis, ZJ, Sommer, IE. Meta-analysis of repetitive transcranial magnetic stimulation in the treatment of auditory verbal hallucinations: update and effects after one month. *Schizophr Res.* 2012 Dec;142(1-3):40-5. PMID: 23031191

56. TEC Assessment "Transcranial magnetic stimulation for the treatment of schizophrenia." BlueCross BlueShield Association Technology Evaluation Center, Vol. 26, Tab 6.
57. Li, Z, Yin, M, Lyu, XL, Zhang, LL, Du, XD, Hung, GC. Delayed effect of repetitive transcranial magnetic stimulation (rTMS) on negative symptoms of schizophrenia: Findings from a randomized controlled trial. *Psychiatry Res.* 2016 Jun 30;240:333-5. PMID: 27138827
58. Hasan, A, Guse, B, Cordes, J, et al. Cognitive Effects of High-Frequency rTMS in Schizophrenia Patients With Predominant Negative Symptoms: Results From a Multicenter Randomized Sham-Controlled Trial. *Schizophr Bull.* 2016;42:608-18. PMID: 26433217
59. Koops, S, van Dellen, E, Schutte, MJ, Nieuwdorp, W, Neggers, SF, Sommer, IE. Theta Burst Transcranial Magnetic Stimulation for Auditory Verbal Hallucinations: Negative Findings From a Double-Blind-Randomized Trial. *Schizophr Bull.* 2016;42:250-7. PMID: 26221051
60. Blumberger, DM, Christensen, BK, Zipursky, RB, et al. MRI-targeted repetitive transcranial magnetic stimulation of Heschl's gyrus for refractory auditory hallucinations. *Brain Stimul.* 2012 Oct;5(4):577-85. PMID: 22410480
61. Rosenberg, O, Gersner, R, Klein, LD, Kotler, M, Zangen, A, Dannon, P. Deep transcranial magnetic stimulation add-on for the treatment of auditory hallucinations: a double-blind study. *Annals of general psychiatry.* 2012;11:13. PMID: 22559192
62. Zhou, DD, Wang, W, Wang, GM, Li, DQ, Kuang, L. An updated meta-analysis: Short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder. *J Affect Disord.* 2017 Jun;215:187-96. PMID: 28340445
63. Cheng, CPW, Wong, CSM, Lee, KK, Chan, APK, Yeung, JWF, Chan, WC. Effects of repetitive transcranial magnetic stimulation on improvement of cognition in elderly patients with cognitive impairment: a systematic review and meta-analysis. *International journal of geriatric psychiatry.* 2018 Jan;33(1):e1-e13. PMID: 28493371
64. Li, H, Wang, J, Li, C, Xiao, Z. Repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults. *Cochrane Database Syst Rev.* 2014;9:CD009083. PMID: 25230088
65. Berlim, MT, Neufeld, NH, Van den Eynde, F. Repetitive transcranial magnetic stimulation (rTMS) for obsessive-compulsive disorder (OCD): an exploratory meta-analysis of randomized and sham-controlled trials. *Journal of psychiatric research.* 2013 Aug;47(8):999-1006. PMID: 23615189
66. Rosa, MO, Gattaz, WF, Rosa, MA, et al. Effects of repetitive transcranial magnetic stimulation on auditory hallucinations refractory to clozapine. *J Clin Psychiatry.* 2007 Oct;68(10):1528-32. PMID: 17960967
67. Prikryl, R, Kasperek, T, Skotakova, S, Ustohal, L, Kucerova, H, Ceskova, E. Treatment of negative symptoms of schizophrenia using repetitive transcranial magnetic stimulation in a double-blind, randomized controlled study. *Schizophr Res.* 2007 Sep;95(1-3):151-7. PMID: 17689931
68. Mogg, A, Purvis, R, Eranti, S, et al. Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: a randomized controlled pilot study. *Schizophr Res.* 2007 Jul;93(1-3):221-8. PMID: 17478080
69. Sachdev, PS, Loo, CK, Mitchell, PB, McFarquhar, TF, Malhi, GS. Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double-blind controlled investigation. *Psychol Med.* 2007 Nov;37(11):1645-9. PMID: 17655805

70. Walpoth, M, Hoertnagl, C, Mangweth-Matzek, B, et al. Repetitive transcranial magnetic stimulation in bulimia nervosa: preliminary results of a single-centre, randomised, double-blind, sham-controlled trial in female outpatients. *Psychother Psychosom.* 2008;77(1):57-60. PMID: 18087209
71. Martin, JL, Barbanoj, MJ, Perez, V, Sacristan, M. Transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder. *Cochrane Database Syst Rev.* 2003(3):CD003387. PMID: 12917964
72. Mantovani, A, Aly, M, Dagan, Y, Allart, A, Lisanby, SH. Randomized sham controlled trial of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for the treatment of panic disorder with comorbid major depression. *J Affect Disord.* 2013 Jan 10;144(1-2):153-9. PMID: 22858212
73. Watts, BV, Landon, B, Groft, A, Young-Xu, Y. A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. *Brain Stimul.* 2012 Jan;5(1):38-43. PMID: 22264669
74. Kapsan, A, Yaroslavsky, Y, Applebaum, J, Belmaker, RH, Grisaru, N. Right prefrontal TMS versus sham treatment of mania: a controlled study. *Bipolar Disord.* 2003 Feb;5(1):36-9. PMID: 12656936
75. Cohen, H, Kaplan, Z, Kotler, M, Kouperman, I, Moisa, R, Grisaru, N. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. *Am J Psychiatry.* 2004 Mar;161(3):515-24. PMID: 14992978
76. Isserles, M, Shalev, AY, Roth, Y, et al. Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder - A pilot study. *Brain Stimul.* 2012 Aug 18. PMID: 22921765
77. Schonfeldt-Lecuona, C, Gron, G, Walter, H, et al. Stereotaxic rTMS for the treatment of auditory hallucinations in schizophrenia. *Neuroreport.* 2004 Jul 19;15(10):1669-73. PMID: 15232304
78. Weaver, L, Rostain, AL, Mace, W, Akhtar, U, Moss, E, O'Reardon, JP. Transcranial magnetic stimulation (TMS) in the treatment of attention-deficit/hyperactivity disorder in adolescents and young adults: a pilot study. *The journal of ECT.* 2012 Jun;28(2):98-103. PMID: 22551775
79. Rabey, JM, Dobronevsky, E, Aichenbaum, S, Gonen, O, Marton, RG, Khaigrekht, M. Repetitive transcranial magnetic stimulation combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: a randomized, double-blind study. *J Neural Transm.* 2012 Oct 18. PMID: 23076723
80. Elbeh, KA, Elserogy, YM, Khalifa, HE, Ahmed, MA, Hafez, MH, Khedr, EM. Repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorders: Double blind randomized clinical trial. *Psychiatry Res.* 2016 Apr 30;238:264-9. PMID: 27086243
81. Hawken, ER, Dilkov, D, Kaludiev, E, Simek, S, Zhang, F, Milev, R. Transcranial Magnetic Stimulation of the Supplementary Motor Area in the Treatment of Obsessive-Compulsive Disorder: A Multi-Site Study. *International journal of molecular sciences.* 2016 Mar 22;17(3):420. PMID: 27011177
82. Deppermann, S, Vennewald, N, Diemer, J, et al. Neurobiological and clinical effects of fNIRS-controlled rTMS in patients with panic disorder/agoraphobia during cognitive-behavioural therapy. Netherlands, 2017. p. 668-77.
83. Praharaj, SK, Ram, D, Arora, M. Efficacy of high frequency (rapid) suprathreshold repetitive transcranial magnetic stimulation of right prefrontal cortex in bipolar mania: a

- randomized sham controlled study. *J Affect Disord.* 2009 Oct;117(3):146-50. PMID: 19178948
84. Bloch, Y, Harel, EV, Aviram, S, Govezensky, J, Ratzoni, G, Levkovitz, Y. Positive effects of repetitive transcranial magnetic stimulation on attention in ADHD Subjects: a randomized controlled pilot study. *World J Biol Psychiatry.* 2010 Aug;11(5):755-8. PMID: 20521875
85. Cordes, J, Thunker, J, Agelink, MW, et al. Effects of 10 Hz repetitive transcranial magnetic stimulation (rTMS) on clinical global impression in chronic schizophrenia. *Psychiatry Res.* 2010 May 15;177(1-2):32-6. PMID: 20378181
86. Mishra, BR, Nizamie, SH, Das, B, Praharaaj, SK. Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: a sham-controlled study. *Addiction.* 2010 Jan;105(1):49-55. PMID: 20078462
87. Van den Eynde, F, Claudino, AM, Mogg, A, et al. Repetitive transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders. *Biol Psychiatry.* 2010 Apr 15;67(8):793-5. PMID: 20060105
88. Boggio, PS, Rocha, M, Oliveira, MO, et al. Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. *J Clin Psychiatry.* 2010 Aug;71(8):992-9. PMID: 20051219
89. Sokhadze, E, Baruth, J, Tasman, A, et al. Low-frequency repetitive transcranial magnetic stimulation (rTMS) affects event-related potential measures of novelty processing in autism. *Appl Psychophysiol Biofeedback.* 2010 Jun;35(2):147-61. PMID: 19941058
90. Kang, JI, Kim, CH, Namkoong, K, Lee, CI, Kim, SJ. A randomized controlled study of sequentially applied repetitive transcranial magnetic stimulation in obsessive-compulsive disorder. *J Clin Psychiatry.* 2009 Dec;70(12):1645-51. PMID: 19709504
91. Mantovani, A, Simpson, HB, Fallon, BA, Rossi, S, Lisanby, SH. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. *Int J Neuropsychopharmacol.* 2010 Mar;13(2):217-27. PMID: 19691873
92. Vercammen, A, Knegtering, H, Bruggeman, R, et al. Effects of bilateral repetitive transcranial magnetic stimulation on treatment resistant auditory-verbal hallucinations in schizophrenia: a randomized controlled trial. *Schizophr Res.* 2009 Oct;114(1-3):172-9. PMID: 19679450
93. Cotelli, M, Calabria, M, Manenti, R, et al. Improved language performance in Alzheimer disease following brain stimulation. *J Neurol Neurosurg Psychiatry.* 2010 Jun 23. PMID: 20574108
94. Amiaz, R, Levy, D, Vainiger, D, Grunhaus, L, Zangen, A. Repeated high-frequency transcranial magnetic stimulation over the dorsolateral prefrontal cortex reduces cigarette craving and consumption. *Addiction.* 2009 Apr;104(4):653-60. PMID: 19183128
95. Khedr, EM, Abo-Elfetoh, N, Rothwell, JC. Treatment of post-stroke dysphagia with repetitive transcranial magnetic stimulation. *Acta Neurol Scand.* 2009 Mar;119(3):155-61. PMID: 18771521
96. Gay, A, Jausent, I, Sigaud, T, et al. A Lack of Clinical Effect of High-frequency rTMS to Dorsolateral Prefrontal Cortex on Bulimic Symptoms: A Randomised, Double-blind Trial. *European eating disorders review : the journal of the Eating Disorders Association.* 2016 Nov;24(6):474-81. PMID: 27633286

97. Gupta, MR, Bablu Lal; Bhatia, Dinesh; Mukherjee, Arun Transcranial Magnetic Stimulation Therapy in Spastic Cerebral Palsy Children Improves Motor Activity. *Journal of Neuroinfectious Diseases* 2016 2016;7(4):1-4. PMID:
98. Chen, R, Spencer, DC, Weston, J, Nolan, SJ. Transcranial magnetic stimulation for the treatment of epilepsy. *Cochrane Database Syst Rev.* 2016 Aug 11(8):CD011025. PMID: 27513825
99. Pereira, LS, Muller, VT, da Mota Gomes, M, Rotenberg, A, Fregni, F. Safety of repetitive transcranial magnetic stimulation in patients with epilepsy: A systematic review. *Epilepsy & behavior : E&B.* 2016 Apr;57(Pt A):167-76. PMID: 26970993
100. Seynaeve, L, Devroye, A, Dupont, P, Van Paesschen, W. Randomized crossover sham-controlled clinical trial of targeted low-frequency transcranial magnetic stimulation comparing a figure-8 and a round coil to treat refractory neocortical epilepsy. *Epilepsia.* 2016 Jan;57(1):141-50. PMID: 26642974
101. Sun, W, Mao, W, Meng, X, et al. Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy: a controlled clinical study. *Epilepsia.* 2012 Oct;53(10):1782-9. PMID: 22950513
102. Saltychev, M, Laimi, K. Effectiveness of repetitive transcranial magnetic stimulation in patients with fibromyalgia: a meta-analysis. *International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation.* 2017 Mar;40(1):11-8. PMID: 27977465
103. Knijnik, LM, Dussan-Sarria, JA, Rozisky, JR, et al. Repetitive Transcranial Magnetic Stimulation for Fibromyalgia: Systematic Review and Meta-Analysis. *Pain practice : the official journal of World Institute of Pain.* 2016 Mar;16(3):294-304. PMID: 25581213
104. Marlow, NM, Bonilha, HS, Short, EB. Efficacy of transcranial direct current stimulation and repetitive transcranial magnetic stimulation for treating fibromyalgia syndrome: a systematic review. *Pain practice : the official journal of World Institute of Pain.* 2013 Feb;13(2):131-45. PMID: 22631436
105. Maestu, C, Blanco, M, Nevado, A, et al. Reduction of pain thresholds in fibromyalgia after very low-intensity magnetic stimulation: a double-blinded, randomized placebo-controlled clinical trial. *Pain research & management : the journal of the Canadian Pain Society = journal de la societe canadienne pour le traitement de la douleur.* 2013 Nov-Dec;18(6):e101-6. PMID: 24308025
106. Lan, L, Zhang, X, Li, X, Rong, X, Peng, Y. The efficacy of transcranial magnetic stimulation on migraine: a meta-analysis of randomized controlled trails. Italy, 2017. p. 86.
107. Leung, A, Shukla, S, Fallah, A, et al. Repetitive Transcranial Magnetic Stimulation in Managing Mild Traumatic Brain Injury-Related Headaches. *Neuromodulation : journal of the International Neuromodulation Society.* 2016 Feb;19(2):133-41. PMID: 26555886
108. Rapinesi, C, Del Casale, A, Scatena, P, et al. Add-on deep Transcranial Magnetic Stimulation (dTMS) for the treatment of chronic migraine: A preliminary study. *Neurosci Lett.* 2016 Jun 03;623:7-12. PMID: 27132086
109. Ambriz-Tututi, M, Alvarado-Reynoso, B, Drucker-Colin, R. Analgesic effect of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic low back pain. *Bioelectromagnetics.* 2016 Aug 22. PMID: 27548757
110. Malavera, A, Silva, FA, Fregni, F, Carrillo, S, Garcia, RG. Repetitive Transcranial Magnetic Stimulation for Phantom Limb Pain in Land Mine Victims: A Double-Blinded, Randomized, Sham-Controlled Trial. *The journal of pain : official journal of the American Pain Society.* 2016 Aug;17(8):911-8. PMID: 27260638

111. Shimizu, T, Hosomi, K, Maruo, T, et al. Efficacy of deep rTMS for neuropathic pain in the lower limb: a randomized, double-blind crossover trial of an H-coil and figure-8 coil. *J Neurosurg*. 2017 Nov;127(5):1172-80. PMID: 28156250
112. Qin, B, Chen, H, Gao, W, et al. Effectiveness of high-frequency repetitive transcranial magnetic stimulation in patients with depression and Parkinson's disease: a meta-analysis of randomized, controlled clinical trials. New Zealand, 2018. p. 273-84.
113. Wagle Shukla, A, Shuster, JJ, Chung, JW, et al. Repetitive Transcranial Magnetic Stimulation (rTMS) Therapy in Parkinson Disease: A Meta-Analysis. *PM & R : the journal of injury, function, and rehabilitation*. 2016 Apr;8(4):356-66. PMID: 26314233
114. Chou, YH, Hickey, PT, Sundman, M, Song, AW, Chen, NK. Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease: a systematic review and meta-analysis. *JAMA neurology*. 2015 Apr;72(4):432-40. PMID: 25686212
115. Shirota, Y, Ohtsu, H, Hamada, M, Enomoto, H, Ugawa, Y. Supplementary motor area stimulation for Parkinson disease: a randomized controlled study. *Neurology*. 2013;80:1400-5. PMID: 23516319
116. Elahi, B, Chen, R. Effect of transcranial magnetic stimulation on Parkinson motor function--systematic review of controlled clinical trials. *Mov Disord*. 2009 Feb 15;24(3):357-63. PMID: 18972549
117. Cohen, OS, Rigbi, A, Yahalom, G, et al. Repetitive Deep TMS for Parkinson Disease: A 3-Month Double-Blind, Randomized Sham-Controlled Study. *J Clin Neurophysiol*. 2018 Mar;35(2):159-65. PMID: 29373395
118. Makkos, A, Pal, E, Aschermann, Z, et al. High-Frequency Repetitive Transcranial Magnetic Stimulation Can Improve Depression in Parkinson's Disease: A Randomized, Double-Blind, Placebo-Controlled Study. *Neuropsychobiology*. 2016;73:169-77. PMID: 27093063
119. Benninger, DH, Iseki, K, Kranick, S, Luckenbaugh, DA, Houdayer, E, Hallett, M. Controlled study of 50-Hz repetitive transcranial magnetic stimulation for the treatment of Parkinson disease. *Neurorehabil Neural Repair*. 2012 Nov-Dec;26(9):1096-105. PMID: 22593114
120. Yang, YR, Tseng, CY, Chiou, SY, et al. Combination of rTMS and treadmill training modulates corticomotor inhibition and improves walking in Parkinson disease: a randomized trial. *Neurorehabil Neural Repair*. 2013 Jan;27(1):79-86. PMID: 22785003
121. Sebastianelli, L, Versace, V, Martignago, S, et al. Low-frequency rTMS of the unaffected hemisphere in stroke patients: A systematic review. *Acta Neurol Scand*. 2017 Dec;136(6):585-605. PMID: 28464421
122. McIntyre, A, Mirkowski, M, Thompson, S, Burhan, AM, Miller, T, Teasell, R. A Systematic Review and Meta-Analysis on the Use of Repetitive Transcranial Magnetic Stimulation for Spasticity Poststroke. *PM & R : the journal of injury, function, and rehabilitation*. 2017 Oct 16. PMID: 29045857
123. Fan, J, Li, Y, Yang, Y, Qu, Y, Li, S. Efficacy of Noninvasive Brain Stimulation on Unilateral Neglect After Stroke: A Systematic Review and Meta-analysis. *Am J Phys Med Rehabil*. 2017 Sep 25. PMID: 28953034
124. Graef, P, Dadalt, MLR, Rodrigues, D, Stein, C, Pagnussat, AS. Transcranial magnetic stimulation combined with upper-limb training for improving function after stroke: A systematic review and meta-analysis. *J Neurol Sci*. 2016 Oct 15;369:149-58. PMID: 27653882

125. Liao, X, Xing, G, Guo, Z, et al. Repetitive transcranial magnetic stimulation as an alternative therapy for dysphagia after stroke: a systematic review and meta-analysis. *Clin Rehabil.* 2017;31:289-98. PMID: 27113337
126. Li, Y, Qu, Y, Yuan, M, Du, T. Low-frequency repetitive transcranial magnetic stimulation for patients with aphasia after stroke: A meta-analysis. *J Rehabil Med.* 2015 Sep;47(8):675-81. PMID: 26181486
127. Le, Q, Qu, Y, Tao, Y, Zhu, S. Effects of repetitive transcranial magnetic stimulation on hand function recovery and excitability of the motor cortex after stroke: a meta-analysis. *Am J Phys Med Rehabil.* 2014 May;93(5):422-30. PMID: 24429509
128. Hao, Z, Wang, D, Zeng, Y, Liu, M. Repetitive transcranial magnetic stimulation for improving function after stroke. *Cochrane Database Syst Rev.* 2013;5:CD008862. PMID: 23728683
129. Hsu, WY, Cheng, CH, Liao, KK, Lee, IH, Lin, YY. Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke: a meta-analysis. *Stroke; a journal of cerebral circulation.* 2012 Jul;43(7):1849-57. PMID: 22713491
130. Choi, GS, Chang, MC. Effects of high-frequency repetitive transcranial magnetic stimulation on reducing hemiplegic shoulder pain in patients with chronic stroke: a randomized controlled trial. *The International journal of neuroscience.* 2018 Feb;128(2):110-6. PMID: 28805107
131. Forogh, B, Ahadi, T, Nazari, M, et al. The Effect of Repetitive Transcranial Magnetic Stimulation on Postural Stability After Acute Stroke: A Clinical Trial. Iran, 2017. p. 405-11.
132. Huang, YZ, Lin, LF, Chang, KH, Hu, CJ, Liou, TH, Lin, YN. Priming with 1-Hz rTMS over contralesional leg motor cortex does not increase the rate of regaining ambulation within 3 months of stroke: A randomized controlled trial. *Am J Phys Med Rehabil.* 2017 Oct 10. PMID: 29023249
133. Guan, YZ, Li, J, Zhang, XW, et al. Effectiveness of repetitive transcranial magnetic stimulation (rTMS) after acute stroke: A one-year longitudinal randomized trial. *CNS neuroscience & therapeutics.* 2017 Dec;23(12):940-6. PMID: 28971620
134. Park, E, Kim, MS, Chang, WH, et al. Effects of Bilateral Repetitive Transcranial Magnetic Stimulation on Post-Stroke Dysphagia. *Brain Stimul.* 2017 Jan - Feb;10(1):75-82. PMID: 27593709
135. Du, J, Yang, F, Liu, L, et al. Repetitive transcranial magnetic stimulation for rehabilitation of poststroke dysphagia: A randomized, double-blind clinical trial. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 2016 Mar;127(3):1907-13. PMID: 26778719
136. Seniow, J, Bilik, M, Lesniak, M, Waldowski, K, Iwanski, S, Czlonkowska, A. Transcranial magnetic stimulation combined with physiotherapy in rehabilitation of poststroke hemiparesis: a randomized, double-blind, placebo-controlled study. *Neurorehabil Neural Repair.* 2012 Nov-Dec;26(9):1072-9. PMID: 22588639
137. Sahlsten, H, Virtanen, J, Joutsa, J, et al. Electric field-navigated transcranial magnetic stimulation for chronic tinnitus: a randomized, placebo-controlled study. *International journal of audiology.* 2017 Sep;56(9):692-700. PMID: 28415897
138. Landgrebe, M, Hajak, G, Wolf, S, et al. 1-Hz rTMS in the treatment of tinnitus: A sham-controlled, randomized multicenter trial. *Brain Stimul.* 2017 Nov - Dec;10(6):1112-20. PMID: 28807845
139. Lehner, A, Schecklmann, M, Greenlee, MW, Rupprecht, R, Langguth, B. Triple-site rTMS for the treatment of chronic tinnitus: a randomized controlled trial. *Sci Rep.* 2016;6:22302. PMID: 26927363

140. Mohammad YM, Kothari R, Hughes G et al. Transcranial Magnetic Stimulation (TMS) relieves migraine headache. Platform presentation at the American Headache Society annual scientific meeting in Los Angeles, June 23, 2006.
141. Defrin, R, Grunhaus, L, Zamir, D, Zeilig, G. The effect of a series of repetitive transcranial magnetic stimulations of the motor cortex on central pain after spinal cord injury. *Arch Phys Med Rehabil.* 2007 Dec;88(12):1574-80. PMID: 18047871
142. Saitoh, Y, Hirayama, A, Kishima, H, et al. Reduction of intractable deafferentation pain due to spinal cord or peripheral lesion by high-frequency repetitive transcranial magnetic stimulation of the primary motor cortex. *J Neurosurg.* 2007 Sep;107(3):555-9. PMID: 17886555
143. Passard, A, Attal, N, Benadhira, R, et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. *Brain.* 2007 Oct;130(Pt 10):2661-70. PMID: 17872930
144. Pomeroy, VM, Cloud, G, Tallis, RC, Donaldson, C, Nayak, V, Miller, S. Transcranial magnetic stimulation and muscle contraction to enhance stroke recovery: a randomized proof-of-principle and feasibility investigation. *Neurorehabil Neural Repair.* 2007 Nov-Dec;21(6):509-17. PMID: 17409389
145. Malcolm, MP, Triggs, WJ, Light, KE, et al. Repetitive transcranial magnetic stimulation as an adjunct to constraint-induced therapy: an exploratory randomized controlled trial. *Am J Phys Med Rehabil.* 2007 Sep;86(9):707-15. PMID: 17709994
146. Valle, AC, Dionisio, K, Pitskel, NB, et al. Low and high frequency repetitive transcranial magnetic stimulation for the treatment of spasticity. *Dev Med Child Neurol.* 2007 Jul;49(7):534-8. PMID: 17593127
147. Khedr, EM, Rothwell, JC, Ahmed, MA, El-Atar, A. Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: comparison of different stimulus frequencies. *J Neurol Neurosurg Psychiatry.* 2008 Feb;79(2):212-5. PMID: 18202212
148. Rossi, S, De Capua, A, Olivelli, M, et al. Effects of repetitive transcranial magnetic stimulation on chronic tinnitus: a randomised, crossover, double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry.* 2007 Aug;78(8):857-63. PMID: 17314192
149. Kirton, A, Chen, R, Friefeld, S, Gunraj, C, Pontigon, AM, Deveber, G. Contralesional repetitive transcranial magnetic stimulation for chronic hemiparesis in subcortical paediatric stroke: a randomised trial. *Lancet Neurol.* 2008 Jun;7(6):507-13. PMID: 18455961
150. Andre-Obadia, N, Mertens, P, Gueguen, A, Peyron, R, Garcia-Larrea, L. Pain relief by rTMS: differential effect of current flow but no specific action on pain subtypes. *Neurology.* 2008 Sep 9;71(11):833-40. PMID: 18779511
151. Hamada, M, Ugawa, Y, Tsuji, S. High-frequency rTMS over the supplementary motor area for treatment of Parkinson's disease. *Mov Disord.* 2008 Aug 15;23(11):1524-31. PMID: 18548577
152. Gabis, L, Shklar, B, Baruch, YK, Raz, R, Gabis, E, Geva, D. Pain reduction using transcranial electrostimulation: a double blind "active placebo" controlled trial. *J Rehabil Med.* 2009 Mar;41(4):256-61. PMID: 19247545
153. Takeuchi, N, Tada, T, Toshima, M, Chuma, T, Matsuo, Y, Ikoma, K. Inhibition of the unaffected motor cortex by 1 Hz repetitive transcranial magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. *J Rehabil Med.* 2008 Apr;40(4):298-303. PMID: 18382826

154. Kranz, G, Shamim, EA, Lin, PT, Kranz, GS, Hallett, M. Transcranial magnetic brain stimulation modulates blepharospasm: a randomized controlled study. *Neurology*. 2010 Oct 19;75(16):1465-71. PMID: 20956792
155. Chang, WH, Kim, YH, Bang, OY, Kim, ST, Park, YH, Lee, PK. Long-term effects of rTMS on motor recovery in patients after subacute stroke. *J Rehabil Med*. 2010 Sep;42(8):758-64. PMID: 20809058
156. Soler, MD, Kumru, H, Pelayo, R, et al. Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. *Brain*. 2010 Sep;133(9):2565-77. PMID: 20685806
157. Anders, M, Dvorakova, J, Rathova, L, et al. Efficacy of repetitive transcranial magnetic stimulation for the treatment of refractory chronic tinnitus: a randomized, placebo controlled study. *Neuro Endocrinol Lett*. 2010;31(2):238-49. PMID: 20424590
158. Kim, BR, Kim, DY, Chun, MH, Yi, JH, Kwon, JS. Effect of repetitive transcranial magnetic stimulation on cognition and mood in stroke patients: a double-blind, sham-controlled trial. *Am J Phys Med Rehabil*. 2010 May;89(5):362-8. PMID: 20407301
159. Martiny, K, Lunde, M, Bech, P. Transcranial low voltage pulsed electromagnetic fields in patients with treatment-resistant depression. *Biol Psychiatry*. 2010 Jul 15;68(2):163-9. PMID: 20385376
160. Lipton, RB, Dodick, DW, Silberstein, SD, et al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. *Lancet Neurol*. 2010 Apr;9(4):373-80. PMID: 20206581
161. Filipovic, SR, Rothwell, JC, Bhatia, K. Low-frequency repetitive transcranial magnetic stimulation and off-phase motor symptoms in Parkinson's disease. *J Neurol Sci*. 2010 Apr 15;291(1-2):1-4. PMID: 20153482
162. Kumru, H, Murillo, N, Samsó, JV, et al. Reduction of spasticity with repetitive transcranial magnetic stimulation in patients with spinal cord injury. *Neurorehabil Neural Repair*. 2010 Jun;24(5):435-41. PMID: 20053952
163. Takeuchi, N, Tada, T, Tushima, M, Matsuo, Y, Ikoma, K. Repetitive transcranial magnetic stimulation over bilateral hemispheres enhances motor function and training effect of paretic hand in patients after stroke. *J Rehabil Med*. 2009 Nov;41(13):1049-54. PMID: 19894000
164. Khedr, EM, Abo-Elfetoh, N. Therapeutic role of rTMS on recovery of dysphagia in patients with lateral medullary syndrome and brainstem infarction. *J Neurol Neurosurg Psychiatry*. 2010 May;81(5):495-9. PMID: 19828479
165. Kang, BS, Shin, HI, Bang, MS. Effect of repetitive transcranial magnetic stimulation over the hand motor cortical area on central pain after spinal cord injury. *Arch Phys Med Rehabil*. 2009 Oct;90(10):1766-71. PMID: 19801069
166. Khedr, EM, Abdel-Fadeil, MR, Farghali, A, Qaid, M. Role of 1 and 3 Hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke. *Eur J Neurol*. 2009 Dec;16(12):1323-30. PMID: 19780802
167. Arfeller, C, Vonthein, R, Plontke, SK, Plewnia, C. Efficacy and safety of bilateral continuous theta burst stimulation (cTBS) for the treatment of chronic tinnitus: design of a three-armed randomized controlled trial. *Trials*. 2009;10:74. PMID: 19698089
168. Di Lazzaro, V, Pilato, F, Profice, P, et al. Motor cortex stimulation for ALS: a double blind placebo-controlled study. *Neurosci Lett*. 2009 Oct 16;464(1):18-21. PMID: 19682544

169. Khedr, EM, Etraby, AE, Hemeda, M, Nasef, AM, Razek, AA. Long-term effect of repetitive transcranial magnetic stimulation on motor function recovery after acute ischemic stroke. *Acta Neurol Scand*. 2010 Jan;121(1):30-7. PMID: 19678808
170. Loo, CK, Sainsbury, K, Mitchell, P, Hadzi-Pavlovic, D, Sachdev, PS. A sham-controlled trial of left and right temporal rTMS for the treatment of auditory hallucinations. *Psychol Med*. 2010 Apr;40(4):541-6. PMID: 19656432
171. Marcondes, RA, Sanchez, TG, Kii, MA, et al. Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: a double-blind controlled, clinical and neuroimaging outcome study. *Eur J Neurol*. 2010 Jan;17(1):38-44. PMID: 19614962
172. Borckardt, JJ, Smith, AR, Reeves, ST, et al. A pilot study investigating the effects of fast left prefrontal rTMS on chronic neuropathic pain. *Pain Med*. 2009 Jul-Aug;10(5):840-9. PMID: 19594842
173. Jayaram, G, Stinear, JW. The effects of transcranial stimulation on paretic lower limb motor excitability during walking. *J Clin Neurophysiol*. 2009 Aug;26(4):272-9. PMID: 19584748
174. Brighina, F, Palermo, A, Panetta, ML, et al. Reduced cerebellar inhibition in migraine with aura: a TMS study. *Cerebellum*. 2009 Sep;8(3):260-6. PMID: 19156474
175. Arias, P, Vivas, J, Grieve, KL, Cudeiro, J. Double-blind, randomized, placebo controlled trial on the effect of 10 days low-frequency rTMS over the vertex on sleep in Parkinson's disease. *Sleep Med*. 2010 Sep;11(8):759-65. PMID: 20674489
176. Lorenz, I, Muller, N, Schlee, W, Langguth, B, Weisz, N. Short-term effects of single repetitive TMS sessions on auditory evoked activity in patients with chronic tinnitus. *J Neurophysiol*. 2010 Sep;104(3):1497-505. PMID: 20592125
177. Emara, TH, Moustafa, RR, Elnahas, NM, et al. Repetitive transcranial magnetic stimulation at 1Hz and 5Hz produces sustained improvement in motor function and disability after ischaemic stroke. *Eur J Neurol*. 2010 Sep;17(9):1203-9. PMID: 20402755
178. Short, EB, Borckardt, JJ, Anderson, BS, et al. Ten sessions of adjunctive left prefrontal rTMS significantly reduces fibromyalgia pain: a randomized, controlled pilot study. *Pain*. 2011 Nov;152(11):2477-84. PMID: 21764215
179. Ahmed, MA, Darwish, ES, Khedr, EM, El Serogy, YM, Ali, AM. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. *J Neurol*. 2012 Jan;259(1):83-92. PMID: 21671144
180. Kim, L, Chun, MH, Kim, BR, Lee, SJ. Effect of repetitive transcranial magnetic stimulation on patients with brain injury and Dysphagia. *Annals of rehabilitation medicine*. 2011 Dec;35(6):765-71. PMID: 22506204
181. Fang, J, Zhou, M, Yang, M, Zhu, C, He, L. Repetitive transcranial magnetic stimulation for the treatment of amyotrophic lateral sclerosis or motor neuron disease. *Cochrane Database Syst Rev*. 2013;5:CD008554. PMID: 23728676
182. O'Connell, NE, Wand, BM, Marston, L, Spencer, S, Desouza, LH. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev*. 2014;4:CD008208. PMID: 24729198
183. Jansen, JM, Daams, JG, Koeter, MW, Veltman, DJ, van den Brink, W, Goudriaan, AE. Effects of non-invasive neurostimulation on craving: a meta-analysis. *Neuroscience and biobehavioral reviews*. 2013 Dec;37(10 Pt 2):2472-80. PMID: 23916527

184. O'Connell, NE, Wand, BM, Marston, L, Spencer, S, Desouza, LH. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev*. 2010(9):CD008208. PMID: 20824873
185. Gunduz, A, Rothwell, J, Vidal, J, Kumru, H. Non-invasive brain stimulation to promote motor and functional recovery following spinal cord injury. India, 2017. p. 1933-8.
186. Koch, G, Bonni, S, Pellicciari, MC, et al. Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal Alzheimer's disease. *NeuroImage*. 2017 Dec 19;169:302-11. PMID: 29277405
187. Kohutova, B, Fricova, J, Klirova, M, Novak, T, Rokyta, R. Theta burst stimulation in the treatment of chronic orofacial pain: a randomized controlled trial. Czech Republic, 2017. p. 1041-7.
188. Goudra, B, Shah, D, Balu, G, et al. Repetitive Transcranial Magnetic Stimulation in Chronic Pain: A Meta-analysis. India, 2017. p. 751-7.
189. Lyon, DE, Schubert, C, Taylor, AG. Pilot study of cranial stimulation for symptom management in breast cancer. *Oncol Nurs Forum*. 2010 Jul;37(4):476-83. PMID: 20591807
190. Umezaki, Y, Badran, BW, DeVries, WH, Moss, J, Gonzales, T, George, MS. The Efficacy of Daily Prefrontal Repetitive Transcranial Magnetic Stimulation (rTMS) for Burning Mouth Syndrome (BMS): A Randomized Controlled Single-blind Study. *Brain Stimul*. 2016 Mar-Apr;9(2):234-42. PMID: 26597930
191. Seppi, K, Weintraub, D, Coelho, M, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. *Mov Disord*. 2011 Oct;26 Suppl 3:S42-80. PMID: 22021174
192. Update on treatments for motor symptom of PD. [cited 03/06/2018]; Available from: <http://www.movementdisorders.org/MDS-Files1/PDFs/EBM-Papers/update-on-treatments-for-motor-symptoms-of-PD.pdf>
193. Update: Treatments for non-motor symptoms of parkinsons disease. [cited 03/05/2018]; Available from: <http://display.mds.prod.titanclient.com/MDS-Files1/PDFs/EBM-Papers/EBM-NMS-Updated15Jan2014.pdf>
194. Shprecher, D, Kurlan, R. The management of tics. *Mov Disord*. 2009 Jan 15;24(1):15-24. PMID: 19170198
195. Winkelman, JW, Armstrong, MJ, Allen, RP, et al. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2016;87(24):2585-93. PMID: PMC5206998
196. BlueCross BlueShield Association Medical Policy Reference Manual "Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders." Policy No. 2.01.50

CODES

Codes	Number	Description
CPT	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

Codes	Number	Description
	90869	;subsequent motor threshold re-determination with delivery and management
HCPCS	None	

Date of Origin: April 2002