



GroupHealth®

Clinical Review Criteria

Repetitive Transcranial Magnetic Stimulation (rTMS) for Patients with Treatment-Resistant Major Depression

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Criteria

For Medicare Members

Requires Medical Director review.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Major depressive disorder is a common health condition, and is associated with substantial morbidity, mortality and health care costs. No single approach is uniformly effective at treating depression. Antidepressant treatment with SSRIs is currently a common first step. Approximately, two-thirds of patients respond to an initial course of antidepressants (O'Reardon et al., 2000). One alternative for non-responders is to switch to a different antidepressant, in the same or another class of medications. Findings from a recent RCT indicate that approximately 1 in 4 individuals who failed an initial course of SSRIs respond to a second one (Rush et al., 2006). Adding psychotherapy is another option for non-responders.

Interest in alternative treatment options, such as transcranial magnetic stimulation (TMS), has grown in recent years. TMS is a non-invasive method of modulating the brain's electrical environment by using magnetic fields. The technique involves applying alternating electrical currents through an insulated coil on the scalp which, ultimately, produces an electrical field in the brain, which in turn induces depolarization of nerve cells and results in the stimulation or disruption of brain activity. Changes in brain activity with TMS can be detected through various imaging techniques (PET, SPECT, or MRI). TMS can be delivered in either individual or repetitive pulses (the latter known as rTMS). Most studies of TMS for depression use repetitive pulses, and target the left dorsal lateral prefrontal cortex (DLPFC). Reported side-effects of TMS are generally mild including headache, local discomfort, and transient change in auditory threshold, which can be prevented by the use of earplugs. Instances of mania and epileptic seizure, however, have been known to occur (Fitzgerald and Daskalakis 2008; George 2010; Shelton, Osuntokun et al. 2010; Slotema, Blom et al. 2010).

Several TMS devices, including the NeuroStar TMS system (Neuronetics, Atlanta, GA) and the Brainsway Deep TMS system (Brainsway Ltd., Jerusalem, Israel), have received 510(k) clearance by the United States Food and Drug Administration (FDA). The devices are indicated for the treatment of major depressive disorder (MDD) in adult patients who have failed one prior antidepressant medication at or above the minimal effective dose and duration. The medical technology and assessment committee (MTAC) previously reviewed TMS technology in 2009, and subsequently in 2011. In each case, the evidence failed to satisfy MTAC criteria due to inappropriate comparators and lack of established long term efficacy.

Medical Technology Assessment Committee (MTAC)

Repetitive transcranial magnetic stimulation (rTMS)

06/01/2009: MTAC REVIEW

Evidence Conclusion: Active rTMS vs. sham treatment for treatment-resistant depression

Efficacy: There is insufficient evidence on the long-term efficacy of rTMS for treatment-resistant depression. In the RCTs, patients were generally evaluated at the end of the treatment period, 4 weeks or less. A pooled analysis of the 4 studies that followed patients for an additional 1-2 weeks also found a significantly higher response rate with rTMS vs. sham treatment. There is sufficient evidence from a meta-analysis of 21 RCTs (Lam et al., 2008) that there is a higher short-term clinical response rate with rTMS compared to sham treatment (NNT=6). **Safety:** In the Lam meta-analysis, there was a low rate of withdrawals due to adverse effects overall, 2% of patients in the active rTMS group and 1.5% in the sham group. Janicak et al. (2008), in a study funded by Neuronetics, compiled safety data from one sham-controlled RCT and two unpublished open-label studies, and found few treatment-related adverse effects. No deaths or seizures were reported among the 218 patients receiving active treatment. A total of 41 serious adverse events were reported. 36 of the 41 were assessed by study investigators as unrelated to the study device. The 5 related events included 3 related to a manufacturing defect in a component of the study device, 1 was left-sided facial numbness and the fifth, deemed probably related, was not specified.

rTMS vs. other established treatment for treatment-resistant depression: There is insufficient evidence to draw conclusions about the safety and efficacy of rTMS for treatment-resistant depression compared to electroconvulsive therapy. One RCT comparing rTMS to ECT in this population was identified (Rosa et al., 2006). The study did not find a significant difference in the rate of clinical remission with rTMS compared to ECT. There were a relatively small number of patients enrolled, a relatively high drop-out rate and no analysis of statistical power, so conclusions can not be made about equivalence of the treatments. There is insufficient evidence to draw conclusions about the safety and efficacy of rTMS for treatment-resistant depression compared to additional trials of antidepressants. No trials were identified comparing monotherapy with rTMS or antidepressants in this population. One RCT compared the combination of rTMS and escitalopram to escitalopram (plus sham rTMS) (Bretlau et al., 2008). The study, which included patients who failed at least one previous trial of antidepressants, used the difference in depression scores as the primary outcome, rather than the more clinically significant outcomes, clinical response or remission. With an appropriate statistical analysis, adjusting for multiple comparisons, there was a significant benefit of the combined active treatment group at the end of the three-week rTMS period, but no difference after an additional 9 weeks of medication treatment.

Articles: Active rTMS vs. sham treatment for treatment-resistant depression

The Pubmed searched yielded three meta-analyses of RCTs comparing rTMS for major depression to sham treatment. Only one of the three meta-analyses (Lam et al., 2008) focused on treatment-resistant depression, the FDA-approved indication and was critically appraised. No major sham-controlled RCTs were published after the meta-analysis literature search date (May 15, 2008). The search of the Cochrane database yielded a systematic review of rTMS for depression but this review had not been updated since 2001 and was therefore excluded. A study that compiled safety data from several trials (Janicak et al., 2008) was reviewed, but an evidence table was not created. **rTMS vs. other established treatment for treatment-resistant depression.** One RCT comparing rTMS to ECT for patients with treatment-resistant depression (Rosa et al., 2006) was identified and critically appraised. Another RCT comparing rTMS and ECT had as its entry requirement, referral for ECT. The investigators did not specify that patients needed to have failed at least one treatment, so this study was excluded from further review. One RCT comparing rTMS to antidepressants for medication-resistant depression (Bretlau et al., 2008) was identified and critically appraised. Two other RCTs that evaluated the combination of rTMS and antidepressants as first-line treatment were excluded. The references for the studies that were reviewed are as follows: Bretlau LG, Lunde M, Uden M et al. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression. *Pharmacopsychiatry* 2008; 41: 41-47. See [Evidence Table 1](#). Janicak PG, O'Rearson 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 Psychiat* 2008; 69: 222-232. Lam RW, Chan P, Wilkins-Ho M et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: A systematic review and meta-analysis. *Can J Psychiatr* 2008; 53: 621-631. See [Evidence Table 2](#). 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 Neuropsychopharm* 2006; 9: 667-676. See [Evidence Table 1](#).

The use of Repetitive transcranial magnetic stimulation (rTMS) for the treatment of treatment-resistant major depression does not meet the *Group Health Medical Technology Assessment Criteria*.

04/18/2011: MTAC REVIEW

Repetitive Transcranial Magnetic Stimulation (rTMS)

Evidence Conclusion: *rTMS vs. sham rTMS:* A recent RCT evaluated the safety and efficacy of daily left prefrontal cortex rTMS compared to sham rTMS for the treatment of antidepressant medication resistant depression in 190 patients with unipolar depression. The primary outcome was remission defined as a Hamilton Scale for Depression (HAM-D) score ≤ 3 or 2 consecutive HAM-D scored less than 10. Thirteen patients in the active rTMS group and five patients in the sham rTMS group experienced remission [Odds ratio 4.18, 95% CI

(1.32-13.24), NNT=12]. There was no significant difference in adverse events by treatment arm. Results from this trial suggest that rTMS is more effective than placebo at treating medication resistant depression; however, this trial does not address the duration of the effect (George 2010). rTMS vs. venlafaxine ER The efficacy of rTMS over the right prefrontal dorsolateral cortex versus venlafaxine ER for the treatment of resistant depression was assessed in a recent RCT that followed 60 patients for 4-weeks. The primary outcome measure was change in Montgomery-Åsberg Depression Rating Scale (MADRS) score. Clinical response (more than a 50% reduction of the MADRS score) and remission (MADRS score ≤ 10 points) were also evaluated. There was no significant difference in mean change in MADRS score, clinical response, or remission rates between the two groups (Bares 2009).

Conclusion: There is insufficient evidence to determine the long-term safety and efficacy of rTMS for the treatment of depression in patients who have failed at least one prior antidepressant medication. Results from one RCT suggest that rTMS may be effective at treating medication resistant depression; however, this trial does not address the durability of the effect. Additionally, studies addressing the efficacy of rTMS differ with regards to the duration of treatment and treatment parameters. More research is necessary to identify the ideal duration of treatment and treatment parameters.

Articles: Studies were selected for review if they included at least 25 subjects and assessed either the safety or efficacy of transcranial magnetic stimulation for the treatment of depression. Studies were excluded if they addressed the safety or efficacy of TMS for the treatment of conditions other than depression; if they compared different TMS applications to each other; or if they lacked a valid comparison group. Two recent meta-analyses were also identified, but not selected for review. One meta-analysis that examined the efficacy of slow-frequency (≤ 1 Hz) rTMS for the treatment of depression was not selected as the trials included were all published before the 2009 review (Schutter 2010). The other meta-analysis was not selected for review because of methodological limitations (Slotema 2010). Additionally, the majority of the articles included in these meta-analyses were also included in a previously reviewed meta-analysis. Two RCTs were selected for review. The following studies were critically appraised: 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-center, randomized study. *J Affect Disord* 2009; 118:94-100. See [Evidence Table](#). 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; 67:507-516. See [Evidence Table](#).

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08/17/2015: MTAC REVIEW

Repetitive Transcranial Magnetic Stimulation (rTMS)

Evidence Conclusion: The BCBS TEC assessment, published in January of 2014, established that the available evidence on the use of TMS therapy for depression does not meet the TEC criteria. More specifically, the TEC assessment was not able to make conclusions with regard to the effect of TMS on health outcomes, net health outcomes, and, as a result, was unable demonstrate that the technology was as beneficial as any established alternative and that results were attainable outside the investigational setting (BCBS 2014). Subsequent to the TEC assessment, a group of European experts made a conflicting conclusion regarding the efficacy of TMS for the treatment of depression. In their analysis of the literature, the European experts made a level A recommendation establishing the efficacy of high frequency rTMS of the left DLPFC in depression (Lefaucheur, André-Obadia et al. 2014).

Effectiveness: In the first meta-analysis, Gaynes and colleagues pooled data from 18 trials with the overall aim to evaluate the efficacy of rTMS in patients with treatment resistant depression. In all three primary outcomes (severity of depression symptoms, response rate, and remission) the investigators reported that rTMS was superior to sham leading to the conclusion that rTMS is a reasonable, effective treatment option in patients with treatment-resistant depression (Gaynes, Lloyd et al. 2014). The second meta-analysis, carried out by Kedzior and colleagues, focused more on the durability of the antidepressant effect. In their analysis, data from 16 studies involving 495 patients demonstrated only a small antidepressant effect during follow up (Kedzior, Reitz et al. 2015). [Evidence Table 1](#) **Safety:** The literature reports several common events to be associated with TMS therapy including problems at the site of coil placement, tension like headaches and light-headedness with the most serious event reported being seizure. Overall, however, the technique appears to be relatively safe and reasonably well tolerated. Collectively, the body of published evidence relating to TMS therapy for depression is plagued with heterogeneity with a wide range of aims, outcomes and varying populations. To add to this, the technology is inherently limited by the lack of any established consensus regarding both the frequency and intensity of stimulation. Historically, TMS therapy for depression has failed MTAC criteria due to insufficient evidence. The current evidence remains conflicting and does not provide clear and convincing evidence that rTMS therapy is an effective and sustainable treatment option for depression. **Conclusion:** There is insufficient evidence to support the

superiority of rTMS over antidepressants. There is evidence to support the short term efficacy of rTMS over sham therapy. rTMS appears to be a relatively safe and well tolerated treatment.

Articles: The literature search identified an evidence based guidelines on the therapeutic use of rTMS in a variety of different conditions. (Lefaucheur, André-Obadia et al. 2014). In addition, a 2014 TEC (technology evaluation center) assessment produced by the Blue Cross and Blue Shield (BCBS) Association in association with Kaiser Permanente was identified (BCBS 2014). As a result, the literature search focused on updating the evidence base established by the guideline and TEC assessment (March 2014 through July 2015). The search yielded just over 200 publications including a variety of case series/reports, clinical trials, review articles, and meta-analyses. No studies were identified comparing rTMS as a monotherapy with antidepressants. The following studies were selected for critical appraisal: Gaynes BN, Lloyd S, Lux L, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *J Clin Psychiatry*. 2014; 75(5):477-489. [See Evidence Table 1](#). Kedzior KK, Reitz SK, Azorina V, et al. Durability of the antidepressant effect of the high-frequency repetitive transcranial magnetic stimulation (rTMS) in the absence of maintenance treatment in major depression: a systematic review and meta-analysis of 16 double-blind randomized, sham-controlled trials. *Depression and Anxiety*. 2015;32:193-203. [See Evidence Table 1](#).

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^{MDCRPC} Medical Director Clinical Review and Policy Committee
^{MPC} Medical Policy Committee

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09/08/2015	Revised LCD L34886 and L35008 Non-Covered Services.

Codes

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