

Repetitive Transcranial Magnetic Stimulation for Major Depressive Disorder

Q. What is repetitive transcranial magnetic stimulation?

A. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulation therapy approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD). In particular, the FDA specifies the use of rTMS “in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode” (FDA, 2011). rTMS involves placing a magnetic field generator, or “coil,” over the brain region of interest (most often the prefrontal cortex for MDD patients). The coil produces magnetic pulses that pass through the skull and create small electrical currents that stimulate neurons within that region of the brain (McClintock et al., 2017). The procedure typically takes between 30 to 60 minutes and does not require anesthesia. rTMS interventions can vary by pulse frequency used (high-frequency vs. low-frequency) and by coil location (left, right, bilateral). More novel forms of rTMS therapy can involve accelerated, deep, and synchronized rTMS (Brunoni et al., 2016).

Q. What are the potential mechanisms of action underlying rTMS?

A. rTMS induces a magnetic field that causes the depolarization of neurons in brain tissue beneath the area where the coil has been placed, as well as in downstream circuits (Liston et al., 2014). Long-term, rTMS can produce lasting effects on neural function (Liston et al., 2014). Although the exact mechanism by which rTMS alleviates depressive symptomatology is not known, rTMS may relieve depressive symptoms by modulating functional connectivity with and between cortical networks (Liston et al., 2014).

Q. Is rTMS recommended as a front-line treatment for major depressive disorder in the Military Health System (MHS)?

A. **No.** However, the 2016 VA/DoD *Clinical Practice Guideline for the Management of Major Depressive Disorder* does give a “Weak For” strength of recommendation for rTMS treatment during a major depressive episode in patients with treatment-resistant MDD.

The MHS relies on the VA/DoD clinical practice guidelines (CPGs) to inform best clinical practices. The CPGs are developed under the purview of clinical experts and are derived through a transparent and systematic approach that includes, but is not limited to, systematic reviews of the literature on a given topic and development of recommendations using a graded system that takes into account the overall quality of the evidence and the magnitude of the net benefit of the recommendation. A further description of this process and CPGs on specific topics can be found on the VA clinical practice guidelines website.

Q. Do other authoritative reviews recommend rTMS as a front-line treatment for MDD?

A. **No.** Other authoritative reviews do not recommend the use of rTMS as a front-line treatment for MDD. However, rTMS is recommended for use in patients with treatment-resistant depression.

Several other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using similar grading systems as the VA/DoD CPGs. These include the Agency for Healthcare Research and Quality (AHRQ) and Cochrane.

- Cochrane: A 2001 systematic review found no strong evidence for benefit from using transcranial magnetic stimulation (TMS) to treat depression (Martin et al., 2001).
- AHRQ: A 2011 comparative effectiveness review of non-pharmacologic interventions for treatment-resistant depression (TRD) in adults found “High” strength of evidence supporting greater reductions in

depressive severity and higher response and remission rates for rTMS compared to sham comparisons (Gaynes et al., 2011).

- VA HRS&D: A 2014 evidence brief sought to answer questions about rTMS from a VA memorandum (VA, 2014). Questions included who may benefit, under what treatment protocol, what the predictors of benefit were, and what the longer term outcomes were. The report found that available evidence did not address those questions due to a number of study limitations (Peterson, McCleery, Waldrip, & Helfand, 2014).

Q. Is there any recent research on rTMS as a treatment for MDD?

A. There have been several large trials of rTMS for TRD (e.g. O'Reardon et al., 2007; George et al., 2010; Levkovitz et al., 2015), including a randomized sham-controlled trial conducted by the National Institute of Mental Health (George et al., 2010). Meta-analyses of trials of rTMS for TRD have consistently found that rTMS significantly reduces depression symptoms in treatment-resistant individuals (Gaynes et al., 2014; Lam, Chan, Wilkins-Ho, & Yatham, 2008) and there is consensus that rTMS for TRD is safe and shows short-term efficacy (Perera et al., 2016; McClintock et al., 2017).

A December 2017 literature search identified a number of trials and reviews that have been published after the earlier literature search was conducted for the *2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder*. A full review of this research is beyond the scope of this brief. As the short-term efficacy of rTMS for TRD has largely been established, much of the recent research has focused on the comparative effectiveness of different rTMS modalities (Brunoni et al., 2016; Blumberger et al., 2016; Dell'Osso et al., 2015). Additionally, rTMS research is now being conducted on long-term efficacy and safety (Concerto et al., 2015; Kedzior, Reitz, Azorina, & Loo, 2015), the efficacy of maintenance rTMS to prevent relapse for TRD (Benadhira et al., 2017), and the neurobiological effects of rTMS on the brains of depressed patients (Kang et al., 2016). Notably, there has been little research to date on the comparative effectiveness and cost-effectiveness between rTMS and other treatments for MDD (psychological, pharmacological, and other somatic treatments) (Voigt, Carpenter, & Leuchter, 2017).

Q. What conclusions can be drawn about rTMS as a treatment for MDD in the MHS?

A. Based on the current evidence base, rTMS is not recommended as a front-line treatment for MDD in the MHS. However, evidence supports the efficacy of rTMS during a major depressive episode in patients with treatment-resistant MDD. Limitations of the evidence base include lack of a standard definition of treatment resistant depression, heterogeneity of the population and interventions, and few head-to-head studies with other non-pharmacologic and pharmacologic interventions. A 2014 VA memorandum states that, "Before rTMS can be incorporated into clinical practice guidelines or treatment algorithms for depression, more research is needed to address a number of questions including who may benefit, under what treatment protocol, and how treatment outcomes will be measured." A 2014 VA HSR&D evidence brief found that the current evidence base does not adequately address these concerns, and a number of VA-funded research efforts seeking to address these questions are underway.

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