Repetitive Transcranial Magnetic Stimulation for Major Depressive Disorder

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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., 2018). 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 for the treatment of MDD?

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 within and between cortical networks (Liston et al., 2014). Neuroimaging studies conducted with humans before and after rTMS over the dorsolateral prefrontal cortex (dlPFC) have found changes in frontal or temporal lobe function, activity, or connectivity after rTMS, including normalizing abnormal connectivity (Eshel et al., 2020). Preclinical studies in recent years have explored a variety of mechanisms and signaling pathways (Luan et al., 2020).

Q. Is rTMS recommended as a treatment for MDD in the Military Health System (MHS)?

A. Yes. The *2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder* suggests offering treatment with rTMS during a major depressive episode in patients with treatment-resistant MDD, with a "Weak For" strength of recommendation.

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 treatment for MDD?

A. Yes. Other authoritative reviews have substantiated the use of rTMS for 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 (Rodriguez-Martin et al., 2001). However, the majority of TMS trials were conducted after this review, which has not been updated.
- AHRQ: A 2011 comparative effectiveness review of nonpharmacologic 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).

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 multisite 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 high-frequency rTMS over the left dlPFC significantly reduces depression symptoms in treatment-resistant individuals compared to sham (Cao et al., 2018; Gaynes et al., 2014; Mutz et al., 2018; Sehatzadeh et al., 2019). Meta-analyses indicate that low-frequency rTMS over the right dlPFC is efficacious (Mutz et al., 2018) and may be non-inferior (Chen et al., 2013) to high-frequency right rTMS, while being better tolerated. There is consensus that rTMS for TRD is safe and shows short-term efficacy (Lefaucheur et al., 2020; McClintock et al., 2018).

As the short-term efficacy of rTMS for TRD has largely been established, much of the recent research has focused on different rTMS modalities, relapse and maintenance treatment, localization and targeting of treatment, predictors of response, and clinical questions such as patient selection and treatment parameters (Fitzgerald, 2020). Of note, a 2018 trial of 164 veterans with TRD did not detect any differences between rTMS and sham on the primary outcome of remission (Yesavage et al., 2018). Participants in this study had high rates of comorbid posttraumatic stress disorder and substance use disorder.

Few studies directly compare rTMS to other treatments for depression. A 2014 trial randomized patients to receive rTMS or an antidepressant (venlafaxine), and found no difference in treatment response (Brunelin et al., 2014). Several small trials compare rTMS to electroconvulsive therapy (ECT), but suffer from methodological issues. A meta-analysis found no differences in response rates between ECT and rTMS groups in studies that excluded patients with psychosis (Ren et al., 2014).

Q. What conclusions can be drawn about the use of 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 use 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.

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