rTMS to sham treatment in participants with TRD.(142-144) One analysis found positive response rates of 25% for the intervention, significantly higher than sham; and remission rates of 17% for the intervention (also higher than sham).(144) Gaynes et al. (2014) showed clinically significant decreases in HDRS depressive severity of >4 points compared with sham.(142) Patients with TRD were found to be three times as likely to achieve a response versus sham and were five times as likely to achieve remission.(142) The NNT for response is between 3.4 and 9 patients, and the NNT for remission was between five and seven patients.(142-144) One meta-analysis found no difference between the effects of unilateral compared to bilateral rTMS in MDD,(145) a finding echoed in a more recent SR that was not identified for inclusion in this evidence synthesis.(146)

A more recent RCT, relevant to consider because it was specific to the Veteran population, suggested the considerable role of placebo effects in rTMS.(147) This study compared up to 30 treatment sessions of left prefrontal rTMS to sham control treatments in 164 Veterans with TRD. Treatment-resistant depression was defined as depression that has not responded to ≥2 adequate medication trials, and comorbidities were high, including PTSD and SUDs. The study found significant reductions in depressive symptoms and high remission rates at post-treatment (39% overall). However, there were no significant differences in these outcomes between rTMS and sham conditions reduction at treatment completion and at 24 weeks measured in ITT analyses using the clinician-administered HDRS, as well as with self-report depression symptom measures on the BDI and MADRS. There were also no significant differences when data were stratified by PTSD. Placebo effects were likely enhanced by expectancy and extensive attention provided by the study treatment team.

The benefits of rTMS outweigh the minimal risks and side effects. The most common adverse events are irritation at the stimulation site and headache. There were no significant differences in adverse events in the most recent Veteran trial.(147) One meta-analysis found no significant increase in side effects or dropouts versus sham.(144) Two meta-analyses compared electroconvulsive therapy (ECT) with TMS. One analysis showed significantly more responders and remitters with ECT compared to TMS but no difference in mental status outcomes, cognitive function, or adverse events. A subgroup analysis showed that ECT was more effective in psychotic depression, but rTMS was as effective as ECT in patients without psychosis (with a response rate of 52.5%).(148) The other analysis showed no difference between the two treatments and described mixed results as to whether ECT has a deleterious impact on cognitive functioning compared with rTMS.(149)

The benefits of rTMS outweigh the harms. This offers an option for patients who have not responded to other treatments, and it may be viewed more favorably than ECT by patients. However, considerable limitations are feasibility and access. Repetitive transcranial magnetic stimulation is not uniformly available across all VA/DoD facilities, and access issues exist for individuals who are distant from treatment facilities. The need for daily treatments also limits many patients' ability to engage in this treatment modality.

The Work Group systematically reviewed evidence related to this recommendation (147) and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(144, 145, 148, 149) Therefore, this is a *Reviewed*, *Amended* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had limitations, including small study effects, higher than optimal discontinuation, lack of measurement for allocation concealment, and/or other issues. The