Theta-Burst Neuromodulation for PTSD (TBS)
ClinicalTrials.gov Identifier: NCT02769312
Version: August 17, 2017

STUDY PROTOCOL AND ANALYSIS PLAN

Participants: 55 adult Veterans, ages 18-70 with current PTSD will participate in study procedures.

Inclusion criteria: Principle inclusion criteria will be diagnosis of chronic PTSD, meeting DSM-5 criteria. Eligible male and female Veterans will be between ages 18-70, and, if in treatment, symptomatic despite ongoing stable treatment regimens for at least 6 weeks prior to study procedures. Ongoing medications and psychotherapy will be allowed to continue unchanged during the study. Veterans must also be willing and able to comply with all study related procedures and visits, and capable of independently reading and understanding patient information materials and providing informed consent.

Exclusion criteria: For safety, participants must meet established screening criteria safety during MRI, which is implemented as a conservative measure given the novel application of TBS in this population, since MRI involves magnetic fields at similar intensity to those emitted from the stimulation coil. These measures require a patient not having the following (unless MRI-safe): Cardiac pacemaker, implanted device (deep brain stimulation) or metal in the brain, cervical spinal cord, or upper thoracic spinal cord. TMS-specific exclusions are pregnancy/lactation, or planning to become pregnant during the study, lifetime history of moderate or severe traumatic brain injury (TBI), current unstable medical conditions, current (or past if appropriate) significant neurological disorder, or lifetime history of a) seizure disorder b) primary or secondary CNS tumors c) stroke or d) cerebral aneurysm. Other exclusions are any primary psychotic disorder, bipolar I disorder, active moderate/severe substance use disorders (within the last month, excluding nicotine/caffeine, assessed with urine drug testing), have active suicidal intent or plan as detected on screening instruments or in the investigative team's judgment is likely to attempt suicide within 6 months, and other conditions or circumstance that, in the opinion of the investigator team, has the potential to prevent study completion and/or to have a confounding effect on outcome assessments.

Procedures and Symptom Measures

Following eligibility determination, participants will be randomized to either active or sham TBS, using urn randomization (Wei & Lachin, 1988) with PTSD symptom severity, mild TBI, sex, and depression diagnosis (yes/no) as blocking variables.

Visit Schedule and TBS Procedures. Veterans will attend 10 TBS/sham sessions, delivered over 10 consecutive business days. Each session will last approximately 10 minutes. 10 unblinded sessions will be offered after the double blind phase. Veterans will return to the PVAMC one month later for a post-treatment follow assessment to durability of changes observed. All stimulation will be performed with a Magstim Super Rapid2+1 stimulator equipped with a double 70mm biphasic figure-of-eight air-cooled coil, available at PVAMC. Following established procedures for TBS (Huang et al., 2005) iTBS "dose" will be determined based on each Veteran's active motor threshold (AMT). AMT will be determined using standard procedures. The stimulator coil will then be placed tangentially to the scalp with the handle pointing posteriorly. Stimulation will be applied over the hand area of the right motor cortex (M1) and localized for each participant based on the optimal position to elicit MEPs in the contralateral FDI.

Once the AMT has been determined, the coil will be placed over the right DLPFC using the Beam Method (Beam et al., 2009), and active TBS will be delivered at 80% of AMT (Li et al., 2014). iTBS parameters will include stimulation of three pulses at 50 Hz, given every 200 ms (5 times per second). Two-second trains of these stimulations will be repeated every 10 seconds for a total of 1800 pulses (delivered over 570 seconds)(Li et al., 2014). Sham procedures will be identical, except will use the Magstim sham coil. Medications and therapy will be held stable to the extent possible during study participation, and changes in treatment during iTBS will be recorded.

Participant Safety. Safety will be assessed at every TBS session by recording spontaneously reported adverse events, and participants will be queried daily about potential side effects associated with TBS such as seizure, headache and dizziness. A licensed physician with experience in both neuromodulation and PTSD will be available at all times during study procedures and all participants will be required to wear hearing protection.

Measures and Participant Assessments

Diagnostic/Screening: Age, demographics, race, education, current treatments and psychopharmacologic medication history will be recorded. SCID-5 - The Structured Clinical Interview for DSM-5 (First, 2014) will be used to establish psychiatric diagnoses, current and lifetime, and inclusion/exclusion criteria.

PTSD: CAPS-5 – The Clinician Administered PTSD Scale (Weathers et al., 2013a) will be used to establish a PTSD diagnosis at baseline, and change in scores over time will capture symptom change after TBS and at the end of the follow up period. PCL-5 – The PTSD Checklist (Weathers et al., 2013b) is a 20-item self-report scale of PTSD symptoms. LEC-5 – The Life Event Checklist (Weathers et al., 2013c) assesses for lifetime trauma exposure.
Mood, Affect and Anxiety: IDS-SR – the Inventory of Depressive Symptoms, Self Report (Rush et al., 2003) is a self-report scale that provides a continuous measure of depression severity. PANAS – The Positive and Negative Affect Schedule (Watson et al., 1988) will evaluate changes in affective status. STAI – The State-Trait Anxiety Scale (Spielberger et al., 1983) will evaluate changes in anxiety outside of PTSD symptoms.
Quality of Life, Function and Sleep: QLESQ-SF – The 18-item Quality of Life Enjoyment and Satisfaction Questionnaire (Ritsner et al., 2005) evaluate QOL and other areas of change related to functioning outside of symptom domains. SOFAS – The Social and Occupational Functioning Scale (Morosini et al., 2000) will evaluate changes in functional status attributable to study procedures. PSQI – The Pittsburgh Sleep Quality Index (Buysse et al., 1989) will assess changes in quality of sleep.
General: CGI – The clinical global impressions of severity and improvement (Guy, 1978) will be used to capture overall symptom severity and improvement associated with treatment.
Treatment Satisfaction – The treatment satisfaction form (Blatt et al., 1998) will gather feedback from participants related to study participation.
Blinding: At double blind endpoint Veterans will be queried as to whether they received active or sham.

DATA ANALYSIS

Feasibility and Acceptability. Feasibility will be evaluated by rates of recruitment, treatment adherence, retention and completion of assessments. Acceptability will be measured by retention and participant reports of acceptability and satisfaction. To determine the feasibility and acceptability of TBS, we will examine rates of session attendance (as a proxy for adherence to TBS procedures), dropouts, completion of assessments, number and severity of adverse events, qualitative exit interviews and satisfaction ratings. Feasibility and acceptability of the sham control will use the same procedures as well as assessment of the quality of the sham as indicated above. We will consider 75% session attendance and satisfaction rates of 70% participants as the minimum indicator of acceptability, and completion of a minimum of 75% of end of treatment and 1-month follow up assessments to reflect feasibility. Based on prior use of TBS for depression, we expect fewer than 5% of participants to experience an adverse event, and those that do occur will match the known profile of TBS.

Data Analysis for RCT. Random assignment of participants with regard to baseline characteristics to TBS and sham groups will be initially assessed. We will include as covariates *a priori* specified variables that are plausibly important for explaining the outcome (i.e., baseline PTSD, depression symptom severity and quality of life) and potentially differentially distributed by random assignment. We will also evaluate the degree to which Veterans report changes in other treatments during the intervention to ensure observed changes are related to TBS. Preliminary data analysis will calculate rates of dropout, distributional properties of dependent and other variables, and differences between those subjects who agree and decline to participate.

We will use generalized linear mixed models (GLMM) for repeated measures as our primary analysis. GLMM has advantages of greater flexibility in handling missing data, modeling effects of time and variance or covariance structures of our repeated measures, and analyzing dependent variables that are not normally distributed (Carbonari et al., 1994). We will test the hypothesis that iTBS results in more rapid improvement in primary outcomes, i.e. decreased CAPS/PCL and increased QLESQ/SOFAS. Next, we will test if participants randomized to iTBS will demonstrate greater change on outcome variables immediately after treatment completion compared to participants randomized to sham. This analysis focuses on end-of-treatment group (iTBS vs. sham) differences only, controlling for baseline differences. Our third objective is to test whether iTBS results in sustained change in primary outcome measures at 1-month follow-up in the iTBS group as compared to the sham group, again net of any baseline differences. Finally, we will test whether (changes in) clinical symptoms relate to (changes in) quality of life/function measures differently after iTBS vs. sham. Secondary outcomes will include evaluation of changes in other variables that are either hypothesized or directly affected by TBS (e.g., depression and sleep, and illness severity and improvement) over time.