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TMS for Suicidal Crisis in Active Duty SMs
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PI: Christopher E Hines, MD

Dwight D. Eisenhower Army Medical Center (EAMC)

Outpatient Behavioral Health Service (OBHS)

Inpatient Psychiatric Service (IPS)

300 E. Hospital Road

Fort Gordon, GA 30905

Research Questions/Hypotheses to be tested

Specific Aim 1: Determine whether active TMS added to standard of care and applied for 9 sessions over 3 days (TMSactive) promotes rapid reduction and sustained attenuation of suicidal crisis more than the control condition of sham TMS added to standard of care (TMSsham).

Hypothesis 1.1: Suicidality will decrease more rapidly in the TMSactive group than in the TMSsham comparison group.

Hypothesis 1.2: Duration of suicidal crisis attenuation after completing the course of TMS will be greater at 1-, 3-, and 6- months when receiving TMSactive than TMSsham.

Specific Aim 2: Determine whether depressive symptoms, post-traumatic anxiety, and quality of life among SMs improve with TMSactive treatment.

Hypothesis 2.1: Completing a course of TMSactive will decrease depressive and anxious symptoms while improving quality of life for up to 6 months versus TMSsham.

Research Method and Design:

General study design: This study is a prospective, single-site, randomized, single-blind research design comparing TMSactive to TMSsham. A total of 9 sessions of TMS over 3 consecutive days will be administered as adjunctive treatment to SOC (usual inpatient/outpatient suicide management) for the active treatment group. This study will include two treatment arms and, due to time limitations, reference retrospective controls for an untreated control group. The conditions of the study groups are listed below.

TMSactive Protocol

Localization: Left prefrontal dorsolateral neocortex.

Dose Delivery: Figure-8 solid core coil at 120% motor threshold, 10 Hz, 4 second train duration, 10 second interval for 30 minutes.

Treatment Dose: ~4k/session, 12-15k/day, 36-45k total pulses.

Sessions: 9 in total; 3/day for 3 consecutive days over and above SOC.

TMSsham Protocol

Localization: Left prefrontal dorsolateral neocortex.

Sham Delivery: Figure-8 solid core coil rendered inert via blocking insert.

Dose: Zero pulses.

Sessions: 9 in total; 3/day for 3 consecutive days over and above SOC.

SOC Psychiatric Protocol

SOC may include hospitalization or outpatient treatment with close follow up. In the inpatient setting patients may receive medication intervention, individual therapy, group/milieu therapy and or CAMS. In the outpatient setting patients may be offered medication intervention, CAMS, individual and/or group therapy or may be recommended for increased monitoring by command.

Intervention Regimen

The TMS used for this study will be a Neuronetics NeuroStar XPLOR magnetic stimulator (Neuronetics, Inc., Malvern, PA; NS 0226 A 15VAC-C) consisting of a controller/power supply and three solid iron core coils (active labeled, active not labeled and sham not labeled). These coils will be placed in a support platform for consistent coil positioning/repositioning. This system is designed specifically for research purposes and has validated physically and acoustically matched TMS research coils which create scalp sensations for use in TMS blinded studies.

A Brainsight 2 TMS System will be used for neuronavigation to assure that the same targeted brain location is stimulated with each treatment. Most previous TMS studies determine the position of the coil over the head using external landmark measurements or by trial and error until the desired response (e.g., finger twitch) is elicited. Recent improvements in stereotactic techniques (navigated TMS or neuronavigation) now enable the focused TMS coil to be positioned over a target location based upon an individual's MRI image or MRI generated 3D curvilinear reconstruction of the brain (49,50).

The initial TMS session will begin with a standard motor threshold determination (MTD) which is the minimum intensity required to evoke cortical excitability resulting in a liminal response in the target muscle (usually a thumb muscle). This determination will be recorded and used for the subsequent TMS sessions. To maintain the single-blind nature of the study the same treatment procedure, including the MTD, will be done for both TMSactive and TMSsham groups.

Repetitive TMS will be delivered to the left dorsolateral prefrontal cortex with a figure-eight solid core coil at 120% motor threshold, 10 hertz (Hz), 4 second(s) train duration, 10s-30s intertrain interval for 30-60 minutes (≥4,000 pulses) 3 times daily for 3 days (total 9 sessions; 36,000-45,000 stimuli). Session will take place with a minimum of 90 minutes between sessions. Sham TMS will use a similar coil containing a metal insert blocking the magnetic field and utilize electrodes on the scalp to deliver a matched somatosensory sensation. Sham patients will also have a small electrical 'tickle' delivered from a TENS unit through a patch on the skin directly under the coil. Active patients will have the same patch placed, but it will not be stimulated.

Data collection: Following informed consent, participants will be asked to complete a collection of paperwork. The following procedures will be completed, in order:

1) Confidential Contact Information Form (CCI; See Appendix B). The CCI asks for demographic information including name, physical street address, two phone numbers at which the Service Member can be reached in the need of an emergency such as eminent threat to self or others, and last four numbers of social security number.

2) Demographic Questionnaire (DQ; see Appendix B). The DQ asks for demographic information including date of birth, date of the assessment (i.e., pre- or post-testing), military history, sex, race, ethnicity, medications, scope of past and current behavioral service utilization, past suicidal ideation or attempt, current or past substance use or disorders and medical history including concussion(s).

3) Primary Outcome. The primary outcome measure for Aim 1 is:

a. The Beck Scale for Suicide Ideation (BSS) is a 19-item clinician administered scales that measure current suicide ideation (SSI-C), suicide ideation at its worst point in the patient's life (SSI-W), and hopelessness (BHS) (33, 34). Each item contains three statements, anchored from 0 to 2 and the scale is divided into three parts. The first part, containing the first five items, is a screen for the patient's attitudes toward living and dying: wish to live, wish to die, reasons for living or dying, active suicide attempt, and passive suicide attempt. If the patient indicates no contemplation of a suicide attempt, they are instructed to skip the second part (Items 6 through 19) and complete the third part, whereas those who indicate contemplating a suicide complete the entire instrument. The second part is used to determine suicidal ideation and the patient's anticipated reactions to those thoughts. This part measures frequency, duration, and acceptance of suicide ideation; control over suicide ideation; and the deterrents and reasons for suicide. The patient's anticipated reactions to the suicidal ideation include planning, opportunity, capacity, expectation, and actual preparation for committing suicide; suicide note and post-suicide arrangements; and deception about their suicidal ideation. The third part identifies the number of previous suicide attempts and the seriousness of intent to die during the last suicide attempt. The inpatient sample produced high internal consistency for both samples with a coefficient alpha reliability estimate of .90, and the outpatient sample produced an alpha of .87. Test-retest stability was performed on 60 inpatients and a correlation of .54 was found between tests administered one week apart, indicating moderate test-retest reliability. For a sample of 108 adolescent inpatients, ages 12 to 17, a coefficient alpha of .95 was estimated, indicating a high level of internal consistency (35). The validity of the BSS has correlated with the SSI .90 for an inpatient sample and .94 for an outpatient sample, providing concurrent validity for the BSS. Additional concurrent validity was ascertained

through an inpatient suicide ideators sample on the Beck Depression Inventory (BDI) .48, Beck Hopelessness Scale (BHS) .48, and previous suicide attempts .32. Construct validity was investigated through the significant correlation with assessment scores on the BDI and BHS. Depression and hopelessness were theorized to be factors in suicide risk. Through principal component analysis of the BSS scores of 126 suicide ideators, Beck, Kovacs, and Weissman (1979) identified and labeled three significant factors: (a) Active Suicide Desire, (b) Preparation, and (c) Passive Suicide Desire (36). The BSS is available from PsychCorp with an option to purchase online.

4) Secondary Outcome(s). Secondary outcomes measures for this study include:

a. The Columbia-Suicide Severity Rating Scale (C-SSRS) is a metric used to distinguish the domains of suicidal ideation and suicidal behavior (37). It consists of 4 constructs: severity of ideation, intensity of suicidal ideation, a behavior scale, and a lethality scale. The severity of ideation consists of a 5-point ordinal scale with 1 = wish to be dead, 2 = nonspecific active suicidal thoughts, 3 = suicidal thoughts with methods, 4 = suicidal intent, 5 = suicidal intent with plan. The intensity of suicidal ideation is comprised of 5 items that are rated on a 5-point ordinal scale with items referring to frequency, duration, controllability, deterrents, and reason for ideation. The behavior scale is rated on a nominal scale that includes actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior. The lethality scale is rated on a 6-point ordinal scale where if the score is 0, potential lethality of attempts is then rated on a 3-point ordinal scale. The C-SSRS has been found to have reasonable convergent and divergent validity with other suicidal ideation and behavior scales (Columbia Suicide History Form, the Montgomery-Asberg Depression Rating Scale, and the Beck Depression Inventory) and high sensitivity and specificity for suicidal behavior classification when compared with another behavior scale and an independent suicide evaluation board (38). The C-SSRS is open source and available online in its original form or a military version.

b. The Public Health Questionnaire (PHQ-9) is a psychometrically sound brief measure of depressive symptoms. It is recommended by the Defense and Veterans Brain Injury Center for the evaluation of depression in Service Members. The PHQ-9 may be used to track depression treatment over time (46). A PHQ-9 score of 5-9 shows a provisional diagnosis for minimal symptoms of depression, a score of 10-14 shows a provisional diagnosis for minor depression, dysthymia, or major depression (mild). A score of 15-19 shows a provisional diagnosis for moderate to severe major depression, a score of 20 or above shows a provisional diagnosis for severe major depression. Question number 9 on the instrument queries for the presence of suicidal ideation. Typical administration time is less than 10 minutes and it is intended for adults aged ≥16. Internal reliability for the instrument was found to be excellent within the Primary Care Study (Cronbach's α of 0.89) and Ob-Gyn Study (Cronbach's α of 0.86). PHQ-9 scores were strongly correlated with Short Form-20 (SF-20) scales. It correlated most strongly with mental health (0.73), general health perceptions (0.55), social functioning, (0.52), role functioning (0.43), physical functioning (0.37), and bodily pain (0.33). The PHQ-9 is open source and available online for download.

c. The Posttraumatic Stress Disorder Checklist (PCL) is a commonly used measure with military (PCL-M), civilian (PCL-C), and specific trauma (PCL-S) populations. The metric consists of 17 items that correspond to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) PTSD symptoms. (42); respondents report how much they have been bothered by each symptom in the past month using a 5-point scale. The anchors for the severity ratings range from 'not at all' to 'extremely.' There are multiple

versions of the PCL: the PCL-M and PCL-S are tied to specific stressors, and the PCL-C is tied to stressful life events in general without specificity of the event. Test-retest reliability is extremely high; the PCL correlates strongly with other measures of PTSD. Used as a continuous measure, the PCL has good diagnostic utility. Typical administration time is less than 10 minutes. The PCL has been shown to have high internal consistency within Vietnam and Gulf War Veterans, female Iraq and Afghanistan Veterans, adults with recent limb loss, females with substance abuse disorders, and community adults (correlations ranging from .75 to .80) (43-45). The data from the PCL-M supports the four-factor model of intrusion, avoidance, hyper arousal, and dysphoria. The data from the PCL-C supports the four-factor model of re-experiencing, avoidance, hyper arousal, and numbing (42). All three versions of the PCL are open source.

d. The Medical Outcomes Survey Short Form 36 (RAND SF36) is considered the gold standard in generic Quality of Life metrics quantifying disease burden. It has been employed in 4000+ peer reviewed scientific publications, including more than fifty publications in each of the following conditions: Arthritis, back pain, migraine HA, sleep disorders, depression, psychiatric diagnosis, trauma, and substance abuse. It has been used in over 400 randomized controlled clinical trials – and has been judged to be a useful tool in evaluating benefits of treatments. There are two versions of the instrument, a 4 week and 1 week time referent. It has been found to be suitable for ages ≥14. The instrument requires 5-10 minutes to complete. The data is summarized in 2 higher order factors, termed Physical Health and Mental Health Composites. Eight subscales also are generating, reflecting physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The mental health Composite has adequate sensitivity/specificity for Major Depression. Mental health subscale does pick up anxiety but is more loaded with depressotypic items. From a psychometric standpoint, factor analytic studies confirm physical and mental health factors. Constituent items correlate highly with their parent scales. Internal consistency is variable, with 7 subscales ≥ .80, with lowest subscale (Social Functioning) = .76, highest (Mental Health) = .90. The Physical and Mental Health Composites internal consistencies = .90. A reliable change is denoted as +/- 6 to 7 points for Physical Health and Mental Health Composite scores; +/- 13-32 points for subscales (specifics delineated in Ware et al., (1994) (39). The physical health scales are responsive to physical interventions. Mental health scales are responsive to behavioral health treatment including psychotherapy and drugs. The original RAND version is open source.

Hospital Emergency room visits and admission/re-admission for any behavioral health reason will be assessed for all participants from enrollment date until last data point (~6 months post intervention.

All cause medical appointments and medical appointments will be assessed for all participants from enrollment date until last data point (~6 months post intervention.

Any attempted or completed suicides

Participants in any arm of the study will be monitored for suicide attempts or completions. Any suicide attempts or completions will be analyzed against other arms for statistical significance.

Timing of Assessments.

1) At baseline: SSI, CSSRS, PHQ9, PCL, and SF36.

2) Before each TMS session: SSI.

3) At the final TMS session (i.e., session 9): PHQ9, PCL, SF36.

4) Recording length of stay for inpatients. Calculated by denoting interval in days from date of admission to readiness/stable for discharge determination by attending psychiatrist (see above).

5) At 1-, 3- and 6- month follow-ups, participants will complete the SSI, PHQ9, PCL, SF-36.

Study population: All patients eligible for the study will be at elevated risk for suicide. Total enrollment target: 110.

Inclusion Criteria

All Active Duty SMs (regardless of sex, ethnicity, sexual or religious orientation) who are admitted to EAMC Inpatient Psychiatric Service (IPS) with active suicidality or elevated risk for suicide regardless of most psychiatric diagnostic co-morbidity (see exclusion criteria). This includes in-patient admissions for suicidality and outpatient SMs with a CSSRS score ≥3.

Age 18 to 60 (average age for EAMC IPS admissions is 28).

Able to speak and read English.

Exclusion Criteria

Combative with staff.

Comatose/catatonia.

Incapacity owing to active mania or psychosis.

Epilepsy, multiple sclerosis, or cerebrovascular accident.

Non-removable metal in the head (Shrapnel; plates, aneurysm coils/clips; metal tattoos etc.)

Implantable devices (pacemakers, stimulators, etc.)

Schizophrenic or borderline personality.

Positive screen for pregnancy.

Already receiving TMS as a treatment for depression.

Non-English reading and speaking subjects

Recruitment

All patients will be recruited from EAMC Behavioral Health Services Careline (BHSC) and will be at elevated risk for suicide. Patients are typically referred to the BHSC through a variety of ways including outpatient self- (walk-in clinic or regular appointment), clinician, and inpatient psychiatric referral(s).

All patients treated within the BHSC are given a standard psychiatric evaluation which includes an assessment of suicide risk using the Columbia Scale for Suicidal Ideation (CSSRS). Study staff will monitor admissions and appointments for patients with an elevated suicide risk (using a cut-off score of ≥3 on the CSSRS). These patients will be approached about participation in the study and if a patient agrees to participate in the study they will be screened further by study staff to determine their study eligibility based upon inclusion/exclusion criteria.

We also will advertise internally to potential referring behavioral health providers through live presentation and flyers. We will NOT directly advertise to potential enrollees.

Group Assignment

All patients eligible for the current study will be given psychiatric standard of care (SOC) for addressing suicide, which may include hospitalization or outpatient treatment with close clinical follow up by a provider from BHSC. In the inpatient setting, patients may receive medication intervention, individual therapy, group/milieu therapy and/or Collaborative Assessment and Management of Suicide (CAMS) therapy. In the outpatient setting patients may be offered medication intervention, CAMS, individual and/or group therapy or may be recommended for increased monitoring by command.

Prior suicide attempts are strongly associated with suicidal tendencies and subsequent attempts. Therefore prior attempts (zero vs. one or more attempts) will be used to stratify the sample to assure roughly equal percentages of patients with and without prior suicide attempts will be assigned to the sham control and treatment groups. Subjects will be randomly assigned with prior suicide attempts used to stratify the sample. Study participants will then be randomized into one of two groups to receive: 1) TMSactive or; 2) TMSsham. As previously noted, TMSactive includes 9 sessions of active TMS over 3 days as adjunctive to SOC. TMSsham occurs at same schedule with true sham technology. Follow-up assessments will be done at 1, 3, and 6 months to determine the endurance of the treatment effects.