PROTOCOL TITLE: *Exploring the effects of exercise training on PTSD symptoms and physical health in older Veterans with PTSD.*

PRINCIPAL INVESTIGATOR: *Katherine S. Hall, PhD, MS*

VERSION NUMBER AND DATE: *v7.12/07/2023*

SPONSOR/FUNDING SOURCE*: RR&D RX003120*

NCT Number: *NCT04199182*

Brief Summary

Older Veterans with PTSD have high rates of physical and psychological comorbidity and functional decline. This study tests whether a 6-month supervised, moderate-intensity exercise program improves PTSD symptoms and physical function compared with a Healthy Aging attention-control program.

Study Design

- Study type: Interventional (clinical trial)
- Allocation: Randomized (1:1)
- Intervention model: Parallel assignment
- Masking: Outcomes assessor masked
- Primary purpose: Treatment / behavioral intervention
- Study duration per participant: 6 months

Arms and Interventions

Experimental: Supervised Exercise (EX)

- 6-month, supervised, group-based exercise program delivered three times per week. Participants will have the option to participate virtually in group sessions (via video telehealth) of in the facility-based program.
- Multi-component program (aerobic, strength, balance, flexibility), progressing from light to moderate intensity using Borg RPE targets consistent with ACSM guidelines for older adults.

Control: Healthy Aging Attention Control (HA-ATC)

- 6-month program of up to 24 group workshops delivered via video and in person.

- Sessions cover aging-relevant topics (e.g., immunizations, medication management, nutrition, finances) and include brief gentle stretching; physical activity content is purposely minimized.

Primary Outcome Measures

- PTSD symptom severity (CAPS-5)
    - Measure: CAPS-5 total score
    - Time frame: Baseline, 6 months
    - Description: Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total score.
- Physical function (6-Minute Walk Test)
    - Measure: 6-minute walk test distance
    - Time frame: Baseline, 6 months
    - Description: Change in distance walked on the 6-minute walk test as an indicator of functional capacity.

Secondary Outcome Measures

- Depressive symptoms (PHQ-9).
    - Time frame: Baseline, 6 months
- Sleep quality and disturbance (PSQI).
    - Time frame: Baseline, 6 months

Eligibility (abbreviated)

Inclusion

- Veteran status
- Age ≥65 years.
- Reside within ~50-mile radius of Durham VAMC.
- Meet DSM-5 diagnostic criteria for PTSD as assessed with CAPS-5.

Key Exclusion

- Severe psychotic disorders or bipolar disorder in past 5 years.
- Prominent suicidal ideation or recent hospitalization for suicidality (past 6 months).
- Significant neurological disorders, uncontrolled diabetes, end-stage liver disease, dialysis, or conditions contraindicating moderate exercise.
- Physical disabilities that preclude safe use of exercise equipment (assistive devices allowed).

- Significant cognitive impairment or dementia.

Data Analysis and Statistical Considerations

General Considerations. The basic design of the study is a two-arm parallel group, longitudinal intervention with replicate measures at baseline and 6 months. Randomization to the treatment groups will be stratified by gender. Since subjects are randomized to either EX or HA-ATC, and the groups should be equal at baseline, the analysis is straightforward. The primary and secondary analyses will be conducted on an intent-to-treat (ITT) basis; patients will be analyzed in the group to which they were randomized, regardless of intervention adherence. Additional supporting analyses focusing on alternative, more restrictive analytic cohorts (e.g., per protocol analysis) may be considered for exploratory analyses to provide additional information about the impact of exposure to the intervention. The main conclusions drawn from this trial will be based on the pre-specified primary and secondary hypotheses outlined below and will be tested with two-sided p-values at the standard 0.05 level. Results from exploratory analyses will be interpreted with appropriate consideration for their exploratory nature.

Primary Analysis (Aim 1). Our primary hypothesis (H_1) is as follows: A 6-month structured exercise program will result in significantly greater improvements in PTSD symptoms (CAPS-5) and physical function (6MWT) when compared to HA-ATC.

Secondary Analyses (Aim 2). The secondary hypotheses of this study are:
The 6-month structured exercise program will result in significantly greater improvements in depression (PHQ-9) and sleep quality.

HUMAN SUBJECTS RESEARCH

Risk/Benefit Assessment

Physical risks.

The risk to human subjects for participation in this study is minimal compared to the potential health benefits they will receive from participating in the moderate-intensity exercise program and receiving detailed health and physical performance evaluations. We do not anticipate any significant physical risks to be associated with participation in this study. Exercise participation has not been previously

associated with serious complications in the general literature or in the experience of Dr. Hall, whom has directed several exercise trials in older adults with comorbid conditions.

We also have precautions in place to minimize risk of health events during moderate-intensity exercise. We have developed a safe and effective exercise prescription that 1) addresses the frequency, intensity, time, and type—volume and progression principles of exercise prescription, incorporating a progressive transitional phase (i.e., 8-12 weeks), during which the duration and intensity of exercise are gradually increased from light to moderate intensity; 2) includes appropriate warm-up and cool-down procedures; 3) promotes education of warning signs/symptoms to participants and supervisory staff (e.g., chest pain, lightheadedness, unusual shortness of breath); and 4) counsels patients to avoid unaccustomed vigorous to near maximal-intensity physical activity. Additional precautions include: 1) adhering to exercise safety guidelines for hypertension, hyper/hypo-glycemia; 2) individualizing the exercise prescription to account for musculoskeletal injuries and limitations; and 3) monitoring for any problems or possible exercise-related symptoms during the exercise sessions. In addition, participants will be instructed to report any symptoms to the exercise leaders. Participants will be referred to their primary provider if any clinical problem is detected. We followed these same guidelines in our pilot exercise for PTSD study and had no significant adverse events.

The physical performance measures are all sub-maximal, self-paced tests that are age- and ability-appropriate for this patient population and are routinely used in clinical research. The physical performance tests include activities such as walking, standing, stepping, and stretching. These activities reflect common activities of daily living and as such, are associated with minimal risk for injury. However, there is a small risk of falls or muscle soreness with physical testing. To minimize risk of injury, these tests will be performed under supervision of trained research staff following standardized protocols.

The risk of doing moderate-intensity exercise is low, and may be associated with risk of injury, falls, fainting, dizziness, or muscle soreness. There is even the risk of sudden death or stroke. To minimize these risks during exercise, participants will be instructed to exercise at a comfortable level and to never push themselves to a point beyond where they feel safe. Participants will also be monitored and instructed to report symptoms such as unusual shortness of breath, dizziness, tightness or pain in the chest or arms, skipping heart beats, numbness, loss of balance, nausea, or blurred vision. In both conditions, there is a potential risk associated with the loss of confidentiality of study data. While it is

not possible to guarantee confidentiality in the group setting, all participants will be asked to sign a confidentiality agreement stating that disclosure of group member identities to anyone outside the group is not permissible.

We have also developed detailed SOPs in the case of serious adverse events during exercise testing or training (see attached). This includes:

- Calling 911 for emergencies (offsite exercise facility)
- Presence of a defibrillator on-site, and all research staff trained in use
- Glucose monitoring device and testing strips on-site, available as needed
- Daily monitoring of rating of perceived exertion (RPE) during exercise and patient reports of intensity

Risk of injury and adverse health events with exercise are further reduced by the presence of trained supervision (clinical exercise physiologist) at all times, with further support provided by the fitness facility staff trained in CPR and First Aid.

Psychological risks. As part of our assessments we will ask participants about their PTSD and depression symptoms, other aspects of their health, and their demographic characteristics (i.e., race, socioeconomic status). The PTSD assessments (CAPS-5, PCL-5) can cause some psychological distress, but any ensuing distress is usually well tolerated. The PHQ-9 depression survey includes a single item about suicidal ideation. In our pilot feasibility study 20% of patients endorsed this item, though none expressed active suicidality upon further probing from the research staff. Dr. Beckham, who has worked with thousands of Veterans with PTSD, will be available "on page" for consultation and to assist patients in the event any acute issues arise during the CAPS-5 or any other study-related assessments. Participants will also be referred to their primary provider.

We have developed a Standard Operating Procedure (SOP) for assisting patients that endorse suicidal thoughts and connecting them with services and their provider (see attached). The SOP for suicidal ideation includes:

- Further probing about intent, means, and plan.
- Electronic communication in CPRS that includes the patient's mental health and primary care providers
- Providing a hand-out that shows the resources available including the Veteran Crisis Line phone number, online chat site, and text response system.

- If suicidal ideation appears active or the patient is in distress they are escorted directly to Psychiatric Emergency Services Clinic (PEC), located in the Durham VA HCS emergency room, to receive immediate care.

In addition, if an individual reveals current intent to harm him/herself or someone else, we will escort (or have escorted) the patient to the hospital's emergency room to be seen by staff in the PEC. In the event this information is revealed over the phone, we will transfer this person directly to the Veterans Crisis Line.

Selection of Subjects

The proposed study will randomize up to 188 patients. Because there may be differences in responses to the intervention by gender, we will stratify randomization by gender. Participants will be Veterans 1) aged 65 years or older; 2) live within a 50 mile radius of DVAMC; and 3) meet diagnostic criteria for PTSD (CAPS-5).

Exclusion criteria:

1) history of any psychiatric disorder with severe psychotic features in the past 5 years (e.g., bipolar disorder, mania), as indicated by ICD-10 codes F20-F29 (ICD-9 category 298.9).
2) prominent suicidal ideation or hospitalization for suicidality in the previous 6 months
3) clinically significant: neurological disorder, systemic illness affecting CNS function, or history of seizure disorder in the past 5 years
4) uncontrolled diabetes (defined as: (1) Abnormal fasting plasma glucose ≥126 mg/dL, random plasma glucose ≥200 mg/dL AND (2) no active medications for diabetes management (Metformin, insulin, etc.) AND (3) no clinical notes in the patient's EHR indicating monitoring by PCP or Endo for diabetes management).
5) end stage liver disease or currently receiving dialysis
6) physical disabilities precluding use of exercise equipment (assistive mobility devices acceptable)
7) significant cognitive impairment or diagnosis of Alzheimer's Disease or Dementia
8) hospitalization or ER visit in the past 6 months for conditions contraindicated for exercise (cardiac event; physical trauma)

We will not exclude patients with PTSD who are currently receiving therapy or patients who are currently taking antidepressant medication, but will apply the following criteria: patients must have been in treatment for at least 2 months, meet symptomatic criteria for inclusion, and do not have plans to discontinue treatment during the course of the trial.

Subject Recruitment

For the purposes of screening, recruiting, and determining eligibility, information will be obtained through both identifiable private information obtained by accessing VA medical records, and written communication with the prospective participant.

Recruitment and enrollment procedures:

1. *Identify potential participants using EHR.* Potentially eligible participants will be identified through a CDW data pull. Patients meeting age and select clinical eligibility criteria will be mailed an introductory letter.
2. *Health care provider referrals*. We will collaborate with individual providers and program directors across the VISN6 MIRECC and Durham VAHCS specialty care clinics (PTSD, Mental Health, Women's Health, CBOCs) and programs (MOVE!) to recruit patients for this intervention.
3. *Face-to-face recruitment at Veteran organizations and therapy groups*. We have had some success with face-to-face presentations to Veteran support groups in the past, identifying a number of eligible and dedicated participants. We will use this same approach, but will make this a more frequent and deliberate part of our recruitment strategy than previously employed.

Regardless of the recruitment source, all potential participants will receive a telephone call from a research assistant (RA) who will administer a screening questionnaire to assess additional eligibility criteria. Individuals meeting these criteria will be scheduled for a supervised baseline appointment to complete informed consent, HIPAA authorization, and baseline assessments.

Inclusion of women and minorities. We will actively recruit women and minorities to participate in this study (using recruitment methods described above). Based on our previous studies, the demographic characteristics of the Durham VA HCS patient population 65 years and older, and PTSD prevalence estimates in this age cohort, we expect that 8% of the enrolled will be female and 77% African American.