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14. ABSTRACT

The purpose of the study is to evaluate the efficacy of an exercise training augmentation for cognitive training intervention to improve memory performance in older Veterans with a diagnosis of amnestic Mild Cognitive Impairment (aMCI). The investigators hope to learn if a combination of aerobic and resistance exercise program will augment an already established efficacious treatment for persons with aMCI. Currently, the study has successfully obtained continuing review approval from Stanford University's IRB, VA Palo Alto's Research and Development Committee, and approval from the U.S. Army Medical Research and Material Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO). The study has successfully randomized five participants, all of whom are currently in the exercise phase of the study. The data collection phase of the study has also begun with the randomization of participants. As the study is currently ongoing and in the data collection phase, we do not have results to report.

15. SUBJECT TERMS
Cognitive training; Veterans; Mild Cognitive Impairment; physical exercise; intervention; older adults

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Introduction

The graying of our Veteran population presents the VA with an increasingly large number of patients experiencing cognitive impairment, such as amnestic Mild Cognitive Impairment (aMCI). Persons with aMCI have a significantly greater risk of developing dementia than persons without cognitive impairment. We address the need to improve cognition and quality of life in Veterans with aMCI through a two-year, randomized controlled trial. This is a two-phased trial: 1) an exercise phase and 2) a cognitive training program. The exercise phase will be either a combined aerobic and resistance exercise program or a stretching exercise program. Several possibilities exist as to how physical activity impacts cognition. For example, physical activity both increases cardiorespiratory fitness and also reduces the rate and severity of several vascular risk factors for cognitive impairment such as hypertension, obesity, and type II diabetes mellitus [1, 2; 3; 4]. Hence, it may be that by improving cardiovascular health and reducing vascular risk factors associated with cognitive impairment, physical activity is able to delay or prevent cognitive impairment. The investigators hope to learn if a combination of aerobic and resistance exercise program will augment an already established efficacious treatment for persons with aMCI. Participants will attend thrice-weekly group exercise sessions at the VA Palo Alto Health Care System (VAPAHCS) for two months and then transition to a four-month long home-based exercise program. After completion of the exercise program, all participants will attend classroom-based cognitive training at VAPAHCS for two weeks. The current study will evaluate the efficacy of an exercise training augmentation for cognitive training intervention to improve memory performance in Veterans with a diagnosis of amnestic Mild Cognitive Impairment (aMCI).

Body

The current study has successfully completed the Start-Up Phase of the project and has now transitioned to the Data Collection Phase of the project. Completion of the Start-Up Phase was contingent on several tasks. The first of these was the submission of obtaining all required regulatory approvals. This was a multi-step process that involved the Stanford University's IRB, VA Palo Alto's Research and Development Committee, and approval from the U.S. Army Medical Research Material Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO). It was necessary to obtain these approvals in a sequential manner which presented an unanticipated delay. Nonetheless all approvals were obtained in December 2012. Once approvals were obtained the process of hiring staff was able to be initiated. This was a lengthier process due to delays in required VA credentialing of staff; however, all staff were successfully hired in May 2013. We parallel processed the hiring of staff with the ordering of study-related equipment and establishment of new laboratory space and were able to officially launch recruitment in June 2013.

The study is currently in the Data Collection Phase. A main goal of this phase is the recruitment of participants into the trial. This will be accomplished through a diverse, multi-modal recruitment plan. One primary form of recruitment has been through the review of electronic medical records at the VA Palo Alto Health Care System. During our initial approval process, we obtained a HIPPA waiver and appropriate approvals to screen using CPRS (VA's Electronic medical record). Study staff received approval from providers to review clinics for potential participants. These clinics include the Geriatric Memory Clinic, VA Outpatient Neuropsychology Service, Stanford/VA Alzheimer's Research Center, and the Mental Illness Research, Education, and Clinical Center. Once potential participants are identified, study staff sends an IRB approved letter from the treating provider to the veteran about the study. This letter includes a contact card so that the veteran would need to "opt-in" to be contacted by study staff regarding a phone screen.

A second mode of recruitment has been through print and online media. Study staff has distributed flyers throughout the VA Palo Alto Health Care System and its Community Based Outpatient Clinics (CBOCs) as well as the Vet Centers in the area. Flyers and brochures have also been posted at over 95 places in the community including but not limited to senior centers, VFWs, and libraries. The flyers were provided by the Medical Media at the VA Palo Alto at no cost to the project. We have also placed recurring advertisements in two local newsletters, each of which is widely distributed to older adults in the Bay Area. We have utilized

online resources to list the study on clinicaltrials.gov and the list of clinical trials available through the Alzheimer's Association (www.alz.org). Information regarding the study has been placed on the VA Palo Alto's Facebook page as well as the weekly newsletter distributed to staff.

A third arm in the recruitment plan is community outreach. Study staff has given twelve informational and recruitment talks throughout the greater Bay Area. These talks have been at a variety of facilities including: senior centers, professional conferences, veteran's fairs, wellness fairs, senior centers, and independent living facilities. Over 150 older adults have attended these talks. Study staff is continually searching for opportunities throughout the Bay Area to discuss the study with older adults and those who work with older adults.

The fourth arm of the recruitment plan is provider referral. Study staff has worked to educate providers in neurology, primary care, neuropsychology, psychiatry, and psychology about the study and the inclusion / exclusion criteria. We have successfully established partnerships with providers in these clinics and receive participant referrals from them.

As of October 22, 2013 we have pre-screened 428 individuals through electronic medical review. Those selected for review were through VA clinics, provider referral, or self-referral. Of those 428 individuals that have been pre-screened, 47 potential participants have completed phone screens. The most frequent reasons individuals were excluded from the pre-screening list were because of exclusionary codes E02 (31% N=134) and E03 (31% N=133). Exclusionary code E02 indicates participant has a diagnosis of dementia and E03 exclusionary code indicates the participant has a history of a neurological disorder. Combined, over half of the prescreening log individuals were excluded due to either a diagnosis of dementia or a history of a neurological disorder. The remaining was excluded for reasons including: acute illness or unstable chronic illness, current severe psychiatric disorder, current severe cardiac disease, orthopedic or musculoskeletal problems, morbid obesity, vision loss, and age.

For those 47 individuals who have completed phone screens, 23 participants were consented by study staff and completed screening measures at VA Palo Alto. Of those 23 participants who were consented and completed screening measures, 5 have been randomized to study treatment arms (Combined Aerobic and Resistance Exercise: 1 participant; Stretching Exercise: 4 participants). Currently there are four veterans that are in the active screening phase meaning they have passed the pre-screening process and are participating in the Screening Process with study staff.

Key Research Accomplishments

- Successful completion of the Start-Up Phase
    - VA Palo Alto Health Care System Research & Development Committee 14-Nov-2012
    - Stanford University IRB 21-Nov-2012
    - USMRMC Office of Research Protections 27-Dec-2012
- Initiation of Data Collection Phase
    - Prescreened 428 individuals
    - Phone screened 47 individuals
    - Screened 23 individuals
    - Randomized five participants
        - 1 randomized in the combined aerobic and resistance exercise program
        - 4 randomized in the stretching exercise program
- Obtained most recent continuing review approval
        - VA Palo Alto's Research and Development Committee 10-Jul-2013
        - Stanford University IRB 10-Jul-2013
        - USMRMC Office of Research Protections 30-Sep-2013

As the Data Collection Phase has only recently begun, we do not have reportable outcomes at this time. We do; however, plan to apply for additional funding based on work supported by this award.

Conclusions

As of October 22, 2013 the study has successfully completed the Start-Up phase and all the associated tasks (i.e., obtaining of regulatory approvals, purchasing of necessary equipment, and hiring of staff). We have now transitioned to the Data Collection Phase (June 2013). To date, we have pre-screened over 400 potential participants. Of that number, 45 older adults have completed phone screens. Of those 45 older adults, 23 participants have been screened and 5 were then randomized. There are currently 4 veterans being actively screened by study staff.

Analyzing recruitment flow is a continuous process and we have made adjustments to our inclusion / exclusion criteria appropriately. Specifically, we have received regulatory approval to: 1) to initiate contact with potential participants through a letter from the primary provider; 2) expand the age range to 50 – 90 so as to be more representative of the aMCI population; and 3) removal of sedentary requirement for participation so as to be more representative of the current population of older adults. We plan to continue this process and make regulatory approved adjustment accordingly to maximize recruitment.

At present there are no pharmacological interventions with demonstrated efficacy for the improvement of cognition related to MCI, thus the results of this research have the potential to make a great impact on the lives of older veterans and civilians alike. Veterans, in particular, experience a larger burden of psychiatric and medical illnesses than non-Veterans, which may place them at higher risk for developing cognitive decline.

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Table 1. Phone Screen Failures

Exclusionary code	Phone Screen Fails (N=24)	Exclusionary code description
E01	10% (N=5)	Current severe psychiatric disorder
E03	8% (N=4)	History of neurological disorder
E06	4% (N=2)	Orthopedic or musculoskeletal problems
E14	2% (N=1)	Did not have sedentary lifestyle for the past six months
E15	2% (N=1)	Unwilling to participate for 8 months
E_Other	23% (N=11)	Participants did not follow up or return voice mails for further screening visits.

Note: E14 is no longer an exclusionary criterion. This was approved by the Stanford IRB on 7-Aug-2013.

Table 2. In House Screen Failures

Exclusionary code	Screen Fails (N=16)	Exclusionary code description
E03	12% (N=2)	History of neurological disorder
E06	6% (N=1)	Orthopedic or musculoskeletal problems
E11	56% (N=9)	Did not have a diagnosis of aMCI
E15	12% (N=2)	Unwillingness to participate for 8 months
E_Other	12% (N=2)	One participant would like to be contacted in Spring 2014 and the other did not follow up with voice mail for further screening.

Table 3. List of Exclusionary Criteria

Exclusionary Criteria	
Screen Code	**Criteria**
E01	Current severe psychiatric disorder, such as Bipolar I, Schizophrenia, or Major Depressive Disorder, determined by the Mini International Neuropsychiatric Interview (MINI).
E02	Diagnosis of dementia, CDR > 0.5; modified Hachinski score ≥ 4; Blessed Orientation Memory Concentration task (BOMC) > 10, or delirium (those with scores indicative of dementia will be referred to the ARC for a full diagnostic work-up).
E03	History of neurological disorder (e.g., multiple sclerosis, seizure disorder, stroke, history of transient ischemic attacks) or systemic illness affecting CNS function (e.g., liver failure, kidney failure, congestive heart failure, systemic cancer)
E04	Acute illness or unstable chronic illness, e.g., history of severe liver disease (cirrhosis, esophageal varices, ascites, portal hypertension, hepatic encephalopathy).
E05	Current severe cardiac disease (e.g., uncontrolled atrial fibrillation, defined as mean 24 hour heart rate > 85 beats/min, or 24 hour maximal ventricular rate >150 beats/min; uncontrolled ventricular arrhythmias, defined as recurrent ventricular tachycardia > 3 beats in succession, or 24 hour PVC count > 20%; active pericarditis or myocarditis; Class III/IV heart failure and / or ejection fraction < 20%; thrombophlebitis; pulmonary disease with a drop in O2 Sat with exercise to 90% without oxygen; embolism within past 6 months).
E06	Inability to participate in an exercise stress test or inability to exercise consistently because of orthopedic or musculoskeletal problems
E07	Morbid obesity (BMI > 39).
E08	Inability to read, verbalize understanding and voluntarily sign the Informed Consent. Veterans meeting any of these exclusion criteria will be excluded from all aspects of this project.
E09	Not a veteran
E10	Not in between the ages of 50-90
E11	Did not have a diagnosis of aMCI
E12	Did not have an available informant to document cognitive impairment and functional status
E13	Did not have sufficient visual and auditory acuity to allow neuropsychological testing
E14*	Did not have sedentary lifestyle for past sixth months (defined as <30 minutes of structured physical activity < three times a week in past six months).
E15	Did not have willingness to participate in exercise training + cognitive training program for 8 months.
E16	Did not have approval of primary provider to participate in an exercise trial.
E17	Refusal to sign the consent and or HIPAA form

Note: *E14 is no longer an exclusionary criterion. This was approved by the Stanford IRB on 7-Aug-2013.