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TITLE: A Combined Training Program for Veterans with Amnestic Mild Cognitive Impairment

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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-phase 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 ten two-hour classroom-based cognitive training at VAPAHCS. 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 study is currently in the Data Collection Phase. The primary goal of this phase is the successful recruitment and randomization of participants into the trial. This is accomplished through a diverse, multi-modal recruitment plan. One primary form of recruitment has been through the review of electronic medical records at the VAPAHCS. During our initial approval process, we obtained a HIPAA 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 have distributed flyers throughout the VA Palo Alto Health Care System and it's 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, Veterans of Foreign Wars USAs (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.

We continued our recruitment efforts to those veterans outside of the VA health care system. By collaborating with a local marketing company, we developed study postcards to be distributed across the Bay Area. The result of this collaboration was the mass mailings of our study postcards to veterans across Santa Clara, San Mateo, Alameda, San Francisco, and Santa Cruz Counties. Over 2,000 postcards were mailed out to veterans aged 64-85 in Alameda County and 3,900 postcards to veterans 50 years and older in San Francisco and Santa Cruz Counties. In addition, we mailed out additional postcards to San Mateo, Santa Clara, and Alameda counties targeting age groups we did not send during the first wave of mailings. Over

5,000 postcards were sent to veterans aged 50-64 in Santa Clara and San Mateo Counties and over 2,800 postcards were mailed out to veterans aged 50-63 in Alameda County. This recruitment method has been quite successful as we have been able to reach thousands of veterans that may not otherwise have heard about the opportunity of the study. We will continue this recruitment method by targeting Alameda and Contra Costa Counties in the upcoming weeks.

Another aim 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.

From September 27, 2014 to September 26, 2015 we have pre-screened 111 individuals through electronic medical review. Those selected for review were through VA clinics, provider referral, or self-referral. In addition to the 111 individuals that were pre-screened, we had many interested veterans call to inquire about the program. In the past year 118 phone screen interviews were completed and 86 potential participants came in for in-house screening visits. To date we have randomized 63 individuals into either the CARE or SE groups. The most frequent reasons individuals were excluded from the in-house screening were because of exclusionary code E11 (45% N=39), which means they did not have a diagnosis of aMCI (amnestic mild cognitive impairment). The remaining was excluded for reasons including: acute illness or unstable chronic illness, current severe psychiatric disorder, current severe cardiac disease, or did not have the willingness to participate.

From September 27, 2014 to September 26, 2015 we have phone screened a total of 118 potential participants. Of those 118 veterans who completed the phone screen interview, 86 participants were consented by study staff and completed screening measures at VA Palo Alto. Of those 86 participants who were consented and completed screening measures, 33 have been identified as eligible for the study program.

Key Research Accomplishments

- Continuation of Data Collection Phase for Past Year
    - Phone screened 118 individuals (out of 341 total)
    - Screened 86 individuals (out of 159 total)
    - Randomized 33 participants CARE=16 SE=17 (out of 63 total)
- Obtained most recent continuing review approval
        - VA Palo Alto's Research and Development Committee 21-Jan-2015
        - Stanford University IRB 3-Jun-2015
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Reportable Outcomes

Preliminary findings from this data, reported in prior reports (see 2013-2014 Annual Report) were essential in securing of four new sources of funding from the Alzheimer's Association, VA, and DOD. First, the Alzheimer's Association awarded Dr. Fairchild a New Investigator Research Grant (NIRG) award for the project, "Exercise and Cognitive Function in Older Adults with MCI". The focus of this NIRG award is to identify cellular and molecular mechanisms of exercise response in the sample of the current DOD TATRC funded project with a particular focus on proteomics which will consist of targeted measurements of circulating plasma proteins with endocrine activity including myokines, hormone-like proteins, growth factors and so forth. Additional intramural funds from the Palo Alto VA RR&D REAP: Innovative Rehabilitation Strategies for Muscle Dysfunction. Through this additional intramural funding, we hope to conduct a small sample of whole genome sequencing, to provide pilot data for future large scale analysis.

In addition to the Alzheimer's Association and local intramural funding, Dr. Fairchild and colleagues were awarded a VA Rehabilitation Research and Development SPiRE Award for the project, "WATER-VET (Water-based Activity to Enhance Recall in Veterans). As in the AANIRG award, the preliminary findings from the current DOD project were encouraging yet it was clear from our enrollment data that approximately 15% of veterans were ineligible due to musculoskeletal issues, which made weight bearing exercise impossible. While water-based work is the most recommended exercise for older adults, it is unknown whether it is appropriate as an augmentation for cognitive training in veterans with MCI. The purpose of the SPiRE is to determine if water-based physical activity is feasible in this population.

Finally, we successfully competed for additional DOD funding to use physical exercise and caregiver skills training for caregivers of veterans with TBI and dementia. This intervention will be delivered to caregivers in their home using mobile-based technology. This is an exciting expansion of the current work to a population that is in great need of intervention.

Thus in the past year, we have secured about $800,000 in additional funding for research that is directly related to the current project.

Conclusions

As of September 26, 2015 the study has successfully continued the Data Collection phase and all the associated tasks (i.e., obtaining of regulatory approvals, purchasing of necessary equipment, and hiring of staff). In the past year, we have phone screened a total of 118 potential participants. Of those 118 veterans who completed the phone screen interview, 86 participants were consented by study staff and completed screening measure at VA Palo Alto. Of those 86 participants who were consented and completed screening measures, 33 have been identified as eligible for the study program (CARE= 16 and SE= 17), bringing out total randomized up to 63.

To enhance our recruitment flow we began to send out mass mailings to veterans across the Bay Area in Santa Clara and San Mateo County. Postcards advertising our study were sent out to thousands of veterans' homes as an opportunity to reach as many veterans as possible. This recruitment method has been quite successful; we were able to reach veterans who may otherwise have not had the opportunity to hear about our study. We will continue this recruitment method in the upcoming weeks by targeting Alameda and Contra Costa Counties.

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.

References

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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
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E16	Did not have approval of primary provider to participate in an exercise trial.
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