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14. ABSTRACT

This study examines the efficacy of two cognitive-behavioral treatments for PTSD-related recurrent nightmares and other sleep difficulties in Veterans of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) in a randomized controlled trial. Participants will be 115 OEF/OIF Veterans in outpatient treatment for PTSD at one of two study sites, the Philadelphia VAMC or the VACHS, West Haven, CT.

During Year Four of this award, data collection was ongoing at the Philadelphia sites (PVAMC and PVAMC affiliated outpatient clinics). Data will be analyzed at the end of the data collection period, and therefore research findings are not yet available. Sixty-five patients have been enrolled in the protocol to date.

15. SUBJECT TERMS
Posttraumatic Stress Disorder, Nightmares, Randomized Controlled Trial, Cognitive-behavioral Treatment, OEF/OIF Veterans

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Section I: Introduction

A substantial proportion of Veterans returning from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) have significant psychological symptoms related to traumatic war zone exposure, including recurrent nightmares and other sleep disturbances. Nightmares are generally distressing and difficult to treat, often persisting despite successful resolution of other Posttraumatic Stress Disorder (PTSD) symptoms. A cognitive-behavioral treatment (CBT), Imagery Rehearsal (IR), appears to have promise for successfully treating nightmares. This study investigates the efficacy of IR in treating OEF/OIF veterans, many of whom likely have mild to moderate traumatic brain injury (TBI). There are three main objectives of this study: 1) to examine the efficacy of IR, combined with psychoeducation about PTSD and nightmares and standard CBT for insomnia (IR + PPCI), compared to psychoeducation about PTSD and nightmares and CBT for insomnia (PPCI) alone, in reducing nightmare frequency and improving global sleep quality in OEF/OIF veterans with PTSD; 2) to determine whether there are moderating effects of neurocognitive impairment on the efficacy of these two forms of CBT for nightmares; and 3) to explore possible neurobiological correlates of treatment-related changes in nightmare frequency and sleep quality, focusing on noradrenergic systems. One hundred and fifteen OEF/OIF Veterans enrolled in treatment for PTSD at the Philadelphia VA Medical Center (PVAMC) or the VA Connecticut Health Care System (VACHS), West Haven, CT, will be randomized to one of two individual treatments: IR + PPCI or PPCI alone. Participants are referred by their mental health treatment providers and assessed for PTSD and war zone-related nightmares. Participants complete a battery of computerized neuropsychological tests at baseline and are stratified in their randomization to either group depending on the results. Once randomized, participants meet for 6 weekly individual sessions of IR + PPCI or PPCI alone. Participants complete self-report questionnaires assessing nightmares, sleep quality, PTSD, and depression, at baseline, immediately after treatment, and again three and six months after treatment. Additionally, participants provide saliva samples for measurement of salivary alpha-amylase, a marker of peripheral noradrenergic activity, both before sleep onset and upon awakening, for two nights before treatment and for two nights before the first post-treatment assessment.

Section II: Progress to Date on 5 Study Tasks in Approved Statement of Work:

1. Obtaining approvals for the study protocol at the study locations.

A. Philadelphia VAMC/University of Pennsylvania:

- Regulatory review of the initial protocol was completed by the PVAMC IRB on 3/13/2008 and the DoD HRPO on 2/13/2009. During the current reporting year, we have submitted the following amendments to this protocol: Study brochure, recruitment of active duty persons, change in recruitment numbers (9/8/11); staff form changes: replace Jackie Halpern with Liz Waldron (4/14/2012).

B. VACHS, West Haven/Yale University:

- Regulatory review of the initial protocol was completed by the VACHS IRB and Research and Development Committee on 6/5/2008 and by the Yale University

IRB on 11/12/2008. The DoD HRP O approved this protocol on 2/24/2009. The protocol for this study site was closed during the current reporting period: closure of protocol at VACHS site (3/7/12), cl osure of protocol at Yale University (10/13/11).

PROBLEMS ENCOUNTERED:

- Delay in transfer of data to primary site: After many delays, copies of all available data were transferred to Philadelphia. Curr ently, the principal investigators are requesting access to identifiable informati on for the participants enrolled at the CT site to allow for veri fication of inclusion and exclusion criteria for those participants.

2. Recruitment, assessment and randomization of 109 participants at the PVAMC site and 6 at the VACHS site (total N=115).

A. Philadelphia VAMC:

- During this reporting period, we received approval for a 2-year no-cost extension as well as reduction in target enrollment number from 160 to 115 (see last annual report for justification).
- The PVAMC site was the source of 37 referrals from treatment providers during the reporting period. Eight y-six percent (32) were male, and 14% (5) were female. Thirty-eight percent (14) were African-American, 14% (5) Hispanic, 38% (14) Caucasian, 2% (1) were Asian, and 5% (2) were of unknown ethnicity. Assessments were scheduled with 16 potent ial participants: Eight Veterans completed both assessment sessions, and a ll were enrolled in the study: five were randomized to IR + PPCI and three to PPCI alone.
- The Philadelphia VAMC-affiliated CBOCs were the source of 57 referrals from treatment providers during the reporting period. Ninety-one percent (52) were male, and 9% (5) were female. Approximately twenty-six percent (15) were African-American, 4% (2) Hispanic, 62% (35) Caucasian, 1% (1) American Indian/Alaskan Native, and 7% (4) of other ethnicity. Assessments were scheduled with 17 potential participants: 19 completed the first assessment, and 15 Veterans completed the second assessm ent as well. Fifteen participants were enrolled in the treatm ent study in the past year: Seven were randomized to IR + PPCI and eight to PPCI alone.

PROBLEMS ENCOUNTERED:

- Technical issues: The VA IT department interrupt ed our ability to conduct our computerized neuropsychological assessment. Our access to the program was discontinued without warning, requiri ng a 6-week process to re-install and re-obtain access to it. We conti nued to enroll participants during this period; however, we lost some data fo r the neuropsychological aspect of this project due to this issue.
- Replacing of independent assessor: The independent assessor for this project left the study in February 2012. Having had advance notice, we

interviewed candidates in late 2011, identified and hired a new assessor in January 2012. Although we started the hiring process at the VA in January 2012, the assessor was not processed, allowed to have patient contact and work on the project until April 14, 2012. This administrative process caused a break in recruitment for this study between January 2012 and April 2012. However, we utilized this period as an opportunity to revisit all sites, introduce the new staff member, and reintroduce the study and its referral requirements to all providers, and restart recruitment at the sites in April 2012.

- Temporary leave of one study therapist: The therapist at the Camden CBOC is currently on maternity leave from May 2012 to September 2012. We look forward to her return.

- Recruitment challenges: As stated above, we were forced to interrupt recruitment for a period of over 3 months in early 2012. However, since re-starting recruitment, we have been very successful in obtaining referrals and enrolling participants. In the last quarter, we obtained 35 referrals and enrolled six participants in the study, with a number of Veterans scheduled to be assessed over the summer.

  The recruitment and retention of OEF/OIF Veterans remains a challenge. These mostly younger men and women often are ambivalent about seeking treatment, and have a multitude of life responsibilities as well as post-deployment symptoms that interfere with consistent attendance at assessment and/or treatment sessions. Our approach to engaging these Veterans in this project is to pre-screen providers' upcoming appointments, have the Veterans' regular providers with whom they already have a relationship initiate contact, make personal contact ourselves with the Veterans, and follow-up with several reminder phone calls. We are confident that we are doing everything possible to engage interested Veterans in this intervention study and have had considerable success with this strategy. We are confident that we will be able to continue our current recruitment rate and even increase it further.

Table 1: Recruitment at PVAMC and affiliated CBOCs

Recruitment Site	Referred	Assessed	Enrolled PPCI+IR	Enrolled PPCI
Willow Grove CBOC	15	4	2	2
Camden CBOC	5	1	0	1
Gloucester CBOC	29	9	3	3
Ft.Dix CBOC	10	5	2	2
PVAMC	35	16	5	3

Total	94	35	12	11

B. VACHS, West Haven:

- The VACHS site received 22 referrals from treatment providers and 14 self-referrals, of which 89% were male and 11% were female, with an average age of 35. Fifty-eight and three tenths percent were Caucasian, 22.2% African-American, and 19.4% Hispanic/Latino. Assessments were scheduled with 12 potential participants, and six Veterans completed the second assessment. Six participants were enrolled in the treatment study.
- The VACHS site has been closed to enrollment since 4/2010.

3. Administration of six sessions of the protocol treatments to participants.

A. Philadelphia VAMC/CBOCs:

- Of the 23 Veterans enrolled at the PVAMC and its affiliated CBOCs this year, 11 have completed all six sessions of treatment and are in the follow-up phase, five have completed all follow-up visits, six are currently in treatment, and six Veterans have withdrawn from the study.
- Treatment fidelity: During Year One of this award, a detailed supervision plan as well as fidelity rating procedures were developed, and these are being used. Study supervisors, Drs. Philip Gehrman and Andrea Phelps, review treatment tapes, and weekly supervision calls with study supervisors are attended by all therapists; these have ensured treatment protocol adherence across sites.

B. VACHS, West Haven:

- Of the six participants enrolled in the treatment study over the course of VACHS's participation, one Veteran withdrew after completing one session of treatment. Five Veterans completed the treatment and all follow-up assessments.

4. Follow-up: re-assessment for detection of treatment effects and maintenance of benefits immediately post-treatment, and at 3 months and 6 months post-treatment.

A. Philadelphia VAMC/CBOCs:

- Six Veterans are currently active in the follow-up phase of the study, and five Veterans completed all study follow-ups this year. Of the six in follow-up, all have completed the first post-treatment assessment and two have completed 3-month follow-up. We have lost no Veterans to follow-up this year.
- In total to date, 30 Veterans have completed the final 6-month follow-up assessment for the study. 41 Veterans completed treatment and the first post-treatment assessment. One participant completed 3-month follow-up but not the 6-month follow-up. Finally, four Veterans withdrew from the study during treatment and eight after randomization but before receiving any treatment. Six Veterans dropped out during follow-up.

B. VACHS, West Haven:

- Five participants completed all post-treatment and follow-up assessments as of December 2010.
- No Veterans remain actively enrolled in this study at VACHS.

5. Statistical analysis of the data and manuscript preparation.

- The project is in the data collection phase, and no statistical analyses currently are being completed.

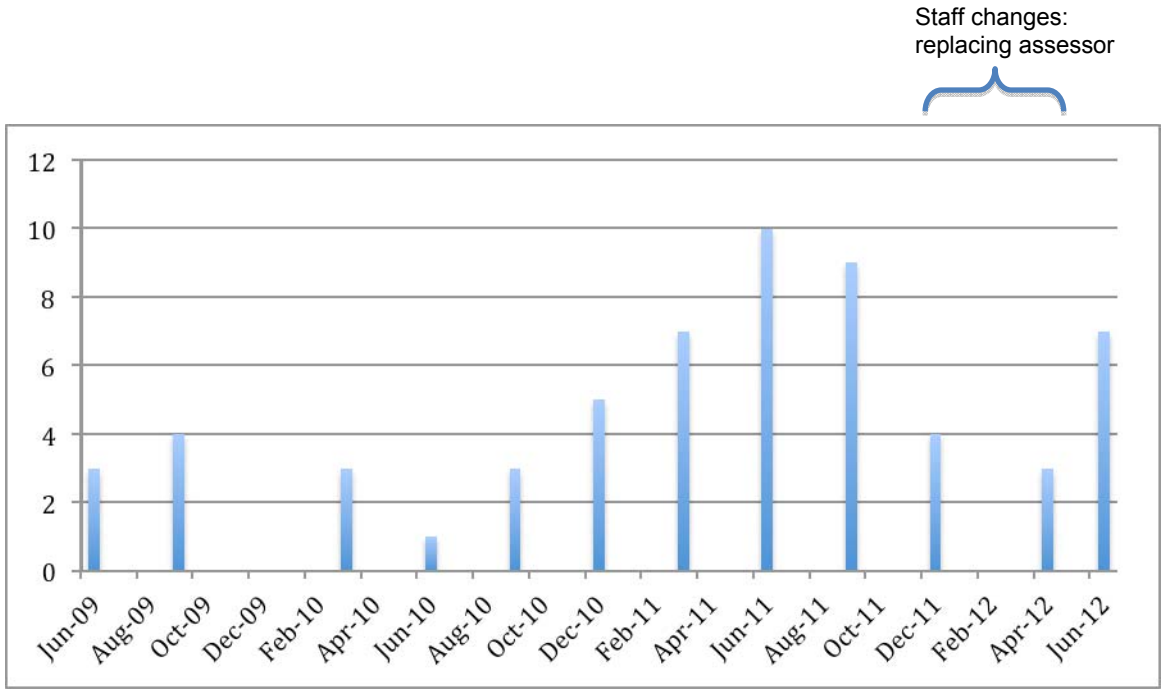
Philadelphia VAMC:

- Entry of data from assessed and enrolled participants is ongoing at the PVAMC and its affiliated CBOCs. We are also in the process of data checking all previously entered data.
- Data from the closed VACHS site is still in the process of being verified and no data have been entered into study databases.

Section III: Key Research Accomplishments:

- Completion of lengthy regulatory reviews at PVAMC, Yale University, VACHS, as well as the DOD HRPO.
- Hiring and training of staff, most recently new staff to recruit, assess, and provide treatment at the PVAMC-affiliated CBOCs.
- Participant recruitment is ongoing at the PVAMC site and its affiliated CBOCs.
- Extensive efforts to boost recruitment rates. These have included modification of the protocol to allow active duty personnel seen at the VA to be included in this study.
- Successful shift of recruitment from the VACHS site, which discontinued recruitment of participants for the study in April 2010, to the PVAMC-affiliated CBOCs.
- Successful increase in recruitment rate, see Figure 1, below.

Figure 1. Number of Veterans enrolled since start of enrollment



Section IV: Reportable Outcomes: Presentations:

Report of study overview, study progre ss and recruitment rate at the Military Operational Medicine Research Program (MOMRP)/Joint Program Committee for Military Operational Medicine (JPC5) In Progress Review (IPR) meeting on March 20-21, 2012.

Section V: Conclusions:

During this contract period, recruitment was ongoing at the Ph iladelphia VAMC and its affiliated outpatient clinics (CBOCs). Due to a staff change, there was an unanticipated, unavoidable 3-month break in recruitment at the beginning of the 2012 calendar year. However, we have been able to maintain a stable enrollment rate through the subsequent three months leading up to this report. In total, we have enrolled 65 participants in this study, 23 of whom during the current r eporting year, with 6 participants currently in the follow-up phase of the study. Of these 23, 15 were enrolled at the CBOCs, showing the value of incorporating these outpatient clinics.

We are steadily progressing toward our enrollm ent goal of 115 participants. We project that we will enroll approximatel y 30 participants in the upcomi ng reporting period. This will place us at 95-100 participant s at this time next year. We will likely require extra time to complete recruitment in order to reach our target number of 115. To this end, we plan to apply for an additional no-cost extension.