AD_____

Award Number:
W81XWH-08-2-0104

TITLE:
CBT for Nightmares in OEF/OIF Veterans

PRINCIPAL INVESTIGATOR:
Richard Ross, M.D., Ph.D.
Gerlinde Harb, Ph.D.

CONTRACTING ORGANIZATION:
Philadelphia Research and Education Foundation
Philadelphia, PA 19104

REPORT DATE:
July 2014

TYPE OF REPORT:
Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

- Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
July 2014	Annual	1 JUL 2013-30 JUN 2014

4. TITLE AND SUBTITLE
CBT for Nightmares in OEF/OIF Veterans

5a. CONTRACT NUMBER

5b. GRANT NUMBER : W81XWH-08-2-0104

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Richard Ross, M.D., Ph.D.; Gerlinde Harb, Ph.D.
email: Richard.ross2@va.gov

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Philadelphia Research and Education Foundation
Philadelphia, PA 19104

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research
And Materiel Command
Fort Detrick, Maryland
21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

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 Six 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. One hundred and eight patients have been enrolled in the protocol and patient enrollment is complete.

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

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	9	**19b. TELEPHONE NUMBER** *(include area code)*

Table of Contents

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, were to be randomized to one of two individual treatments: IR + PPCI or PPCI alone. Participants were referred by their mental health treatment providers and assessed for PTSD and war zone-related nightmares. Participants completed a battery of computerized neuropsychological tests at baseline and were stratified in their randomization to either group depending on the results. Once randomized, participants met 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 provided 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 and R&D committee 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:
    - 11/4/13 - Removed Caitlin Cassidy from staff form
    - 12/20/13 - Changed file transfer mechanism to Penn + Box file transfer

- 2/12/14 - Added Janeese Brownlow, Catherine Collins & Gabrielle Sorlo to staff form
- 6/2014 - Added Adina Weissman to staff form and removed Catherine Collins & Gabrielle Sorlo from staff form; changed, in the protocol, room number where data are stored

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 HRPO approved this protocol on 2/24/2009. The protocol for this study site was closed at Yale University on 10/13/11 and at the VACHS site on 3/7/12.

PROBLEMS ENCOUNTERED:

- The PVAMC IRB determined that this protocol now is classifiable as "international research" due to our Australian therapy supervisors and collaborators. The IRB required us to complete paperwork to obtain approval to perform "international research," which was submitted in July 2014. This process does not preclude us from carrying out the research activities of this protocol.

2. Recruitment, assessment and randomization of 102 participants at the PVAMC site and 6 at the VACHS site (total N=108).

A. Philadelphia VAMC:

- Recruitment of participants was ongoing during most of this reporting period. We recruited participants until early June 2014, when, after a period of reduced referrals, it was determined that the effort and cost of recruitment could not be sustained. We were in contact with DoD personnel to obtain approval to stop recruitment, and we ceased recruiting at 102 participants, just short of our target of 109, which, when added to 6 VACHS participants would have made a total of 115 participants.
- The PVAMC site was the source of 30 referrals from treatment providers during the reporting period. Ninety percent (27) were male, and 10% (3) were female. Forty-seven percent (14) were African-American, 6% (2) Hispanic, and 47% (14) Caucasian. Assessments were scheduled with 11 potential participants. 7 veterans were enrolled in the study. Three were randomized to IR + PPCI and four to PPCI alone.
- The Philadelphia VAMC-affiliated CBOCs were the source of 60 referrals from treatment providers during the reporting period. Eighty-eight percent (53) were male, and 12% (7) were female. Approximately twenty-five percent (15) were African-American, 7% (4) Hispanic, 58% (35) Caucasian, 1.5% (1) American Indian/Alaskan Native, 1.5% (1) Asian, and 7% (4) of other ethnicity. Assessments were scheduled with 12 potential participants: 7 were enrolled in the study. Three were randomized to IR + PPCI and four to PPCI alone.

PROBLEMS ENCOUNTERED:

Technical issues: Our main technical issue this year was the result of an upgrade to the MIRECC server system in October 2013. This upgrade caused a change in the file structure, and we lost our ability to digitally transfer videorecordings of therapy sessions to the supervisor and collaborator in Australia, Dr. Andrea Phelps. We continued to work with the Philadelphia VAMC Information Security and Privacy officers as well as the Philadelphia VAMC IRB to establish a new, secure route for the transfer of the recordings, which received approval in March 2014.

Recruitment challenges:

- OEF/OIF Veterans are a challenging group of individuals to engage in studies and maintain in treatment and follow-up. Their unique combination of posttraumatic (and comorbid) symptomatology, younger age (often having families with young children), and work obligations often prevent regular attendance at clinical or research appointments. We have developed many recruitment strategies over the last several years to aid in recruiting and maintaining participants in this study. These have included: outreach to providers and careful review of all upcoming appointments of mental health and post-deployment primary care providers to identify potential participants; frequent reminder phone calls; and flexible scheduling. We are confident that we have approached all potentially eligible Veterans at the PVAMC and its CBOCs. For unclear reasons, the recruitment rate dropped in 2014, and we believe that the potentially eligible OEF/OIF Veterans currently in treatment at the PVAMC and its CBOCs have already been studied or approached by our staff. An insufficient number of new patients are currently engaging in mental health treatment in the Philadelphia area to allow us to project an increase in our recruitment rate. We therefore decided to stop recruitment before reaching our goal of 115 participants.
- Despite the loss of a second study therapist, we succeeded in getting referrals from most recruitment sites. A Philadelphia-based therapist was able to travel to two CBOCs, and some participants were willing to travel to a location different from their recruitment site.
- New recruitment site: We obtained approvals for adding a new recruitment site at the Coatesville VAMC (CVAMC), approximately 1 hour from the Philadelphia VAMC. However, it became apparent that the start up of a new site would necessarily divert existing resources from operations at the PVAMC and its CBOCs as we would not have been able to hire additional staff. Therefore, there was a consensus with our program officer that energy and resources should remain focused on the PVAMC and its CBOCs and that expanding recruitment to the CVAMC and its CBOCs should be deferred. Eventually, we decided to close the protocol at the CVAMC in early 2014 without having had a chance to recruit any patients from that site.

Table 1: Recruitment at PVAMC and affiliated CBOCs for reporting period

Recruitment Site	Referred	Assessed	Enrolled PPCI+IR	Enrolled PPCI
Willow Grove CBOC	2	1	0	1
Camden CBOC	3	1	1	0
Gloucester CBOC	8	1	1	0
Ft.Dix CBOC	47	9	1	3
PVAMC	30	11	3	4
Total	90	23	6	8

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:

- All Veterans enrolled during the reporting period have completed treatment. We have no Veterans in active treatment at this time.
- Treatment fidelity: No active treatment is taking place, and therefore supervision of therapists has ended. We are currently in the process of ascertaining which external rater (an expert in the field of Imagery Rehearsal and CBT-I) will conduct the final fidelity analysis of a percentage of all therapy recordings.

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 immediately post-treatment and maintenance of benefits at 3 months and 6 months post-treatment.

A. Philadelphia VAMC/CBOCs:

- Eleven Veterans are currently active in the follow-up phase of the study. Of the eleven in follow-up, all have completed the first post-treatment assessment and four have completed the 3-month follow-up. We have lost no Veterans to follow-up this year.

- In total to date, 56 Veterans have completed the final 6-month follow-up assessment for the study. We had 5 drop-outs during the follow-up period: 4 Veterans completed treatment and the first post-treatment assessment but did not return to complete the 3- or 6-month follow-up; one participant completed the 3-month follow-up but not the 6-month follow-up. Finally, sixteen Veterans withdrew from the study during treatment and fourteen after randomization but before receiving any treatment.

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.
- Our data monitoring committee requested that we complete a review to ascertain that the participants enrolled at the VACHS site met all of the study's inclusion and exclusion criteria. After obtaining all the necessary permissions to access the pertinent computerized medical records, we completed this review and determined that the VACHS participants were included appropriately in the study.

5. Statistical analysis of the data and manuscript preparation.

- The project is still in the data collection phase, and no statistical analyses are currently being completed. Limited data are analyzed for the purpose of poster presentations, see below.

Philadelphia VAMC:

- Entry and checking of data from assessed and enrolled participants at the PA and CT sites has been ongoing at the PVAMC.
- We are beginning to work with the study statisticians to clean data and create the study databases and scoring of study measures to prepare for statistical analysis. We will have regular meetings with the study statisticians beginning this summer.

Section III: Key Research Accomplishments:

- Completion of lengthy regulatory reviews at PVAMC, Yale University, and VACHS, as well as the DOD HRPO.
- Hiring and training of staff
- Participant recruitment is now complete at the PVAMC site and its affiliated CBOCs and at the discontinued VACHS site.
- 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 over the last 3 recruitment years such that our target enrollment (n=115) was almost achieved (final n=108) despite many challenges in recruiting from this population.
- Current efforts aimed at completing follow-up data collection and data entry and cleaning to prepare for statistical analyses.

Section IV: Reportable Outcomes: Presentations:

Completed Poster presentation:

Harb, G. C., Waldron, E. A., Brownlow, J. A. & Ross, R. J. (2014). Lucid dreaming and the treatment of nightmares in OEF/OIF/OND veterans with PTSD. Poster presented at the annual meeting of the American Academy of Sleep Medicine, Minneapolis, MN.

Upcoming poster presentation:

Harb, G. C., Cook, J. M., Phelps, A. & Ross, R. J. (2014). Nightmares of U.S. Iraq and Afghanistan War Veterans with PTSD: Content and Characteristics. Poster to be presented at the annual meeting of the International Society for Traumatic Stress Studies, Miami, FL.

Section V: Conclusions:

We have enrolled a total of 108 participants between the PA (102) and CT (6) sites and have discontinued enrollment of additional participants to ensure our ability to complete follow-up assessments and data analysis within the project's budget. We are currently focusing efforts on data entry, checking, and cleaning in collaboration with our statisticians at the University of Pennsylvania.