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Award Number: W81XWH-07-1-0283

TITLE: Predictors of Treatment Response to Fluoxetine in PTSD Following a Recent History of War Zone Stress Exposure

PRINCIPAL INVESTIGATOR: Paul B. Hicks, M.D., Ph.D.

CONTRACTING ORGANIZATION: TEMPVA Research Group, Inc.
Temple, TX 76504

REPORT DATE: July 2012

TYPE OF REPORT: Annual

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

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Michael L. Adams, Ph.D., LTC; Brett Litz, Ph.D.; Keith Young, Ph.D.; Jed Goldart, M.D., Tom Velez, Ph.D., Walter Penk, Ph.D., Kathryn Kotrla, M.D.

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14. ABSTRACT

Although selective serotonin reuptake inhibitors (SSRIs) are routinely prescribed for acute stress disorder and early PTSD and recommended in the VA-DoD best practice guidelines, the efficacy of SSRIs as an early intervention for PTSD in service members returning from war-zone duty has still not been determined. Consequently, this study was designed to conduct a controlled trial of fluoxetine as an early intervention for recently redeployed soldiers, as well as to develop methodologies for understanding the multiple factors that may predict outcome. The Brooke Army Medical Center IRB, the regional IRB for the Carl R. Darnall Army Medical Center, has given full approval. A CRADA between TEMPVA Research Group, Inc and the Carl R. Darnall Army Medical Center has been executed. Human Research Protection Office (HRPO) Office of Research Protections (ORP) U.S. Army Medical Research and Materiel Command (USAMRMC) Fort Detrick has been completed and full approval has been given for enrollment. Continuing review was approved in April 2011. 40 participants have been enrolled and recruitment continues. A second performance site, the Central Texas Veterans Health Care System, was added to aid recruitment. A no-cost extension has been requested until June 30, 2013.

15. SUBJECT TERMS

Fluoxetine, Posttraumatic Stress Disorder, Antidepressants

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	18	19b. TELEPHONE NUMBER *(include area code)*

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INTRODUCTION:

Although selective serotonin reuptake inhibitors (SSRIs) are routinely prescribed for acute stress disorder and early PTSD and recommended in the VA-DoD best practice guidelines, the efficacy of SSRIs as an early intervention for PTSD in service members returning from war-zone duty has still not been determined. Consequently, this study was designed to conduct a controlled trial of fluoxetine as an early intervention for recently redeployed soldiers, as well as to develop methodologies for understanding the multiple risk factors that may predict outcome. Fluoxetine was selected as the psychopharmacologic agent for this study because it is well tolerated, it has a very favorable cost-benefit advantage as a generic drug, and the fact that it is the only SSRI with at least preliminary studies demonstrating its efficacy in recent-onset, war-related PTSD. Studies focusing on targeting chronic combat-related PTSD with SSRIs have shown mixed results with some small open-label studies suggesting efficacy, while two controlled trials with Vietnam veterans were negative. In a recent study of survivors of war violence in Europe, Israel, and South Africa, fluoxetine was shown to significantly reduce PTSD symptoms. Because in all prior trials there is considerable variability of response to fluoxetine, we plan to examine several predictors of efficacy. We argue that the efficacy of SSRIs for recently redeployed soldiers at risk for chronic PTSD is moderated by multiple personal, deployment, and environmental factors. It is expected that not all subjects will respond to fluoxetine. For those that do not respond to fluoxetine alone, augmentation with either buspirone or buproprion will be offered based on their reasonable tolerability, low cost and the recent findings documenting their utility as adjunctive treatments for depression.

BODY:

The approval letter has been received from the Brooke Army Medical Center IRB, the regional IRB for the Carl R. Darnall Army Medical Center. The CRADA between TEMPVA Research Group, Inc. and CRDAMC has been executed. The protocol has been approved by the Central Texas Veterans Health Care System IRB and the Research and Development Committee. The Human Research Protection Office (HRPO) of the Office of Research Protections (ORP) U.S. Army Medical Research and Materiel Command (USAMRMC) Fort Detrick has given full approval for initiation of the study. We have used the VA-donated administrative trailer (12'X52') to provide sufficient office space to perform the study over the past year. Information regarding the study has been presented to 158 potential participants. Of those, 40 signed a consent form. Of the 40 that signed a consent form, 20 met exclusion criteria, 4 did not complete inclusion/exclusion assessments and therefore did not qualify, and 16 have been randomized. Of the 16 randomized, 8 have been lost to follow-up and 4 withdrew for personal reasons after completing part of the trial, and 4 have completed all 32 weeks of the trial (Phase I and Phase II). In July 2012, an additional 3 have enrolled, 1 has been randomized, and 2 are in the process of baseline assessments. All 3 have been enrolled from CTVHCS. Because the research coordinators are available only on a part-time basis in the future, we will be enrolling only from CTVHCS. We have met with key administrators of clinical programs at CTVHCS, disbursed flyers and pamphlets, and continue to promote the project. We have found the need to work more closely with primary care providers because mental health providers are working with individuals with complex medication regimens that preclude their enrollment. In addition, we have made contact with the Texas Army National Guard site in Temple to be able to present to the National Guard troops at the next opportunity. These troops would be seen at CTVHCS.

The two research assistants that have been part of this study are available for part-time support over the next year on this project. One has a master's degree in counseling psychology and the other has a Ph.D. in counseling education. Both have considerable clinical experience, as well as some research experience. Both Drs. Peggy Pazzaglia and Paul Hicks are credentialed and privileged at both Carl R. Darnall Army Medical Center and CTVHCS.

The continuing review from the BAMC and VA IRBs has been approved (see Appendix). PR064845 is registered in ClinicalTrials.gov, No. NCT00633685.

Project Tasks:

Task 1: Submission of the Proposal to the IRBs

- The proposal must be approved by both the Brooke Army Medical Center IRB and the Central Texas Veterans Health Care System Human Subjects Subcommittee.
- **Completed**

Task 2: Recruitment and Training of Study Personnel

- Hire two master's prepared research assistants
- Training on recruitment procedures and research assessments (SCID, CAPS, etc.)
- **Completed**

Task 3: Preparation of Over-Encapsulated Blinded Medications for the First Phase of the Clinical Trial

- Purchase of the fluoxetine and gelatin capsules from VA pharmacy suppliers (purchased each 3 months throughout the first 15 months of the study)
- Over-encapsulation of fluoxetine and empty gelatin capsules by CTVHCS Pharmacy staff
- Transfer of medications prepared by the CTVHCS Pharmacy directly to the Carl R. Darnall Medical Center Pharmacy
- The Fluoxetine and placebo capsules have been prepared and transferred to the CRDAMC Pharmacy.
- **Completed**

Task 4: Recruitment/Clinical Trial

- Enrollment of a minimum 20 subjects per month for 15 months
- Double-blind, placebo-controlled trial of fluoxetine + usual psychological care for 12 weeks
- Open-label extension of the fluoxetine trial for 20 weeks
- **In progress**

Task 4: Data Collection and Transfer to the Boston VA National PTSD Research Center

- Data will be stored on compact discs for storage
- Compact discs will be sent on a monthly basis to the National PTSD Research Center for database development
- The post-doctoral fellow working with Dr. Brett Litz will maintain the database under the oversight of Dr. Litz

Task 5: Data Analysis at the Boston VA National PTSD Research Center

KEY RESEARCH ACCOMPLISHMENTS: Recruitment continues.

REPORTABLE OUTCOMES: Not applicable.

CONCLUSIONS: Not applicable.

REFERENCES: Not applicable.

APPENDICES:

Appendix A: BAMC IRB Continuing Review Approval letter

Appendix B: CTVHCS IRB Continuing Review Approval letter
Appendix C: Request for No-Cost Extension

SUPPORTING DATA: Not applicable

Appendix A: BAMC IRB Continuing Review Approval letter

DEPARTMENT OF THE ARMY
BROOKE ARMY MEDICAL CENTER
3851 ROGER BROOKE DR.
FORT SAM HOUSTON, TX 78234

REPLY TO
ATTENTION OF:

MCHE-CI

November 16, 2011

MEMORANDUM FOR:	Michael Adams, PhD
FROM:	Brooke Army Medical Center (BAMC) Institutional Review Board
PROJECT TITLE:	[363502-15] Predictors of Treatment Response to Fluoxetine in PTSD Following a Recent History of War Zone Stress Exposure
REFERENCE #:	C.2007.145
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
IRB APPROVAL DATE:	November 2, 2011
EXPIRATION DATE:	December 1, 2012
REVIEW TYPE:	Full Committee Review

1. Congratulations! The Brooke Army Medical Center (BAMC) Institutional Review Board (IRB) reviewed and APPROVED your continuing review application for your aforementioned protocol and supporting documents at the fully convened IRB Board meeting of November 2, 2011.

Your protocol was reviewed for regulatory compliance under Full Committee Review, based on the applicable federal regulations. No changes were directed to the previous approval criteria under 32 CFR 219.111 and 21 CFR 56.111.2.

2. An amendment was submitted along with this continuing review requesting the extension of the study timeline of the project to 76 months and extend enrollment to 31 August 2012.

3. Protocol C.2007.145 will automatically terminate on December 1, 2012. If you plan to continue beyond this date, the required continuing review progress report is due to the BAMC IRB by 25 September 2012 for the December 2012 IRB meeting. The IRB will attempt to assist you by sending a reminder; however, submission of the continuing review report is your responsibility. Failure to submit the report on time will result in the expiration of your protocol and a requirement to cease all research activities until the entire protocol can be resubmitted.

4. If at any time you have questions regarding your responsibilities as a Principal Investigator, please contact Lt Col David Bush at (210) 916-1005 or david.m.bush1@us.army.mil. On behalf of the entire IRB, we wish you much success with your research protocol. We look forward to reviewing the progress of your study in the coming months.

This document has been electronically signed in accordance with all applicable regulations, and a copy is retained within our records.

The following documents were reviewed in this submission:

- Continuing Review/Progress Report
- Literature Review
- Protocol - Protocol V.10
- ICD and HIPAA
- Protocol Deviation Log
- Adverse Event Log
- CV/Resume - Adams, Schirner, Reeve, Pazzaglia, Litz, Hicks, Browning , Blackburn
- Training/Certification - Adams, Schirner, Reeve, Pazzaglia, Litz, Hicks, Browning , Blackburn

Appendix B: VA IRB Continuing Review Approval letter

Department of Veterans Affairs

Memorandum

Date: March 28, 2012

From: Associate Chief of Staff, Research (151)

Subj: Approval to Continue Research

To: Paul Hicks, M.D., Ph.D.

1. The Subcommittee on Research Safety and the Institutional Review Board have approved the continuing review for the protocol titled, "Predictors of Treatment Response to Fluoxetine in PTSD Following A Recent History of War Zone Stress Exposure".

2. The Research and Development (R&D) Committee has accepted the continuing review.

3. All training requirements for your study personnel are completed and up to date.

4. All requirements for the safe conduct of this protocol are complete.

5. You may continue your study.

6. A continuing review of this protocol is required annually. Approval for this protocol is in effect until your next continuing review renewal date. Your next renewal date is March 26, 2013. A reminder will be sent to you 90 days in advance of your renewal date. Failure to receive renewal of the approval by that date will result in lapse of approval for this project.

7. If additional information is needed, please contact Paul B. Hicks, M.D., Ph.D., Associate Chief of Staff, Research at 254-743-2643.

William F. Harper, M.D.
Chief of Staff

IRB APPROVAL - Continuing Review

Date: March 24, 2012
From: John W. Klocek, Ph.D., Chairperson
Investigator: Paul B. Hicks, M.D., Ph.D.
Protocol: Predictors of Treatment Response to Fluoxetine in PTSD Following A Recent History of War Zone Stress Exposure
ID: 00308 Prom#: 0016 Protocol#: N/A

The following items were reviewed and approved at the 03/14/2012 meeting:

- Abstract (Received with 2/8/12 packet)
- Amendment - Page 20 of Protocol (03/13/2012; 12)
- Amendment - Protocol revision (03/13/2012; 12)
- Amendment - Protocol Rvw Fm for Rev/Amend ICF and HIPAA (02/08/2012)
- Budget Page - 10-1313-4
- Consent Form (4, Mar 2011)
- Consent Form (5, Feb 2012)
- Continuing Review (02/08/2012)
- Memo from PI resp to SIDS (03/13/2012)
- Chklst Rvw Privacy Confidentiality and IS in Res (02/08/2012)
- Protocol (12/08/2011)
- Request for Waiver of Informed Consent Requirments (07/14/2011)
- HIPAA Authorization (3, Jan 2011)
- HIPAA Authorization (Version 4, Feb 2012)
- Project Data Sheet (02/08/2012)
- Request to Review Research Proposal/Project (02/14/2012; No changes)

The following Institutional Review Board (IRB) members were not in attendance and did not vote: Paul B. Hicks, M.D., Ph.D.

Approval is granted for a period of 12 months and will expire on 03/13/2013. Your Continuing Review is scheduled for 01/09/2013, and the requirements are attached.

The protocol was determined to have the following level of risk:
Moderate

The protocol was determined to have the following level of benefit to participants:
Prospect for direct benefit to participants

1. The IRB reviewed the above continued review documents at the March 14, 2012, meeting. The IRB members approved the request for continued human use for 12-months continuation.

2. The continuing review approval period is from March 14, 2012, to March 13, 2013.

3. Your are reminded that any modifications to the study documents must be reviewed by the IRB. Completion or cessation of this study should be reported to this Subcommittee as soon as possible. If modifications of any kind are put into place without IRB approval, this is a violation and non-compliance with federal and VHA regulations and policies.

4. Your study will be subjected to further continuing review prior to March 13, 2013. Request the continuing review submission forms be submitted to this office by January 9, 2013, for review by the IRB. If the protocol or study documents are modified in any way or discontinued for any reason before the next continuing review, please notify the Subcommittee.

5. Investigators are reminded that they are personally responsible for the careful, thoughtful execution of studies involving human subjects and their protected health information (PHI). Conscious disregard of subjects' rights as outlined in the study documents or failure to comply with all safeguards listed in the protocol will be met with severe sanctions. Confidentiality of human subject identity/personal data is mandatory.

6. You may begin to use VA Research Consent Form and HIPAA Authorization stamped March 14, 2012.

7. If additional information is needed, you can contact me at extension 53785 or Ms. Thomas, Program Specialist, at extension 41974.

John W. Klocek, Ph.D.

Subcommittee on Research Safety (SRS)
Temple VA Medical Center
Temple, TX

APPROVAL - Continuing Review

Date: March 8, 2012
From: Randy Zavodny, M.S., Chairperson
Investigator: Paul B. Hicks, M.D., Ph.D.
Protocol: Predictors of Treatment Response to Fluoxetine in PTSD Following A Recent History of War Zone Stress Exposure
ID: 00308 Prom#: 0016 Protocol#: N/A

The following items were reviewed and approved at the 03/06/2012 meeting:

- Abstract (02/10/2012)
- Continuing Review (02/10/2012)
- Chemical inventory (02/14/2012)

The following Subcommittee on Research Safety (SRS) members recused themselves (or were otherwise excused) from deliberations and did not vote: Jeff Browning, Ph.D. The following Subcommittee on Research Safety (SRS) members were not in attendance and did not vote: Paul B. Hicks, M.D., Ph.D.

1. The study, 00308, was reviewed, discussed and approved.

2. Please note final continuing review approval is constituted by full approval of the applicable subcommittees, Research and Development Committee and receipt of a final approval memo from the Associate Chief of Staff for Research.

3. A continuing review of this protocol is required annually. Approval for this protocol is in effect until your next continuing review renewal date. Your next renewal date is March 5, 2013. A reminder will be sent to you 90 days in advance of your renewal date. Failure to receive renewal of the approval by that date will result in lapse of approval for this project.

4. If the protocol is modified in anyway or discontinued for any reason please notify the Subcommittee.

5. Any biosafety/radioisotope events must be reported in writing by the investigator to this Subcommittee within 24 hours of the occurrence, whether or not these are attributed to the research project itself or to unrelated factors.

6. Thank you for your cooperation and for your support of our efforts to conduct research safely.

7. If you have any questions or concerns, please do not hesitate to contact Ruth Merton, Program Specialist, 254.743.1787.

Randy Zavodny, M.S.

The following other committee reviews are scheduled:
Institutional Review Board (IRB) [03/14/2012]
Research & Development (R&D) Committee [04/24/2012]
Subcommittee for Information and Data Security [01/07/2013]

Approval by each of the following is required prior to study continuation (unless Exempt):
Subcommittee for Information and Data Security
Research & Development (R&D) Committee

Appendix C: Request for No-Cost Extension

Central Texas Veterans Research Foundation

A Nonprofit Corporation Supporting Research and Education Activities of the Central Texas Veterans Health Care System

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June 20, 2012

Mr. Ayi Ayayi
Contract Specialist
U.S. Army Medical Research Acquisition Activity
MCMR-AAA-E
820 Chandler Street
Fort Detrick, MD 21702-5014
Phone: (301) 619-4018
ayi.ayayi@us.army.mil

RE: Project W81XWH-07-1-0283 PR064845 (UNCLASSIFIED)

Dear Mr. Ayayi,

As the Sponsored Program Office for the above referenced project, the Central Texas Veterans Research Foundation would like to formally request a no-cost extension for a period of one year. The request is due to extended time required to ensure adequate enrollment in the project.

The possibility of a no-cost extension to this project has already been discussed with the Science Officer for this project, Meropi Athanasiou, Ph.D. A proposed revised budget is attached.

Please call me at 254-744-4162 (cell) if you have any questions. Thank you for your assistance with this matter.

Sincerely,

Maggie McCarthy
Executive Director

Central Texas Veterans Research Foundation

A Nonprofit Corporation Supporting Research and Education Activities of the Central Texas Veterans Health Care System

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Revised Budget for July 1, 2012 to June 30, 2013

Remaining Funds	
Proposed salary costs for Research Coordinators (as needed basis only)	
Proposed costs for medications	
Proposed costs for participant payments	
Proposed costs for consultants for data analysis	

Executive Director – Maggie McCarthy
President – Paul B. Hicks, M.D., PhD
Accountant – Linda Jander, CPA

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