AD_____

Award Number: **W81XWH-11-1-0073**

TITLE: **Randomized Controlled Trial of Sertraline, Prolonged Exposure Therapy and their Combination in OEF/OIF Combat Veterans with PTSD**

PRINCIPAL INVESTIGATOR: **Sheila A. M. Rauch, Ph.D.**

CONTRACTING ORGANIZATION:
VA Ann Arbor Healthcare System/ University of Michigan Medical School
Ann Arbor, MI 48103

REPORT DATE: **December 2012**

TYPE OF REPORT: **Annual Report**

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE December 2012	**2. REPORT TYPE** Annual Report	**3. DATES COVERED** 01 December 2011-30 November 2012

4. TITLE AND SUBTITLE

Randomized Controlled Trial of Sertraline, Prolonged Exposure Therapy and their Combination in OEF/OIF Combat Veterans With Post-Traumatic Stress Disorder

5a. CONTRACT NUMBER

5b. GRANT NUMBER W81XWH-11-1-0073

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Sheila A. M. Rauch, PhD.; Margaret R. Venners, MPH, MSW; Andrew Defever, Rebecca Mayer, Israel Liberzon, MD; Luan Phan, MD; Brian Martis, MD; Antony King, PhD;, Murray Stein , MD; Carolyn Allard, PhD; Sonya Norman , PhD; Mark West, MBA; Ron Acierno, PhD; Peter Tuerk, PhD; Mark Hamner, MD; Hugh Myrick, MD; Erica Yuen, PhD; Wendy Muzzy, MRA; Naomi Simon, PhD; Laura Morris, Rebecca Ojserkis

E-Mail: sherauch@med.umich.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
VA Ann Arbor Healthcare System/ University of Michigan Medical School
Ann Arbor, MI 48103

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

The current proposal aims to directly compare the psychotherapy and medication treatments for PTSD considered to have the most evidence for effectiveness. While both SSRI and PE have demonstrated efficacy, there are significant individual differences in clinical responses to both treatments. To achieve best clinical outcomes and to utilize available treatment most effectively, it is critical to examine how PTSD and related psychopathology and functional impairment change with these treatments alone and in combination. Further, in order to inform clinical practice, we plan to examine psychological and neurobiological predictors of response to treatment and mechanisms of change during treatment (pre to post treatment change) based on previously identified predictors, including emotion regulation and processing with fMRI in response to emotional challenge tasks, DNA and mRNA (pre and post treatment), and cortisol response to awakening.
Start-up activities were completed in 2012Q1 and the primary activity and focus is this year has been on recruitment. To date, we have recruited and randomized 45 Veterans.

15. SUBJECT TERMS none provided

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	8	**19b. TELEPHONE NUMBER** *(include area code)*

Table of Contents

INTRODUCTION

PTSD is a major public health concern and a growing problem for the VA and the DOD [1, 2]. Soldiers returning from Afghanistan and Iraq show PTSD rates of between 12 to 20% [3-6] with significant psychological, physical, and economic burdens for sufferers and society as a whole [7, 8]. Based on available treatment guidelines [9], the two first line treatments for PTSD include exposure therapy (such as PE) and selective serotonin reuptake inhibitors (SSRIs; such as SERT). To date, there have been no randomized, direct comparisons of medication, psychotherapy, and combined treatment among veterans or active duty troops. The current study aims to provide this critical data in a typical sample of OEF/OIF returnees with significant combat-related PTSD. Further, emphasis is placed on continued, comprehensive collection of outcome data to assess the acceptability, adherence, compliance, and symptom change in each treatment arm throughout the study period. In addition, substantial morbidity remains in a high percentage of PTSD veterans [10, 11] even after PE or SSRI treatment are administered, suggesting that further treatment optimization and individual treatment matching are urgently needed if substantial personal and social costs are to be reduced. Identifying specific predictors, large effect size correlates of treatment response, or putative mechanisms involved in treatment response will be critical steps toward achieving the goals of treatment optimization and individual treatment matching. To inform treatment choices beyond what can be provided through standard clinical outcomes, we will examine neurobiological predictors and proximal correlates of effective treatment, and candidate mechanisms involved. Delineation of these factors and their specificity to medication or PE is a critical step towards treatment refinements, improved effectiveness and efficiency of PTSD treatment, enhanced dissemination, and individualized treatment. This is obviously an ambitious set of goals; however, the combined expertise of the research group involved, the synergy of the aims, and the efficient design offer both a unique opportunity to examine multiple processes simultaneously, and to obtain the highest quality of critically needed data. To restrict the examination to just one system or one mechanism would be a missed opportunity to study these complex and interrelated systems and their interacting in impacts on treatment.

BODY

This project will consist of seven primary tasks to be accomplished over the 5 year funding period at four sites: Veterans Affairs Ann Arbor Healthcare System (VAAAHS) /University of Michigan (UM), VA San Diego Healthcare System (VASDHS)/University of California San Diego (UCSD), VA Charleston VA Medical Center (VAMC)/ Medical University of South Carolina (MUSC), and Massachusetts General Hospital (MGH)/Harvard Medical School.

Task 1: (COMPLETE) Start-up activities and regulatory approvals

- Primary site (VAAAHS/UM) obtained Full approval at VA Ann Arbor Healthcare System (Dec 2010), University of Michigan (Dec 2010), and HRPO (Jun 2011)
- MGH obtained full approval from MGH (Aug 2011) and HRPO (Sep 2011)
- VAMC/MUSC obtained full approval from the MUSC IRB (Jul 2011), the VA R&D Committee (Aug 2011) and HRPO (Feb 2012)
- VASDHS/UCSD obtained full approval from UCSD IRB (May 2011), the VA R&D Committee (Sep 2011) and HRPO (Apr 2012)
- All sites have key positions hired in order to begin recruitment
- Payment processes in place and being fulfilled in a timely manner

- Subawards completed

<u>Task 2</u>: Training of study faculty and staff (initial completed; ongoing training related to staff turnover)

- All sites have key positions hired and trained in order to recruit patients
- Training completed this year:
    - Dr. Stefan Schmertz (MGH) successfully completed training and was approved to start seeing patients for the study in 2012Q3
    - MGH has selected Don Robinaugh as their Fidelity Rater for the study in 2012Q3. Mr. Robinaugh completed fidelity training in 2012Q4
    - Bethany Wangelin, a new psychotherapist for VAMC/MUSC, completed training and began seeing patients in 2012Q3
    - A new primary IE, Megan Sullivan (VAMC/MUSC), was hired in 2012Q3 and began her role in early 2012Q4. A back-up IE, Kimberly Veronee, was trained for cases in which the primary IE becomes unblinded. Ms. Veronee completed training and began conducting assessments in 2012Q3
- Remaining staff hires and training include:
    - VASDHS/UCSD is still actively recruiting a second psychiatrist for the study
    - A second psychotherapist, Dr. Elizabeth Goetter (MGH), was added to the study in 2012Q3 and her training is expected to be complete no later than 2013Q1
- Ongoing training and education efforts:
    - Conference calls continue to be held regularly every Monday to discuss logistical and procedural matters with the full study team, including PI's, Co-I's, and Study Coordinators
    - Dr. Naomi Simon has continued to lead monthly Pharmacotherapy calls
    - Dr. Peter Tuerk has continued to lead weekly Psychotherapy calls
    - Dr. Katherine Porter and Dr. Jeanne Duax lead bi-monthly recalibration independent evaluator calls
    - Psychotherapy Fidelity training lead by Dr. Peter Tuerk was completed in 2012Q3
    - Pharmacotherapy Fidelity training lead by Dr. Sheila Rauch and Dr. Naomi Simon started in 2012Q3 and concluded in 2012Q4

<u>Task 3:</u> Set up study forms and refine all procedures (Initial set-up completed; ongoing changes to address any apparent issues)

- All study forms complete and in use at all sites
- The Data Coordinator Center (DCC) completed the data validation checklist, which was reviewed and approved by the PROGrESS study team in 2012Q2. This checklist drives the process for identifying discrepant or missing data. A query and resolution process has been designed to document and resolve these issues using electronic Data Clarification Forms (eDCFs) sent by the DCC
- The query and resolution process was piloted with the Ann Arbor site and successfully implemented at all 4 sites in early 2012Q3. This process will occur on a monthly basis.
- From these edit checks, sites cleaned data in preparation for the first DSMB meeting
- The Data Manager worked closely with the Biostatistician and Study PI to provide analysis-ready datasets and reports for the first DSMB meeting held in 2012Q3
- Based on feedback from the study team, additional refinements were made to data reports to assist with study management and monitoring activities in 2012. These include revision of study summary reports and the addition of reports on subject enrollment

- On-site monitoring visits were completed by the Study Monitor in 2012Q2 and 2012Q4 and occur every 6 months
- Laboratory procedures finalized – supplies ordered and shipments sent to sites for initial recruitment
    - Lab supply ordering procedures established and ongoing throughout study
    - Packaging and Shipping procedures for lab samples finalized
- fMRI protocol finalized
    - Off-site travel participant procedures finalized, first participants successfully traveled and reimbursed

<u>Task 4:</u> Recruit and randomly assign Operation Enduring Freedom/Operation Iraqi Freedom/ Operation New Dawn(OEF/OIF/OND) returnees with combat related Posttraumatic Stress Disorder (PTSD) to PE+ placebo (PE/PLB), sertraline + enhanced medication management (SERT), or PE + sertraline (PE/SERT)

- All sites are actively recruiting with 189 total patients screened and 45 patients randomized as of December 10, 2012
    - MGH started recruitment on November 29, 2011
        - 51 patients screened
        - 18 patients consented
        - 10 patients randomized
        - 4 patients terminated study
    - VAAAHS/UM started recruitment on December 12, 2011
        - 36 patients screened
        - 17 patients consented
        - 14 patients randomized
        - 2 patients terminated study
    - VAMC/MUSC started recruitment on February 14, 2012
        - 72 patients screened
        - 25 patients consented
        - 12 patients randomized
        - 2 patients terminated study
    - VASDHS/UCSD started recruiting on April 10, 2012
        - 30 patients screened
        - 12 patients consented
        - 9 patients randomized
    - Combat Controls (recruited at the VAAAHS/UM site only)
        - Started recruitment on August 24, 2012
        - 6 consented
        - 1 enrolled and completed study

<u>Task 5:</u> Conduct neurobiological mechanism study including assessment of genetics/genomics, brain function (first 210 interested participants), and hypothalamic–pituitary–adrenal (HPA) axis function

- Recruitment for the neurobiological mechanism study (fMRI substudy) began in 2012Q1
- As of Dec 10, 2012, 23 patients have consented to fMRI substudy
- 13 are enrolled (11 from VAAAHS/UM, 1 from MGH and 1 from VAMC/MUSC)
    - 13 patients have completed the pre-scan (Intake)
    - 4 patients have completed the post scan (Week 24)

- The discrepancy between number of patients enrolled versus the number consented is due to the size limitations of the bore diameter of the fMRI scanner (60cm). Study sites outside of Ann Arbor have been instructed to take a conservative approach to screening patients for fMRI procedures to attenuate the possibility of having costs for patients traveling to Ann Arbor whom may not be able to participate due to these parameters.

Task 6: Follow-up of all returnees for one year from treatment initiation

- As of December 10, 2012, 5 patients completed Week 36 research assessment

Task 7: Data cleaning, initial statistical analyses and dissemination of results

Not applicable for this reporting period

Delays/Challenges/Barriers

- Recruitment challenges
    - Barriers to recruitment:
        - Patients not meeting eligibility criteria and/or meeting exclusion criteria
        - Patient not wanting randomization to medication and/or therapy
        - Patients not returning phone calls made as a follow-up to referrals
        - Attenuation of patient flow through the clinic due to seasonal decline in referrals
        - There was improvement in recruitment rates during Q42012. The focus in 2013 will be continued improvement by expanding recruitment to CBOCs, increasing advertisements, etc. Sites will be closely monitored for underperformance and areas of improvement.

KEY RESEARCH ACCOMPLISHMENTS

- Establishing regulatory procedures to allow for a DOD funded study to run at VA and non-VA sites
- Obtaining a COC for this complex study
- Creating materials and procedures for staff training of independent evaluators, therapists, fidelity raters, etc.
- Completion of first DSMB meeting in Q32012 with no major issues or complaints
- First site monitoring visit completed for all sites
- Second monitoring visit completed for MGH, MUSC and AAVA. Second monitoring visit for UCSD is scheduled for February 2013

REPORTABLE OUTCOMES

Not applicable this reporting period

CONCLUSION

Data collection is ongoing and results are not available. However, emphasis in the coming year will continue to rest on recruitment and retention at all sites.

REFERENCES

1. Hoge, C.W., J.L. Auchterlonie, and C.S. Milliken, *Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan.* JAMA: Journal of the American Medical Association, 2006. **295**(9): p. 1023-1032.
2. Greenberg, P.E., et al., *The economic burden of anxiety disorders in the 1990s.* Journal of Clinical Psychiatry, 1999. **60**(7): p. 427-435.
3. Hoge, C.W., et al., *Combat Duty in Iraq and Afghanistan, Mental Health Problems, and Barriers to Care.* The New England Journal of Medicine, 2004. **351**(1): p. 13-22.
4. RAND, *Invisible Wounds of War: Summary and Recommendations for Addressing Psychological and Cognitive Injuries*. 2008, Rand Center for Military Health Policy: Arlington, VA.
5. MHAT, *Operation Iraqi Freedom 06-08: Iraq, Operation Enduring Freedom*. 2008, Office of The Surgeon General United States Army Medical Command, Mental Health Advisory Team
6. Smith, T.C., et al., *New onset and persistent symptoms of posttraumatic stress disorder self reported after deployment and combat exposures: Prospective population based US military cohort study.* BMJ: British Medical Journal, 2008. **336**(7640): p. 366-371.
7. Hoge, C.W., et al., *Association of posttraumatic stress disorder with somatic symptoms, health care visits, and absenteeism among Iraq War veterans.* The American Journal of Psychiatry, 2007. **164**(1): p. 150-153.
8. Marciniak, M., et al., *Medical and productivity costs of anxiety disorders: Case control study.* Depression and Anxiety, 2004. **19**(2): p. 112-120.
9. Cahill, S.P., et al., *Cognitive-behavioral therapy for adults*, in *Effective treatments for PTSD: Practice guidelines from the International Society for Traumatic Stress Studies (2nd ed.).* 2009, Guilford Press: New York, NY US. p. 139-222.
10. Rothbaum, B.O., et al., *Cognitive-behavioral therapy*, in *Effective treatments for PTSD: Practice guidelines from the International Society for Traumatic Stress Studies.* 2000, Guilford Press: New York, NY US. p. 60-83.
11. Keane, T.M., et al., *Implosive (flooding) therapy reduces symptoms of PTSD in Vietnam combat veterans.* Behavior Therapy, 1989. **20**(2): p. 245-260.

APPENDICES

Not applicable this reporting period