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14. ABSTRACT The proposed study seeking to identify predictors of differential response to SSRI's is significant given the widespread use of SSRI's. Unfortunately, no subjects have yet been recruited into the study because regulatory approvals have been delayed. Protocols have been developed and IRB approvals have been achieved. Staff have been trained and standard operating procedures are in place. At the time of this report in December, 2010, HRPO approval is pending.					
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INTRODUCTION:

As part of the STRONG STAR Consortium, this project proposes to study the assessment and treatment of alcohol dependence comorbidity among OEF/OIF military personnel and separated veterans who have PTSD and were exposed to combat-related trauma. A particularly important aspect of this study is to evaluate the hypothesis that there are subgroups of patients who have different phenomenological presentations of alcohol dependence comorbidity; and further that these subgroups have fundamental differences in their serotonin biology that cause them to respond differently to medication treatment with selective serotonin reuptake inhibitors (SSRI's). These objectives are being approached in two different ways. First, we plan to conduct a randomized clinical trial evaluating the efficacy of sertraline (an SSRI) in the treatment of Dual Diagnosis PTSD-Alcohol Dependent patients who are OEF/OIF veterans seeking treatment in the Texas Veterans Health Care System. Second, we plan to develop a protocol to assess the drinking behaviors and phenomenological characteristics of active-duty military personnel receiving treatment for psychiatric symptoms at Fort Hood. In the first year of the project funding, we developed the research protocol to examine sertraline efficacy in different subgroups of Dual Diagnosis PTSD-Alcohol Dependence veterans seeking treatment in the South Texas and Central Texas Veteran's Health Care Systems. Though only first year project funds have been released to date, it has taken us another year of the project period seeking to obtain final regulatory approvals from HRPO.

BODY:

Protocol Development

We developed the study protocol to evaluate the efficacy of sertraline in OEF/OIF veterans seeking treatment for PTSD-Alcohol Dependence Dual Diagnosis in the South Texas (STVHSC) and Central Texas (CTVHSC) VA systems. The Protocol was developed by Dr. Roache to assess patients for serotonin biological factors and to assess them for their phenomenological classification as to validated sub-type of alcohol dependence. The protocol also was developed with the collaboration of Drs. Sudie Back and Kathleen Brady who are experts in Dual Diagnosis treatment at the Medical College of South Carolina (MUSC) and who have developed an evidence-based, integrated psychotherapy for Dual Diagnosis. The therapy known as COPE, integrates standard CBT for alcohol dependence with Exposure Therapy for PTSD. The Developed Protocol is described below.

Study Protocol. The study is a two-site, randomized, placebo-controlled, double-blind parallel-group treatment of 240 male and female veterans of OEF/OIF campaigns who have PTSD and Alcohol Dependence. All patients will receive 12-weeks of an integrated, manualized cognitive and behavioral psychotherapy as the standard of care and will be randomized to receive either sertraline (150 mg) or placebo as an adjunct to treatment. Randomization will be stratified based upon the Onset Precedence (before vs. after) of Alcohol Dependence symptoms (i.e., were symptoms of alcohol dependence preceding or subsequent to battlefield-related trauma exposure). *Post-Hoc* clustering techniques will be used to derive two subgroups of patients and data will be analyzed for the hypothesis that patients classified as Type-A will respond favorably to sertraline whereas patients classified as Type-B will do less well with sertraline than with placebo. – See the final study protocol attached in the Appendix.

Regulatory Preparation & IRB Approval

We have obtained final approval of the study approval from the primary IRB of the UT Health Science Center at San Antonio and the associated STVHCS R&D Office, and also from the IRB of the CTVHCS. These approvals from the VA sites were delayed due to several issues involving identifying the VA personnel necessary to support the study. Each of these performance site Regulatory authorities have now approved the protocol, but HRPO has not. The protocol was initially submitted to HRPO on April 28, 2010, and we have twice responded to stipulations from HRPO. Our last submission was on September 20, 2010 and we expect that HRPO approval is imminent. Below is a cumulative record of all the regulatory submissions and approvals.

- Protocol submitted for UTHSCSA IRB pre-review 27 Jan 2009. The responses to the pre-review were submitted to the UTHSCSA IRB office 12 Feb 2009. The IRB meeting is scheduled for 3 Mar 2009.
- Protocol submitted for STVHCS Research and Development Committee review 2 Feb 2009. Response to stipulations provided back to the committee 4 Mar 2009.
- Response to UTHSCSA IRB full-board review was submitted on 30 April 2009. And the study was approved on 8 May 2009.
- Protocol submitted for South Texas Veterans Health Care System (STVHCS) Research and Development (R&D) Committee review 2 February 2009. Response to administrative review stipulations provided back to the R&D Office on 4 March 2009. Reviewed by R&D Committee on 11 March 2009. Response to Committee stipulations submitted to R&D Office on 21 April 2009.

- Received UTHSCSA IRB approval on 8 May 2009.
- Submitted Amendment #1 to the UTHSCSA IRB on 29 May 2009- Changed number of drinking days assessed by Time-Line Follow-Back (TFLB) from 60 to 30, changed administration of the Structured Clinical Interview for Diagnoses (SCID) to administration of the MINI SCID, added more study measures [Beck Scale for Suicidal Ideation (SSI) Screen, Quantity and Frequency Interview (QFI), Profile of Mood States (POMS), Behavioral Check List (BCL), and Clinical Institute Withdrawal Assessment of Alcohol (CIWA) Scale, and removed the Beck Anxiety Inventory (BAI). The consent form was also revised to reflect protocol changes.
- Additional response to R&D Office stipulations submitted on 9 Jun 2009.
- Received UTHSCSA IRB approval for Amendment #1 on 12 Jun 2009.
- Reviewed by the Temple VA Medical Center IRB on 9 Dec 2010 and tabled. The PI is working on submitting a protocol amendment to the UTHSCA IRB to include the VA requested changes.
- Amendment # 2 submitted to UTHSCSA IRB on 7 Jan 2010 to add/remove study staff.
- Additional response to R&D Office stipulations submitted on 7 Jan 2010.
- Submitted the Progress Report for Continuing Review to UTHSCSA IRB on 20 Jan 2010. Approval is pending.
- Amendment # 2 to UTHSCSA IRB approved on 29 Jan 2010.
- UTHSCSA IRB Progress Report for Continuing Review approved on 12 March 2010.
- Submitted UTHSCSA IRB Progress Report for Continuing Review approval letter to HRPO on 23 March 2010.
- Submitted UTHSCSA IRB protocol version 28 May 2009, stamped VA consent form, and UTHSCSA IRB approval letters for Amendments #1 and #2 to HRPO on 31 March 2010 for pre-review while we are awaiting the STVHCS R&D office approval.
- Additional response to STVHCS R&D Office stipulations submitted on 6 April 2010.
- Submitted Amendment #3 to the UTHSCSA IRB on 6 April 2010 to add Dr. Julianne Flynn as a VA investigator.
- Amendment #3 to UTHSCSA IRB approved on 20 April 2010.
- STVHCS R&D Office approved on 26 April 2010.
- Submitted VA Audio Consent to STVHCS R&D Office on 27 April 2010.
- STVHCS R&D Office approved VA Audio Consent on 28 April 2010.
- Submitted the STVHCS approval letter to HRPO on 28 April 2010.
- Pre-review comments from HRPO received 6 April 2010. The PI is working on the response.
- Submitted UTHSCSA IRB amendment #4 on 27 May 2010 to add new study personnel.
- Amendment #4 to UTHSCSA IRB approved on 10 June 2010.
- Response to HRPO pre-review comments submitted on 16 July 2010.
- Received additional pre-review request for changes from HRPO on 2 Aug 2010.
- Response to HRPO additional pre-review request for changes submitted on 24 Aug 2010.
- Received additional pre-review request for changes from HRPO on 1 Sept 2010.
- Response to HRPO additional pre-review request for changes submitted on 1 Sept 2010.
- Received additional pre-review request for changes from HRPO on 8 Sept 2010.
- Response to HRPO additional pre-review request for changes submitted on 20 Sept 2010.

Hiring and Training of Study Staff & Site Preparation

Dr. Roache has been working to develop the study procedures for the treatment protocol and Dr. Javors has done so for the biological assessments required for the study. Mr. Jonathon Polanco has been appointed as the Study Coordinator in conjunction with Mr. Bill Murff who will oversee the two site coordination. Dr. Klocek has been appointed to the PTSD Center of Excellence at the CTVHCS and he will provide both study coordination and serve as the lead therapist for the study at the CTVHCS. Jeslina Raj, Psy.D. and Jennifer Guajardo have been trained to provide psychotherapy at the San Antonio site and Dr. Klocek is overseeing their continued training for fidelity to the COPE manual.

Developing Procedures for Two Site Coordination.

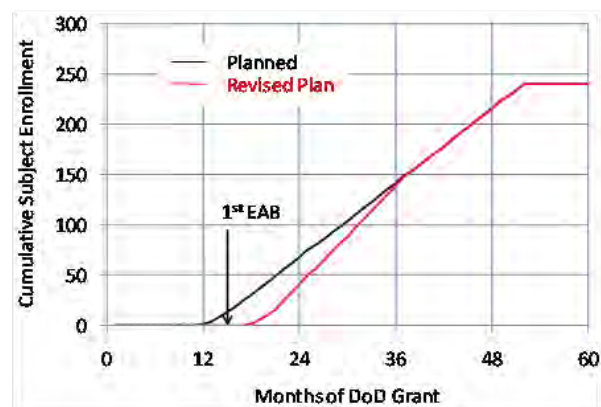
Mr. Murff at UTHSCSA has taken on the role of Coordinating the two site study. Dr. Roache, Mr. Murff, and Mr Polanco all three visited the CTVHCS site in Waco to deliver study materials and identify any site needs. At this visit, we:

- Determined how UTHSCSA accounts could be used to compensate subjects in Waco.
- Provided CTVHCS with study supplies.
- Determined that Dr. Roache would provide blood collection and processing equipment and supplies.
- Resolved how the contract pharmacy would provide compounded, blinded medication to the CTVHCS.

Since the visit, Dr. Javors has simplified the blood collection and processing protocol to enable the CTVHCS personnel to ship specimen samples to San Antonio once per week.

Participant Recruitment, Therapy, Data Collection & Monitoring

Patient Accrual. – The SOW originally planned to begin patient accrual by the end of the first year. Delays in regulatory approval have prevented any patient accrual through the end of the second year. Though we obtained final protocol approvals from the local IRB's in this reporting period, we have been working with HRPO to obtain DoD approval which we expect to be imminent. To date only Year 1 funds have been released and expended, so the study still has four full years of funding remaining. At the EAB meeting in March, Dr. Roache presented a plan for increased rates of patient accrual that will allow the study to achieve full recruitment within 4 years of final HRPO approval.



Database, Data Entry, and Data Analysis

We have met with the STRONG STAR Database Core and begun planning the study database programming needs. We have resolved the randomization process and planned for the coordination of database activity between the two sites.

Reports, Publications

none

KEY RESEARCH ACCOMPLISHMENTS:

- No research patient accrual has been achieved.
- The final study Protocol and study procedures have been developed and the protocol has received local IRB approvals but has not yet received HRPO approval.
- The HRPO approval process has required protocol modifications which must now be submitted back through the local IRB's though we expect that approval to move quickly.
- Personnel have hired and trained in study procedures.
- The PI attended and presented the study status to the Advisory Board on April 23, 2010.

REPORTABLE OUTCOMES:

- Dr. Roache attended and presented at the Advisory Board Meeting in San Antonio on April 23, 2010.
- All study staff including Dr. Roache and the VA Co.I.,s attended the 3rd Annual STRONG STAR Investigators Meeting in August 2010 and also the National Trauma Institute annual scientific meeting. At the annual meeting, we finalized the Adverse Events monitoring plan and were informed that the Research Nurse at the Waco site was being hired.

CONCLUSION:

The proposed research is focused upon the OEF/OIF veteran-population within the VA Health Care system. However, the hypotheses, study design, and treatments are not unique to the VA and the results are extremely important to the DoD and approaches to enhance warrior resilience. It is important to discover the biological basis for behavioral disorders such as alcohol dependence and PTSD. It is perhaps even more important to understand the biological basis of individual differences in treatment response so that we can predict who will respond in what ways. Given our hypothesis that some patients actually may not respond well to SSRI's, it is critical to gain this information as soon as possible and to get it out into the VA/DoD and public domain so that doctors will not make the mistake of producing iatrogenic complications in their treatments. The notion that SSRI treatment can actually exacerbate drinking problems is not generally recognized by the treatment community and needs to be better understood so that iatrogenic harm can be avoided. Thus, the proposed research has potentially great impact upon the health care of OEF/OIF veterans, but equally so for the general public and the general medical practice in the U.S. and the world. In order to facilitate this information, the results will be published in major medical journals and press-releases will be issued to popular media outlets.

REFERENCES:

None

APPENDICES:

None

SUPPORTING DATA:

None