

AD_____

Award Number: W81XWH-06-1-0257

TITLE: Efficacy of Adjunct Sleep Interventions for PTSD

PRINCIPAL INVESTIGATOR: Anne Germain, Ph.D.

CONTRACTING ORGANIZATION: University of Pittsburgh School of Medicine
Pittsburgh, PA 15260

REPORT DATE: March 2007

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY) 01-03-2007		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 17 FEB 2006 - 16 FEB 2007	
4. TITLE AND SUBTITLE Efficacy of Adjunct Sleep Interventions for PTSD				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-06-1-0257	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Anne Germain, Ph.D. E-Mail: germaina@upmc.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Pittsburgh School of Medicine Pittsburgh, PA 15260				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 In this first year of funding, we have successfully achieved all goals initially set in our statement of work and task timeline for the first 20 months of the award. Recruitment has been delayed and accrued at a slower pace than initially anticipated for clinician-initiated referrals. However, we have rapidly changed our recruitment strategy and continue to seek opportunities to collaborate effective with our colleagues at the VAPHS to facilitate and enhance recruitment of military veterans with sleep disturbances to our research program. This award has also significantly contributed to other reportable outcomes included a peer-reviewed manuscript currently in press, several presentations, and provided preliminary data for other applications for federal funding by the PI.					
15. SUBJECT TERMS Sleep, PTSD, prazosin, behavioral treatments of nightmares and insomnia.					
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	33	19b. TELEPHONE NUMBER (include area code)

Efficacy of Adjunctive Sleep Interventions in PTSD (PR054093)
Updated Progress Report
February 16 2006- September 30 2007 (Updated Report)

Table of Contents

	<u>Page</u>
Introduction.....	1
Body.....	1
Key Research Accomplishments.....	7
Reportable Outcomes.....	7
Conclusion.....	8
References.....	N/A
Appendices.....	9

Efficacy of Adjunctive Sleep Interventions in PTSD (PR054093)

Updated Progress Report

February 16 2006- September 30 2007 (Updated Report)

I. INTRODUCTION.

PTSD-related sleep disturbances are often resistant to first-line PTSD treatments. Although adjunctive pharmacological or behavioral sleep interventions are often required to adequately reduce nightmares and insomnia in veterans with PTSD, the efficacy and durability of adjunct sleep interventions have not been formally evaluated and compared. The overarching objective of this study is to investigate and compare the efficacy and durability of adjunctive sleep-focused interventions on sleep, daytime PTSD symptoms, and mood in a sample of 90 male and female veterans who receive PTSD treatment but who continue to experience nightmares and insomnia. The proposed study will contribute to the development of effective therapeutic strategies for PTSD, and provide novel information regarding predictors of sleep treatment response in PTSD.

II. BODY.

Research accomplishments associated with each task outlined in the approved Statement of Work.

The tasks and timeline initially proposed and approved for Year 1 in the statement of work is provided here. Progress and outcomes on each of the task listed in Table 1 are detailed below.

Table 1. Proposed Task Timeline	Year 1 (02/16/06 – 02/15/2006)			
	Months 1-4	Months 5-8	Months 9-12	Status
Task				Completed
Personnel Hiring & training				Completed
Finalizing IRB approvals				Completed
Advertisement development				Completed
Order start-up supplies and material				Completed
Subject recruitment & enrollment				Ongoing
Randomization and treatment delivery				Ongoing
Telephone Follow-ups				Ongoing
Data safety and monitoring plan				Ongoing

Task 1: Personnel Hiring & Training

Since funding was awarded in February 2006, all staff members have been hired and completed all requirements of training in ethical conduct of research, research data handling and protection, and conflict of interest as requested by both the University of Pittsburgh and VA Pittsburgh Healthcare System (VAPHS) Institutional Review Board. Staff members described below are personnel members who had not yet been identified at the time the award was granted.

Douglas E. Moul, MD, MPH, D,ABSM. Dr. Moul is the study physician for this study. Dr. Moul is a staff psychiatrist at Western Psychiatric Institute and Clinic, and an expert in self-report and polysomnographic measurements of insomnia. Dr. Moul is responsible for verifying findings for physical exam and blood tests performed during the screening process to ascertain participants' fitness to participate. Dr. Moul is also responsible for all aspects related to prazosin/placebo administration and clinical management of participants randomized to the prazosin/placebo arms. He assists the research coordinator in the consent process, so that he can accurately address questions raised by the participants regarding medications and side effects or any other concerns related to medications. Dr. Moul acts as the blind physician in the treatment phase of the study.

Abdul Hakim, MSW, Project Coordinator. Mr. Hakim Mr. Hakim has received extensive training in administering and rating clinical assessments and therapeutic interventions to adolescents and adults with mood,

anxiety and substance related disorders during his prior employment at Western Psychiatric Institute and Clinic as a psychiatric specialty counselor. Mr. Hakim is an OEF veteran, with 17 years of military experience (both active and reserve). As a Major in the medical service corps, Mr. Hakim was assigned as the Plans and operations Officer (G3) for TF 44 Med FWD and the executive officer of the 339 Combat Support Hospital. He worked with several combat stress detachments while deployed to Afghanistan and used his extensive mental health background to help evaluate, establish, treatment, and redeployment procedures for assigned soldiers suffering from PTSD. Mr. Hakim coordinated with Landstuhl Regional Medical Center and Walter Reed Army Medical Center with the psychological evaluations of assigned OEF veterans and established procedures to assist and monitor these veterans after redeployment to their home station units. His unique first-hand experience, and training and experience in clinical psychiatry provide him with a strong clinical background and understanding of this population. Mr. Hakim is currently involved in an ongoing program for maintenance of inter-rater reliability on the CAPS and SCID with assessors involved in other research studies at the Department of Psychiatry of the University of Pittsburgh School of Medicine. He has received detailed written information for use of each assessment instrument, and continues to receive updates as new knowledge and research findings become available. Certification and regular rating of audiotaped assessment will continue to perform for the main outcome measures. Mr. Hakim participates in bi-monthly supervision meetings with the Principal Investigator, co-investigators, and collaborators to discuss assessment problems and ensure consistency in handling them with other research assessors, and with the Principal Investigator. Mr. Hakim also created all manuals for the studies Standards of Operations (SOPs) necessary for the study.

Naomi Pittle, LMSW, Research Therapist (May 06- March 2007) Mrs. Pittle's primary appointment was in research at the VAPHS with the Mental Illness Research, Education, and Clinical Center (MIRECC). To concretize our collaboration with the VAPHS, Mrs. Pittle's services were under contract with the University of Pittsburgh. She is currently acting as the therapist for this study. Mrs. Pittle has 12 years of experience of working with military veterans with severe mental health disorders and with homeless veterans. She came to our group in May 2006, and undertook a training program in behavioral sleep medicine consisted of didactic training; listening to audiotaped sessions of behavioral treatment of comorbid insomnia in PTSD and older adults; direct observations of interventions sessions targeting PTSD-related nightmares and comorbid insomnia. She was trained to deliver an 8-week treatment program targeting the behavioral treatment of insomnia and nightmares in combat veterans with PTSD. She met weekly with the PI for supervision. Mrs. Pittle also completed the training for administering the CAPS, SCID, and SLEEP-SCID. She regularly attended clinical workshops on mental health issues related to PTSD in OIF/OEF returnees, and development aspects related to sleep disturbances. Mrs. Pittle left our team in March 2007 to accept a full-time position at the VAPHS as a social worker at the Department of Emergency Medicine at the VAPHS.

Robin Richardson, LMSW, Research Therapist. (April 2007 – now). Mrs. Richardson was hired to replace Mrs. Pittle. Mrs. Richardson is an experienced clinical social worker with expertise in the behavioral treatment of anxiety disorders including PTSD. She has also considerable experience in the assessment of psychiatric disorders, and has gained experience in the assessment and diagnosis of sleep disorders over the last 24 months. She initiated her training in behavioral sleep medicine in February 2006, under the supervision of the Principal Investigator. Mrs. Richardson has completed an intensive training workshop on the behavioral treatment of insomnia at the University of Rochester, NY. Mrs. Richardson has observed Dr. Germain deliver a standard, 8-week cognitive-behavioral interventions targeting primary insomnia in 3 patients, and has delivered this intervention in 12 research participants with primary or comorbid insomnia as of May 2007. She completed the training with the PI to deliver the behavioral sleep intervention targeting insomnia and nightmares used in the ongoing clinical trial and has conducted the intervention in 3 research participants randomized to BSI since May 2007.

Colleen Walsh, B.Sc. Mrs. Walsh has replaced Mrs. Gottermeyer as the entry clerk for this study. Mrs. Walsh also assist the coordinators in preparing participants' study binders, and posting recruitment flyers.

All research personnel also completed the following training activities:

Visit of Murray Raskind, MD, consultant. Dr Raskind is an expert on the use of prazosin in military veterans with PTSD-related sleep disturbances, visited our research group on August 7-8 2006. His visit included a seminar on the literature review and update on clinical issues relevant to the use of prazosin in veterans with PTSD, and a 40-hour study group and training session for the study physicians, coordinator, PI, pharmacy, and psychopharmacology laboratory.

Welcoming home military personnel. The PI, coordinator, and therapist attended the one-day seminar entitled “Welcoming home military personnel, held at the Pittsburgh VA on November 3, 2006. The seminar aimed at training health care professionals and workers of psychological and medical difficulties commonly encountered by OIF/OEF returnees and clinical and community services available for referral and care of this cohort of veterans.

Short Sleep Course. The Coordinator and therapist attend a day-long training session on the assessment and treatment of sleep disorders, offered by the Pittsburgh Mind Body Center on December 8, 2006. This one-day training course consisted in an introduction to normal sleep and wakefulness regulatory mechanisms, and assessment and treatments of sleep disorders.

Staff members also regularly attend Grand Rounds presentations held at Western Psychiatric Institute and Clinic on relevant topics, such as assessment and treatment of PTSD in returning veterans, assessments of anxiety, mood, grief, and sleep disorders, and updates on pharmacological and non pharmacological treatments of anxiety, mood, grief, and sleep disorders.

Task 2: Finalizing IRB approvals

This task has been achieved despite initial delays. As previously explained to Dr. Bart-Knauer, this process is complicated by the fact that both the VAPHS and University of Pittsburgh have distinct IRB approvals process, distinct requirements, and separate processes for review that do not operate on the same time line. Nevertheless, finally approval for this study was granted by both institutions on February 1, 2006 (VAPHS), and on January 13, 2006 (University of Pittsburgh). Renewal of the University IRB approval was submitted to both institutions in September 2006, to avoid delays in the renewal process. Approvals for the renewal was granted by the University on August 31, 2007; and by the VAPHS on December 27, 2006. The IRB renewal by the University of Pittsburgh has been granted on July 24, 2007, is currently under review at the VAPHS.

Task 3: Advertisement development

Posters and brochures for recruitment were developed by Mr. Hakim, the project coordinator. A press release and newspaper advertisements have also been developed by Mr. Hakim. Television advertisements have also been developed, and aired on the local television station since December 31, 2006. All recruitment ads have been reviewed and approved by the University of Pittsburgh, VAPHS IRB, and Department of Defense U.S. Army Medical Research and Materiel Command's Human Research Protection Office (HRPO). We have also developed a website (<http://www.veteranssleep.pitt.edu>) that provides information about this research study. The website has already received all necessary approvals before being launched in September 2007.

Task 4: Order start-up supplies and material

All material and supplies required for the study were ordered and available by September, 2006. A desktop computer for Mr. Hakim, and a laptop computer for the research therapist have been received, and equipped with all data protection software as required. Personal data assistants (PDAs) have been tested, and are now equipped with the software use for the electronic sleep diary developed by our computer program expert, Joseph Shields. Supplies of prazosin, and gelatine capsules are now in stock at the University Research Pharmacy. Procedures have been established with the University Research Pharmacy. The randomization list was prepared and delivered to the pharmacy by the research statistician, Amy Begley, M.Stats.

Task 5: Subject recruitment and enrollment

Recruitment was initiated on October 1, 2006. Recruitment uses several venues. First, clinicians at the VAPHS PTSD Clinic and OIF/OEF clinics have received information about the study and selection criteria. As requested by the VAPHS IRB, clinicians can refer patients to our study by providing recruitment brochures, or obtaining screening consent and a signed HIPAA form (VA Form 1045). This process has yielded 42 referrals, as of September 30, 2007. While this is an

Table 1. Demographic information of participants who have provided written, informed consent as of September 30, 2007.

Ethnic Category	Sex		
	Females	Males	Total
Hispanic or Latino	0	1	1
Not Hispanic or Latino	4	37	41
Ethnic Category Total of All Subjects*	4	38	42
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	6	7
White	3	32	35
Racial Categories: Total of All Subjects	4	38	42

appreciable number of referral given the work load from clinicians who are not typically involved in research activities of the VAPHS clinics, this is significantly below 3-4 referrals per week initially anticipated by the clinicians at the VAPHS. Therefore, we have significantly augmented the use of television and newspapers advertisements, and of posted flyers and brochures. These media advertisements have yielded contacts from 292 other veterans between the ages of 18 and 60 years old directly contacted our research team about the ongoing study on the treatment of sleep disturbances in military veterans. Of the total individuals who contacted us, we were able to reach and initiate the telephone screen with 233, and to complete both the telephone script and screening telephone interview with 159 individuals. Of these, 58 were invited for a consent visit, and 42 showed up for this visit and provided written, informed consent.

Table 1 presents the demographic of the 42 individuals have provided written, informed consent for this study as of September 30, 2007. Of the participant of provided written, informed consent, 24 were excluded during the screening procedures due to poor compliance with study procedures (n = 12: no-shows or no longer interested or no reason provided for withdrawing participation), current untreated severe PTSD, depression, of alcohol / substance use (n = 8), or sleep apnea (n = 4). Of the remaining 18 participants, all completed the baseline assessments and sleep study, 12 have been randomized to treatment (5 to BSI, 7 to medication). Six are currently completing the baseline assessments. Three participants withdrew after randomization: one randomized to placebo withdrew due to side effects; one who was randomized to prazosin moved out of state two weeks into the treatment phase; and one did not initiated treatment due to time constraints. Three have completed the acute intervention phase and the 4-month follow-up assessments. One participant completed the acute treatment phase and is currently in the follow-up period.

Task 6: Randomization and treatment delivery

Between November 2006 and September 2007, 13 individuals have been randomized (5 to BSI, 7 to medications). No deviation to the randomization or treatment delivery protocols has been reported. Unexpected, adverse side effects have not occurred. Two participants randomized to medications withdrew their participations (1 randomized to placebo, and randomized to prazosin), and one participant randomized to BSI withdrew prior to session 1.

Task 7: Telephone Follow-ups

Telephone follow-up have been completed in 3 participants. One participant had initiated the follow-up period.

Task 8: Data safety and monitoring plan

Since February 2006, the PI has held and lead weekly team meeting to closely monitor the progress of the study. After recruitment started in October 2006, these meetings are also used to review, verify and achieve consensus on participants' eligibility and safety to participate in the study; verify if any member of team has become aware of the new information that alters the risk/benefit assessment of the present study, verify that confidentiality has been protected and no breach has occurred; and search the literature on new information that may affect the current assessment of the risk/benefit ratio. For instance, the PI presented a peer-reviewed article, published by Raskind et al., entitled, "A Parallel Group Placebo Controlled Study of Prazosin for Trauma Nightmares and Sleep Disturbance in Combat Veterans with Posttraumatic Stress Disorder", published in *Biological Psychiatry*, in October 2006 to the research team. The study procedures, dosage of prazosin, side effects and adverse/unanticipated events, and outcomes were carefully reviewed. This new study did not alter our assessment of the risks and benefits of the current study. A recent review of the literature on the effects of prazosin on sleep disturbances, by Dierks and colleagues and published in *Annals of the Pharmacotherapy* was also presented and discussed during the weekly team meeting in July 2007.

The need to reassess inclusion and exclusion criteria to ensure that the right to participate in research study was ethically balanced against safety issues during meetings held in April and May 2007: It rapidly became clear to this group of investigators that a significant portion of OIF/OEF veterans refuse or decline to use medications for posttraumatic stress symptoms, and are often not optimally adherent to the treatment plan offered by the primary care provider or psychiatrist. Therefore, we have sought IRB approvals to include veterans who are not on an SSRI, provided that the CAPS score is < 80 and that they not present severe distress and impairments. A Data and Safety Monitoring Plan Report is required for all IRB renewals. This report was provided and approved by all IRBs involved in this clinical trial.

A Data and Safety Monitoring Board (DSMB) is also included in the ongoing clinical trial, and was convened in April 2007. The DSMB includes Drs. Ellen Frank, Wesley Thompson, and Terry Keane. Summaries of recruitment results, study procedures, and any unexpected/adverse event that were provided to the members for review. Recommendations made by the DSMB were incorporated in the research protocol, consent forms, and other documents as necessary. These modifications have all been submitted for approval to all IRBs involved in the present trial. A list of recommendations and actions taken is provided in the DSMB report provided in Appendix III.

Problems in accomplishing any of the tasks.

Recruitment posed a challenge in the present study in the first 8 months of the award. The primary barrier encountered for recruitment relates to the initially target recruitment sites. We initially proposed to recruit veterans mostly from the local VA clinics by using advertisement posters and brochures, and via referral from VA clinicians at the local PTSD and OIF/OEF clinics. This currently strategy provides an average of 4 patients per month, for a total of 20 since October 8, 2006 which is clearly not sufficient, and below the expected 20 or more, based on estimates provided by our VA collaborators prior to the award proposal submission.

Another barrier encountered for recruitment relates to the fact that prazosin, the experimental medication in the present study, is commonly used by psychiatrists and physicians at local VA clinics. To date, 9 potential participants who were referred to us from these clinics were already on prazosin for several weeks at low doses (e.g., 1 to 6 mg) with minimal or no improvements in nightmares and insomnia (the expected effective doses typically range between 6mg and 10 mg, according to published reports). These individuals were not willing to be randomized to prazosin if they participated in the study, despite our best efforts to provide education and information regarding different dose increase/decrease schedule for prazosin, and associated risks involved in the present study.

Finally, the launching of recruitment efforts was slightly delayed due to extended time required for submission, review, and obtaining approvals from institutional review boards (IRBs) from the University of Pittsburgh and VA Pittsburgh Healthcare system, which operate on some significant different and timelines. As soon as approvals were secured from both IRBs and the DoD, recruitment efforts were initiated.

To overcome these difficulties, we have used the following strategy:

1. Given the insufficient flow of veterans coming for VA clinics, we have used public media to advertise and recruit veterans since December 2006. A series of television ads is being conducted for two weeks, every five weeks. Newspapers and television ads proved to be a successful, cost-efficient means to recruit veterans. The first series of ads lead a total to of 75 additional contacts in over 2 weeks, and continues to produce 10 to 20 calls per advertisement period. Televisions and newspapers advertisements have now become our primary mode of recruitment, while we continue to inform VA clinicians of the ongoing study.

2) The PI attends weekly team meetings at the PTSD clinic, and regularly visit the OIF clinic and discuss with clinicians about the ongoing research study and the fact that one aim is to compare the effects and durability of prazosin compared to a behavioral interventions. We seek feedback and information regarding factors that interfere with referring potential individuals to our research study. While clinicians clearly support our research efforts, the integration of research into this clinic setting is a new concept. We believe that regular, on-site visits and discussions with clinicians will foster more frequent referrals to our study.

3) The collaboration with the VAPHS is much more complex than initially outlined, and administrative requirements that differ between the University and the VAPHS have impeded recruitment efforts due to restrictions regarding which staff member can or cannot interact with a given research participant. Therefore, we submitted a modification request to both IRBs (VAPHS and University) to have two consent forms for participants recruited from the VA, and participants who are not recruited from the VA. This modification was reviewed by all IRBs involved, and approved. This allows all University-approved staff to screen, assess, and administer research treatments to research participants who are recruited via public advertisements, whereas only VA credentialed staff will interact with research participants who are recruited by VA clinicians. While the research protocol remains the same, and while the content of the consent form is identical, a separate consent forms by used for research participants who are recruited from VA clinicians, and individuals who contact us from public advertisements. Several reasons made this change necessary in order to improve recruitment. According to the VAPHS IRB regulations, the majority of the research staff at the University do not meet competency requirements for research. At the VAPHS, credentialing requires and a very different, relatively lengthy process (but similar in content) and exhaustive credentialing procedures for research study staff. This credentialing process is required before research staff can be in contact with research subjects and research data. We understand that this credentialing process that is derived from clinical care practices, and may be necessary given that boundaries between research and clinical care within the same VA entity may be blurred at times. However, in the context of the current research study which is conducted at University, with the PI who is not VA clinician or research, and with research staff hired by and working at the University, it is not feasible, for budgetary, time, and logistical reasons to submit the University research staff to VA credentialing requirements. Hiring VA research staff is not possible given the budgetary limitations, and again, higher costs associated with VA research compared to the University research costs. Some of the research staff has completed the required credentialing process at the VAPHS. However, the amount of time dedicated to these administrative issues cannot be dedicated to active recruitment of research participants. Given that the majority of research participants are not recruited from the VA, this investment of time and efforts is not justified. While the personnel who are currently credentialed will maintain their credentials for participants who are VA patients, a clearer separation between requirements for VA and non-VA participants will improvement effort and staff management and redirect it toward recruitment efforts as it is necessary. The University of Pittsburgh approved this modification on January 31, 2007. Approval from the VAPHS IRB was granted on

April 4, 2007. This request for modification was submitted with our progress report to the U.S. Army Medical Research and Materiel Command's Human Research Protection Office (HRPO) on Feb 5, 2007, and approved.

KEY RESEARCH ACCOMPLISHMENTS.

None at this time.

REPORTABLE OUTCOMES.

Peer-reviewed Manuscript:

In a peer-reviewed paper in press at *Sleep Medicine Reviews*, we have recently proposed a neurobiological model of PTSD as it persists across the sleep-wake cycle (see Appendix). This award number is acknowledged in this article.

Presentations:

The following presentations regarding the scientific and clinical rationale, design and methods of our ongoing clinical trial were PI from February 2006 until September 2007. These presentations aimed 1) educating the scientific and clinical community involved in the care of military veterans with PTSD about the ongoing clinical trial; 2) promoting the importance of sleep in the re-adjustment process following redeployment to the USA in OIF/OEF service members; and 3) enhancing the visibility of the study to enhance recruitment.

Germain A, Nofzinger EA. Efficacy of adjunctive sleep interventions in for PTSD. Abstract accepted for an oral presented at the 2006 DOD Military Health Research Forum, San Juan, Puerto Rico, May 2006.

Brief Behavioral Treatment of Insomnia in Military Veterans: A Pilot Study. Multidisciplinary Sleep Conference, University of Pittsburgh, January 18, 2006.

Treatment of Nightmares Comorbid With Posttraumatic Stress Disorder (PTSD). West Virginia University, Department of Behavioral Medicine and Psychiatry, Clinical Grand Rounds, Morgantown, WV, April 12, 2006.

Treating Sleep Disturbances in Military Veterans with PTSD. Presentation at the Pittsburgh VA Brown Bag Lunch Seminar.

Efficacy of Adjunctive Sleep Interventions in PTSD. Invited presentation for the VISN-4 MIRECC External Advisory Board, April 24, 2007.

Correlates and treatments of sleep disturbances in PTSD. Young Investigator Lecture Series, Western Psychiatric Institute and Clinic, October 12, 2007.

Funding applied for based on work supported by this award:

- Early in the course of our ongoing clinical trial, we have found that a considerable number of military veterans report insomnia related to post-deployment adjustment disorders, but do not meet diagnostic criteria for PTSD. Therefore, we have developed and submitted an R34 proposal aimed at adapting and testing a brief behavioral treatment of insomnia previously developed by our team over the course of another study funded by National Institutes of Mental Health (NIMH) (AG20677). Preliminary findings on the efficacy of this brief behavioral treatment of insomnia are provided in Appendix. Recruitment data and clinical observations derived from the current clinical trial provided preliminary data for this application. Our NIMH proposal, entitled "Brief Behavioral Treatment of Comorbid Insomnia in Returning Veterans" was favorably reviewed in April 2007, and underwent second review in October 2007 (Score 146, Percentile 16.7%). Further information and final decision regarding fundability of this study at this time is awaited. If not funded, this proposal will be resubmitted for re-review in March 2008.

- We have submitted an Investigator-Initiated Research Award proposal in response to recent announcements by the Department of Defense for PTSD research (W81XWH-07-PTSD-IIRA), where we propose to include functional neuroimaging to the ongoing clinical trial. We propose to expand upon personnel and infrastructures set in place for our ongoing clinical trial to create unique opportunities to gather novel insights into a) the neurobiological correlates of PTSD during sleep and of response to sleep treatments. We also propose to explore neurobiological predictors of sleep treatment response across the sleep-wake cycle.
- Dr Germain is also a co-investigator on another proposal for an Investigator-Initiated Research Award submitted in response to recent announcements by the Department of Defense for PTSD research (W81XWH-07-PTSD-IIRA) (PI: Yuval Neria, Ph.D., Columbia University), and entitled, *Efficacy of Lunesta vs. Cognitive Behavioral Treatment of Insomnia in OIF/OEF veterans*. Preliminary data regarding the feasibility of using actigraphy in OIF /OEF veterans for 8 consecutive weeks were drawn from our ongoing award. The treatment manual used in our ongoing trial also served as the basis for the insomnia treatment proposed in this project. Dr. Germain will be responsible for training and supervising therapists in behavioral sleep interventions for insomnia in OIF/OEF returnees in this proposal.
- We have submitted developed and submitted an R21 proposal to NIMH aimed at exploring the neurobiological underpinnings of PTSD during REM sleep relative to wakefulness. This proposal is entitled, *“Neurobiological Correlates of REM sleep in PTSD”*, awaits review at NIMH, which is scheduled for October 25, 2007. Recruitment data derived from the current clinical trial provided preliminary data for this application.

Research training activities conducted under this award:

- *Jason Munsie, BA, Masters student in social work (September 2007-August 2007).* Mr. Munsie completed a research internship required as part of the Masters’ Program in Social Work at the University of Pittsburgh with our research team under the close supervision of the PI. During his internship, Mr. Munsie assisted the research coordinator in maintaining SOPs and tracking recruitment and enrollment data. He completed extensive training in the assessment of sleep and psychiatric disorders.
- *Miriam Stoll* is a student at the University of Pittsburgh, Department of Psychology who completed her undergraduate research project under the supervision of Dr. Germain, between September 2006 and April 2007. She conducted a comparative study on the prevalence and severity of grief symptoms in OIF/OEF and Vietnam veterans using data collected during the screening phase of the ongoing clinical trial. This preliminary analysis indicated that bereavement is highly prevalent in returning veterans and that the severity of daytime PTSD symptoms and of sleep disturbances do not differ in these two cohorts of veterans. These findings were presented as a poster at the annual Psychology Research Day of the University of Pittsburgh (April 2007).
- *Ryan Stocker* is a student at Slippery Rock University, Department of Psychology, who completed her undergraduate research project under the supervision of Dr. Germain between May and August 2007. Mr. Stocker is also an OIF veteran. During his research internship, he conducted a literature review on the co-occurrence of PTSD and traumatic brain injury in military veterans.

CONCLUSION.

At this point in time, we have achieved all goals initially set in our statement of work and task timeline for the first 20 months of the award. Recruitment has been delayed and accrued at a slower pace than initially

anticipated for clinician-initiated referrals to the study. However, we have rapidly changed our recruitment strategy and continue to seek opportunities to collaborate effective with our colleagues at the VAPHS to facilitate and enhance recruitment of military veterans with sleep disturbances to our research program. No unexpected adverse events have been reported, and all but two participants to date who were randomized to one of the three treatment arms completed the protocol with minimal difficulties. Three participants withdrew after randomization. We continue to explore new and creative venues to enhance recruitment efforts and success, and to actively seek opportunities to expose the study publicly via television interview on sleep and PTSD, and television and newspapers advertisement.

REFERENCES.

None.

APPENDICES

- Appendix I** **Germain A**, Moul DE, Franzen PL, Miewald JM, Reynolds CF, III, Monk TH, & Buysse DJ. Effects of a Brief Behavioral Treatment for Late-life Insomnia: Preliminary Findings. *Journal of Clinical Sleep Medicine*, 2:403-406, 2006. Also available online at: <http://www.aasmnet.org/jcsm/Articles/020406.pdf>
- Appendix II** **Germain A**, Buysse DJ, Nofzinger EA. Sleep-specific Mechanisms Underlying Posttraumatic Stress Disorder: Integrative Review and Neurobiological Hypotheses. *Sleep Medicine Reviews*, *in press*.
- Appendix III** Report from the Data Safety and Monitoring Board Meeting, April 25, 2007

SUPPORTING DATA.

None provided at this time.

Appendix I

Germain A, Moul DE, Franzen PL, Miewald JM, Reynolds CF, III, Monk TH, & Buysse DJ. Effects of a Brief Behavioral Treatment for Late-life Insomnia: Preliminary Findings. *Journal of Clinical Sleep Medicine*, 2:403-406, 2006. Also available online at: <http://www.aasmnet.org/jcsm/Articles/020406.pdf>

SCIENTIFIC INVESTIGATIONS

Effects of a Brief Behavioral Treatment for Late-Life Insomnia: Preliminary Findings

Anne Germain, Ph.D.; Douglas E. Moul, M.D., M.P.H.; Peter L. Franzen, Ph.D.; Jean M. Miewald, B.A.; Charles F. Reynolds, III, M.D.; Timothy H. Monk, Ph.D., D.Sc.; Daniel J. Buysse, M.D.

Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA

Study Objectives: Insomnia is a chronic and prevalent sleep disorder in adults older than 65 years. Hypnotics raise safety concerns in this group, and standard behavioral treatments are time consuming. This preliminary report addresses the effects of a brief behavioral treatment for insomnia in older adults who present with the typical psychiatric and medical comorbidities of aging.

Methods: Thirty-five older adults (10 men, 25 women, mean age = 70.2 ± 6.4 years old) were randomly assigned to a brief behavioral treatment for insomnia (BBTI; n = 17) or to an information-only control (IC; n = 18) condition. All subjects completed clinician-administered and self-report measures of sleep quality, as well as a sleep diary, at baseline. Interventions were delivered in a single individual session with a booster session administered 2 weeks later. Postintervention assessments were completed after 4 weeks.

Results: Significant improvements in self-report and sleep diary mea-

asures and mild-to-moderate improvement in anxiety and depression were observed after treatment in participants randomly assigned to BBTI, as compared with participants randomly assigned to IC. At post-treatment assessment, 12 BBTI participants (71%) and 7 IC participants (39%) met criteria for response. Nine BBTI participants (53%) met criteria for remission, whereas, in the IC group, 3 participants (17%) met the criteria.

Conclusion: BBTI was associated with significant improvements in sleep measures and in daytime symptoms of anxiety and depression. BBTI appears to be a promising intervention for older adults with insomnia.

Keywords: Insomnia, aging, sleep, stimulus control, sleep restriction

Citation: Germain A; Moul DE; Franzen PL et al. Effects of a brief behavioral treatment for late-life insomnia: preliminary findings. *J Clin Sleep Med* 2006;2(4):403-406.

Insomnia is a prevalent disorder among older adults and a frequent complaint encountered in primary care clinics.¹⁻³ Because more than 75% of patients with insomnia receive treatment in primary care settings,⁴ finding effective interventions for this population that could be delivered in primary care settings is an important goal for aging and mental health services research.

Although hypnotics can be efficacious for the short-term treatment of insomnia, their use raises safety concerns regarding side effects, including cognitive impairment and risks of injuries in older adults.^{6,7} Behavioral interventions for insomnia may offer safer alternatives for older adults. Meta-analyses support the efficacy of stimulus control⁵ and sleep restriction⁶ for the behavioral treatment of insomnia^{7,8} in both younger and older adults,^{9,10} whereas sleep hygiene has shown little efficacy when used alone.

Typically, behavioral insomnia treatments are delivered by highly trained clinicians in individual or group sessions over a 6- to 8-week period. These resources may not be readily available or practical in usual care settings. Recent studies have focused on briefer interventions^{11,12} and interventions that can be delivered by primary care nurses.¹³ We present a study that is a preliminary report of findings from an ongoing study of a brief behavioral treatment of insomnia (BBTI) in older adults with the typical psychiatric and medical comorbidities associated with aging.

Commentary Follows on Pages 407-408

METHODS

Participants

Participants were recruited from primary care clinics and the general public via media advertisements. Data collected from participants enrolled between May 2004 and July 2005 are included in the present report. Written informed consent was obtained from all participants. Eligible participants were older than 60 years and met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnostic criteria for primary insomnia but without the medical or psychiatric exclusion criteria. Participants with stable medical or psychiatric conditions were allowed to participate. The Charlson Comorbidity Index was used to screen for medical conditions,^{14,15} and the PRIME-MD Patient Health Questionnaire was used to screen for mood, anxiety, and substance use disorders.¹⁶ Sleep disorders were assessed using a structured interview developed locally.

Disclosure Statement

This was not an industry supported study. Dr. Buysse is a consultant for Actelion, Cephalon, Eli Lilly, GlaxoSmithKline, Merck, Neurocrine, Neurogen, Pfizer, Respiroics, Sanofi-Aventis, Servier, Sepracor, and Takeda. Dr. Reynolds has received research support from GlaxoSmithKline, Pfizer, Forest, BMS, and Lilly. Drs. Germain, Moul, Franzen, Miewald, and Monk have indicated no financial conflicts of interest.

Submitted for publication June 6, 2006

Accepted for publication June 27, 2006

Address correspondence to: Daniel J. Buysse, M.D., Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213; Tel: (412) 246-6413; Fax: (412) 246-5300; E-mail: buyssedj@upmc.edu

Individuals using prescribed or over-the-counter hypnotics were included if they reported insomnia and agreed to continue to use the sleep aids. Individuals with unstable or untreated psychiatric, medical, or sleep disorders were excluded. This was determined based on the review of clinical data obtained during the face-to-face visit, in which clinician-administered assessments, self-report measures, and the review of medical charts were gathered from each participant. This review was conducted during weekly consensus meetings. Nine participants who were found to require prompt attention for the presence of new or worsening mood ($n = 5$) or anxiety disorders ($n = 4$) were excluded. One participant was excluded during the screening procedures for substance abuse disorder, and another was excluded due to worsening of a neurodegenerative disease. Participants who endorsed symptoms of restless legs syndrome, periodic leg movement disorder, or delayed sleep phase syndrome on most nights associated with difficulty falling or staying asleep were excluded at the clinical interview ($n = 5$) and referred to their primary care physicians with specific recommendations for further evaluation. Participants who endorsed symptoms consistent with sleep apnea (e.g., snoring, recalled or witnessed apneas, subjective reports of excessive daytime sleepiness) were referred to their primary care doctors for further evaluation ($n = 7$). For some individuals who reported symptoms consistent with sleep apnea, screening sleep studies were conducted; 3 participants were excluded due to significant sleep apnea ($AHI > 20$) and referred to their primary care physicians. None of the participants included in the present study had a diagnosis of obstructive sleep apnea.

MEASURES

Sleep measures included the Pittsburgh Sleep Quality Index (PSQI)¹⁷ and the Pittsburgh Sleep Diary.¹⁸ The PSQI is a 19-item self-report questionnaire that assesses 7 clinically relevant components of sleep quality (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction) in the preceding month. Each component is rated on a 0- to 3-point scale referring to the composite score derived from the frequencies of each disturbance, in which 0 is equal to not in the past month and 3 is equal to 3 or more times a week, with a global score range from 0 to 21. The global PSQI score is then the sum of these 7 component scores. A cut-off score of 5 has been shown to discriminate between good and bad sleepers.¹⁷ The PSQI has good internal consistency (Cronbach $\alpha = .83$) and test-retest reliability ($r = .85$). The Pittsburgh Sleep Diary is a diary of sleep-wake behavior that comprises wake time and bedtime portions. The wake time portion is completed upon awakening in the morning and asks questions regarding the times at which the participant went to bed and attempted to fall asleep; the number, cause, and duration of nocturnal awakenings; the final time out of bed; and the total estimated time spent asleep while in bed. The bedtime portion of the diary is completed right before bedtime and asks questions about the preceding day, including the times of meals, naps, and exercise sessions; the consumption of caffeine, alcohol, and tobacco; and the use and doses of medications (prescribed and over-the-counter). Sleep diary measures of interest included sleep latency, total sleep time, wake time after sleep onset (WASO), and sleep efficiency. Sleep efficiency was calculated as the percentage of time spent asleep divided by the total time spent

in bed. Depression and anxiety were assessed by the Hamilton Rating Scale for Depression¹⁹ and the Hamilton Rating Scale for Anxiety.²⁰ An independent assessor who completed these latter clinician-administered scales remained blind to participants' assignments. Participants were also instructed not to discuss the intervention they received with the assessor.

Treatments

Seventeen participants (12 women; age mean $\pm$ SD 70.9 ± 5.3 years) were randomly assigned to receive BBTI, and 18 (13 women; age 69.6 ± 7.3 years) were randomly assigned to receive an information-only control (IC) condition. The computer-generated blocked randomization scheme was stratified by sex and by age (< 74 years old, > 74 years old), and the randomization sequence was concealed until interventions were assigned.

BBTI participants received a single, 45-minute intervention session conducted by a masters-level adult psychiatric and primary care nurse practitioner who had been trained to deliver the BBTI intervention. This session included education about mechanisms that regulate sleep, factors that influence sleep, and behaviors that promote or interfere with sleep quality. Participants received a workbook containing educational material and treatment instructions. Based on information derived from baseline assessment of sleep diary measures, simple tailored instructions based on stimulus control and sleep restriction were provided to each participant. Specifically, 4 instructions, tailored for each BBTI participant, included: (1) reduce time spent in bed to closely match your number of hours of sleep; (2) get up at the same time every day of the week; (3) do not go to bed unless you are sleepy; and (4) don't stay in bed unless you are asleep. For safety reasons, the minimum time allowed in bed each night was 6 hours. Activities to be performed during the day and night while awake were also discussed. Participants were instructed to follow these instructions for the following 4 weeks. Two weeks later, BBTI participants returned for a 30-minute booster session. This second session aimed at reviewing educational material, assessing treatment adherence, and modifying recommended sleep schedules if necessary. Specific recommendations to increase time spent in bed included: (1) increase time in bed by 15 minutes if the sleep latency is less than 30 minutes and WASO is less than 30 minutes each night; (2) maintain the new time in bed for 1 week; and (3) increase the time in bed by 15 minutes if the sleep latency and WASO remain less than 30 minutes, and decrease time in bed by 15 minutes if the sleep latency and WASO are longer than 30 minutes.

The IC condition was intended to emulate the type of behavioral instructions most primary care patients might receive. Participants assigned to IC received 3 brochures published by the American Academy of Sleep Medicine on insomnia, sleep and aging, and sleep hygiene. The nurse practitioner also led this session. The subjects were instructed to read and review the brochures over the following weeks. Two weeks later, they received a follow-up telephone call from the nurse practitioner to answer questions that may have arisen. Posttreatment assessments were completed 4 weeks after the first visit. After the randomly assigned intervention, IC participants were then offered BBTI. None of these subjects are included in the current report.

Treatment response was defined as a reduction of 3 points or more²¹ on the PSQI or an increase in sleep efficiency of at least

10%, based on sleep diary measures. Remission was defined as meeting response criteria and having a PSQI score of 5 or less after treatment or sleep efficiency greater than 85% after treatment. The latter remission criteria reflect clinical thresholds for identifying good sleepers.^{17,22}

Statistics

Independent t-tests were computed to assess group differences on baseline measures and on pretreatment to posttreatment score changes on sleep and clinical measures. The magnitude of pretreatment to posttreatment changes was also assessed using Cohen d effect-size coefficients.²³

Specifically, Cohen's d effect sizes were computed by using the mean change scores for each treatment group. Because of the paired design, conservative effect sizes estimates were computed using original standard deviations.²⁴ Small, medium, and large effect sizes are indicated by d values of .20, .50, and .80, respectively.

RESULTS

Thirty-five participants (25 women; age 70.2 ± 6.4 years) were randomly assigned to the 2 interventions. Mean insomnia duration was 18.0 years (SD = 18.5 years; range = 1.3 to 57.7 years). All but 2 participants were Caucasian. No participant was withdrawn or withdrew after randomization.

Eleven participants were recruited from primary care clinics (6 randomly assigned to BBTI, 5 to IC), and 24 (11 in BBTI, 13 in IC) were recruited via advertisements and referrals. The treatment groups did not differ at baseline on sleep and clinical measures (all p values > .1). Six BBTI participants and 8 IC participants were currently using hypnotics. The mean number of current comorbid medical conditions (mean $\pm$ SD = 5.2 ± 1.7 in BBTI and 6.1 ± 3.0 in IC) did not differ between the 2 groups (p > .1). The most common medical conditions were arthritis and joint diseases (n = 12 in BBTI; n = 14 in IC), irregular heart rate (n = 3 in BBTI, n = 10 in IC), and high blood pressure (n = 8 in BBTI, n = 9 in IC), bladder problems (n = 8 in BBTI, n = 7 in IC), cancer (n = 7 in both groups), and other health problems (n = 10 in BBTI, n = 9 in IC). Overall, most participants endorsed

subthreshold psychiatric symptoms on the PHQ. Ten BBTI participants and eight IC participants endorsed mild depressive symptoms (PHQ scores = 5 to 9). Two IC participants endorsed moderate depressive symptoms (PHQ scores = 9 and 10). The most common psychiatric condition was generalized anxiety (n = 8 in BBTI, n = 9 in IC). No participant met criteria for panic disorder. One BBTI participant and two IC participants endorsed symptoms consistent with generalized anxiety disorder on the PHQ.

No adverse events were reported in either treatment group. Pretreatment to posttreatment differences for sleep diary, PSQI, and clinical ratings were significantly greater in the BBTI group, compared with the IC group (Table 1). Twelve of the 17 BBTI participants (71%) met criteria for response, and 9 (53%) also met criteria for remission after treatment. Seven of the 18 participants assigned to the IC condition (39%) met criteria for response, and 3 (17%) met criteria for remission.

DISCUSSION

These preliminary findings suggest that a brief behavioral intervention can reduce insomnia in older adults presenting with the typical comorbidities of aging. The BBTI group showed large improvements in overall sleep quality, sleep latency, WASO, and sleep efficiency, as well as marked reductions in depression and small changes in anxiety, whereas the IC group did not. Total sleep time was not significantly increased after treatment in the BBTI group and likely reflects a direct consequence of acute, mild sleep restriction and stimulus control as part of the BBTI condition. Of note, previous meta-analyses have generally reported small effect sizes and high variability for the effects of behavioral interventions on total sleep time in older adults.¹⁰ In a study of the effectiveness of a 6-session cognitive-behavioral treatment of chronic insomnia in primary care patients, Espie and colleagues¹³ observed minimal improvements in total sleep time after treatment and a mean increase of 34 minutes at a 1-year follow-up assessment. An assessment of the durability of the observed therapeutic gains associated with BBTI is currently under way and will clarify whether total sleep time increases at follow-up assessments. All other sleep measures indicated an overall clinically significant improvement in sleep consolidation

Table 1—Sleep and Clinical Scores Before and After Intervention in the 2 Study Groups

Measures	BBTI (n = 17)				Information Control (n = 18)				Score Differences Between Groups	
	Before		After		Before		After		Student t test	Cohen d
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
PSQI	10.59	2.67	6.65	3.41	9.94	3.76	10.0	2.70	-4.06‡	1.37
Sleep Diary										
SL, min	38.32	30.80	16.80	10.03	29.67	19.83	26.85	22.02	-2.13*	.80
TST, min	340.52	72.15	333.04	64.21	387.08	74.75	393.05	72.72	-1.79†	-.63
WASO, min	61.21	42.66	27.72	29.22	47.91	27.44	35.55	28.59	-2.28*	.67
SE, %	76.96	12.34	86.82	10.46	83.10	6.79	86.41	7.17	1.84†	.64
Depression ^a	4.94	2.86	2.64	2.17	6.53	3.69	7.47	5.19	-2.11*	.67
Anxiety ^a	3.24	1.39	2.57	1.91	3.83	2.31	4.47	4.03	-0.95	.34

BBTI refers to brief behavioral treatment of insomnia; PSQI, Pittsburgh Sleep Quality Index; SL, sleep latency; TST, total sleep time; WASO, wake after sleep onset; SE, sleep efficiency.

*p < .05

†.05 < p < .10

‡p < .01

^aMean scores reflect total scale score minus sleep-item scores.

after treatment in the BBTI group, reflected in improved sleep quality.

The magnitude of effect sizes observed for BBTI on other sleep variables (quality, sleep latency, WASO, sleep efficiency) is comparable with those reported for standard longer behavioral and cognitive-behavioral interventions for insomnia.^{7-9,10} Specifically, large effect sizes ($d \geq 1.00$) for sleep quality and moderate to large effect sizes for sleep latency (range: 0.52 - 1.00) and WASO (range: 0.64 to 1.03) have been reported for behavioral treatments of insomnia in both young and older adults. Effect size estimates for sleep efficiency are lower in older adults (0.38), compared with younger ones.¹⁰

These preliminary findings are consistent with previous studies that have shown that brief behavioral insomnia interventions can be efficacious¹³ and remain efficacious in older adults who present with the typical psychiatric and medical comorbidities associated with aging. The response rate observed in the present study (71% for BBTI) is slightly higher than the response rate reported by Edinger and colleagues (38% to 60%) 3 months after a 2-session intervention that combined sleep education, sleep restriction, and stimulus control.¹¹ However, the use of different measures to assess treatment response (sleep efficiency and PSQI scores in the present study vs sleep latency and WASO in Edinger et al) may explain this difference. Remission rates based on achieving normal scores on self-report questionnaires in the study by Edinger et al and the present one are nevertheless similar: 56% at the 3-month follow-up and 53% after treatment, respectively.

This preliminary report has some limitations. Given the relatively small sample size, it is not possible to further investigate the possible role of concurrent use of hypnotics or other medications known to affect sleep (e.g., antidepressants, β -adrenergic receptor-blocking agents) on the effects of BBTI, nor is it possible to investigate these medications as possible moderators of treatment response and remission. Similarly, the number of psychiatric and medical comorbidities may also influence treatment outcomes. Future analyses in a larger sample will be needed to assess the possible effects of these factors on BBTI outcomes. Nevertheless, the present preliminary findings are encouraging and suggest that BBTI may be amenable to use in primary care settings.

ACKNOWLEDGEMENTS

This research was supported by funds received from grants awarded by the National Institute of Health AG20677, AG00972, RR000056, and MH24652. We wish to thank Laurie Brar, MSN, CRNP, and Grant Shevchik, MD, and the office staff of Partners in Health.

REFERENCES

1. Hohagen F, Rink K, Kappler C, et al. Prevalence and treatment of insomnia in general practice. a longitudinal study. *Eur Arch Psychiatry Clin Neurosci* 1993;242:329-36.
2. Ustun TB, Privett M, Lecrubier Y, et al. Form, frequency and burden of sleep problems in general health care: a report from the WHO Collaborative Study on Psychological Problems in General Health Care. *Eur Psychiatry* 1996;11:5s-10s.
3. Shochat T, Umphress J, Israel AG, Ancoli-Israel S. Insomnia in primary care patients. *Sleep* 1999;22 (Suppl 2):S359-65.
4. Ohayon MM, Caulet M. Insomnia and psychotropic drug consumption. *Prog Neuropsychopharmacol Biol Psychiatry* 1995;19:421-31.

5. Bootzin RR, Nicassio PM. Behavioral treatments of insomnia. In: Hersen M, Eisler RE, Miller PM, eds. *Progress in behavior modification* (vol. 6). New York: Academic Press; 1978:1-45.
6. Spielman AJ, Saskin P, Thorpy MJ. Treatment of chronic insomnia by restriction of time in bed. *Sleep* 1987;10:45-56.
7. Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. *Am J Psychiatry* 1994;151:1172-80.
8. Murtagh DR, Greenwood KM. Identifying effective psychological treatments for insomnia: a meta-analysis. *J Consult Clin Psychol* 1995;63:79-89.
9. Montgomery P, Dennis J. Cognitive behavioural interventions for sleep problems in adults aged 60+. *Cochrane Database Syst Rev* 2002;CD003161.
10. Irwin MR, Cole JC, Nicassio PM. Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age. *Health Psychol* 2006;25:3-14.
11. Edinger JD, Sampson WS. A primary care "friendly" cognitive behavior insomnia therapy. *Sleep* 2003;26:177-82.
12. Mimeault V, Morin CM. Self-help treatment for insomnia: bibliotherapy with and without professional guidance. *J Consult Clin Psychol* 1999;67:511-19.
13. Espie CA, Inglis SJ, Tessier S, Harvey L. The clinical effectiveness of cognitive behaviour therapy for chronic insomnia: implementation and evaluation of a sleep clinic in general medical practice. *Behavi Res Ther* 2001;39:60.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies. *J Chronic Dis* 1987;40:373-83.
15. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? *Med Care* 1996;34:73-84.
16. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA* 1999;282:1737-44.
17. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index (PSQI): a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193-213.
18. Monk TH, Reynolds CF, Kupfer DJ, et al. The Pittsburgh Sleep Diary. *J Sleep Res* 1994;3:111-20.
19. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
20. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50-5.
21. Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M. Psychological treatment for insomnia in the management of long-term hypnotic drug use: a pragmatic randomised controlled trial. *Br J Gen Pract*. 2003;53:923-8.
22. Morin CM. *Insomnia: Psychological assessment and management*. New York-London: The Guilford Press; 1993.
23. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988:567.
24. Dunlap WP, Cortina JM, Vaslow JB, Burke MJ. Meta-analysis of experiments with matched groups or repeated measures designs. *Psychol Methods* 1996;1:170-7.
25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th ed. Washington, DC: American Psychiatric Association; 1994.

Appendix II

Germain A, Buysse DJ, Nofzinger EA. Sleep-specific Mechanisms Underlying Posttraumatic Stress Disorder: Integrative Review and Neurobiological Hypotheses. Sleep Medicine Reviews, *in press*.



CLINICAL REVIEW

Sleep-specific mechanisms underlying posttraumatic stress disorder: Integrative review and neurobiological hypotheses

Anne Germain*, Daniel J. Buysse, Eric Nofzinger

Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Room E-1124, Pittsburgh, PA 15213, USA

KEYWORDS

Posttraumatic stress disorder;
 Sleep;
 Arousal;
 Amygdala;
 Medial prefrontal cortex;
 Insomnia;
 Nightmares

Summary Posttraumatic stress disorder (PTSD) is a prevalent disorder that is associated with poor clinical and health outcomes, and considerable health care utilization and costs. Recent estimates suggest that 5–20% of military personnel who serve in current conflicts in Iraq and Afghanistan meet diagnostic criteria for PTSD. Clinically, sleep disturbances are core features of PTSD that are often resistant to first-line treatments, independently contribute to poor daytime functioning, and often require sleep-focused treatments. Physiologically, these observations suggest that PTSD is partially mediated by sleep disruption and its neurobiological correlates that are not adequately addressed by first-line treatments. However, polysomnographic studies have provided limited insights into the neurobiological underpinnings of PTSD during sleep. There is an urgent need to apply state-of-the-science sleep measurement methods to bridge the apparent gap between the clinical significance of sleep disturbances in PTSD and the limited understanding of their neurobiological underpinnings. Here, we propose an integrative review of findings derived from neurobiological models of fear conditioning and fear extinction, PTSD, and sleep–wake regulation, suggesting that the amygdala and medial prefrontal cortex can directly contribute to sleep disturbances in PTSD. Testable hypotheses regarding the neurobiological underpinnings of PTSD across the sleep–wake cycle are offered. © 2007 Elsevier Ltd. All rights reserved.

Introduction

Posttraumatic stress disorder (PTSD) is a clinical syndrome characterized by re-experiencing, avoid-

ance, and hyperarousal reactions that persist for more than 1 month after exposure to a traumatic event. Violent crimes, including rape and physical assaults, combat exposure, and natural disasters constitute examples of traumatic events that can involve threat to integrity of the self or others and can be accompanied by intense fear, helplessness, or horror.¹ Trauma exposure is not a rare event:

*Corresponding author. Tel.: +1 412 246 6436; fax: +1 412 246 5300.

E-mail address: germaina@upmc.edu (A. Germain).

more than two-thirds of the general population is exposed to at least one traumatic event over their lifetime.² Epidemiological studies indicate that community prevalence estimates of PTSD range from 1% to 10%,^{2,3} with higher estimates reported in victims of interpersonal violence (20–30%)^{2–4} and combat veterans (15–30%).⁵ In veterans of the current Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF), Hoge et al.⁶ found that 31% of OEF service members and 71–86% of OIF service members reported multiple combat experiences, and as many as one out of nine troops returning from Afghanistan, and one out of six troops returning from Iraq endorse clinically significant PTSD symptoms.⁶ These estimates are likely to rise over time, as indicated in a recent report that indicated that 33.4% of OIF/OEF returnees evaluated at VA Healthcare facilities between 2002 and 2006 met diagnostic criteria for mental disorders, including PTSD.⁷ PTSD is often a chronic condition, and is associated with enormous health care costs in both military and civilian samples.⁸ Recommended first-line treatments for PTSD include selective serotonin reuptake inhibitors (SSRIs), and cognitive-behavioral approaches such as exposure-based and cognitive therapy.^{9,10}

There is growing evidence that sleep disruption that occurs following trauma exposure may constitute a specific mechanism involved in the pathophysiology of chronic PTSD and poor clinical outcomes. Subjective and objective sleep disturbances occurring early after trauma exposure, as well as heightened sympathovagal tone during REM sleep, are associated with an increased risk of meeting criteria for PTSD at subsequent assessments conducted up to 1 year later.^{11–13} Sleep disturbances are a core feature of PTSD. Nightmares and insomnia are diagnostic symptoms of PTSD,¹ and other sleep disturbances such as sleep avoidance, sleep terrors, nocturnal anxiety attacks, simple and complex motor behaviors and vocalizations, acting out dreams, sleep apnea, and periodic leg movement disorders are also frequently reported and observed by PTSD patients.^{14,15} Additionally, sleep disturbances independently exacerbate daytime symptoms, and contribute to poor clinical outcomes in PTSD, such as increased severity of depression,¹⁶ suicidality,¹⁶ and general psychiatric distress,¹⁷ poorer quality of life and functioning,¹⁷ and poorer perceived physical health,¹⁸ and increased alcohol and drug use.^{19,20} While these associations between sleep disturbances and poor clinical outcomes are derived from a posteriori observations, they stress the need for prospectively monitoring the possible

development sleep disturbances in trauma-exposed individuals, and the role of sleep disturbances as mediators of the relationship between PTSD and clinical outcomes. Finally, sleep disturbances are often resistant to recommended first-line interventions.^{21,22} Adjunctive sleep-focused pharmacological or behavioral interventions are commonly used to alleviate PTSD-related nightmares and insomnia. Of note, the use of benzodiazepines remains highly common in PTSD, possibly for alleviating daytime anxiety symptoms and sleep disturbances, despite the absence of evidence supporting their efficacy.^{25,26} Effective treatments of nightmares and insomnia also associated with improvements in daytime PTSD symptoms, depression, quality of life, and perceived physical health (e.g.,^{23,24,27} see also Ref. 4 for review). Together, these observations raise the possibilities that (1) trauma exposure directly alters sleep-wake regulation mechanisms, (2) PTSD is partially mediated by sleep-specific mechanisms, and (3) normalization of altered neurobiological mechanisms underlying sleep disturbances in PTSD requires targeted treatments.

The overarching goal of this paper is to integrate convergent lines of evidence derived from sleep neuroimaging studies in related disorders, from waking neuroimaging studies conducted on PTSD patients, and from animal models of fear conditioning to provide a preliminary model and testable hypotheses of the neurobiological underpinnings of PTSD during rapid-eye movement (REM) and non-REM (NREM) sleep. Prior sleep findings in PTSD samples are only briefly reviewed here. Extensive critical review of prior qualitative and polysomnographic studies of sleep in PTSD samples and review of pharmacological and behavioral treatments that target PTSD-related sleep disturbances are available elsewhere.^{28–30} Findings derived from sleep neuroimaging studies in healthy human subjects are then briefly reviewed. Because the hyperactivity of the amygdala and impaired function of the medial frontal cortex are neurobiological correlates of PTSD, which result from animal and human studies suggesting that the amygdala and medial prefrontal cortex directly influence the regulation and/or expression of REM and NREM sleep are highlighted. The neurobiology of fear conditioning and fear extinction, complementary animal models of PTSD in humans, their effects on sleep, as well as neuroimaging findings observed in PTSD samples are also presented. Findings from these areas of research evidence potentially significant dual roles of the amygdala and medial prefrontal cortex as both critical structures involved in the fear response and PTSD, and important modulator of

NREM and REM sleep. Based on this observation, preliminary models and hypotheses regarding potential neurobiological correlates of PTSD during NREM and REM sleep are described.

An in-depth understanding of the sleep-specific underpinnings of PTSD, acquired with state-of-the-science measurement methods, is essential to guide for development, refinement, and testing of innovative prevention and interventions strategies across the sleep-wake cycle. More broadly, better empirically derived models of PTSD during sleep may generate novel insights into the pathophysiology, prevention, and treatment of other adjustment and stress-related disorders, such as those affecting cohorts of combat-exposed military veterans, as well as of victims of violent crimes and terrorist attacks, and survivors of natural disasters. Finally, elucidating the neurobiological underpinnings of PTSD during sleep can inform efforts to identify the mechanisms subserving resistance of sleep disturbances to first-line treatments of PTSD, as well as the distinct mechanisms underlying treatment response to sleep treatments in PTSD, and other stress-related disorders.

Sleep neuroimaging findings in healthy human subjects

Consistent with animal models of sleep regulation, sleep neuroimaging studies in healthy humans indicate that specific patterns of neuronal activation and deactivation characterize NREM and REM sleep relative to wakefulness. Specifically, whole-brain glucose metabolism and blood flow are reduced by 30–40% during NREM sleep in healthy subjects relative to wakefulness.³¹ NREM sleep is also associated with relative reduced metabolic activity and blood flow in the wake-promoting areas including the pontine and midbrain reticular formation and thalamus, as well as in associative cortices.^{31,32} A relative increase in neuronal activity in regions involved in the generation and maintenance of sleep, such as the dorsal pontine tegmentum and basal forebrain has also been observed.³¹ Some studies have reported reduced activity of paralimbic cortices, including the anterior cingulate gyrus and parahippocampal gyrus during NREM sleep relative to wakefulness, whereas others have not.³¹ Braun et al.³² suggested that this disengagement of paralimbic structures and isolation of limbic structures (e.g., amygdala, hippocampus) from other heteromodal cortices may facilitate the restorative function of NREM sleep.^{31,32} The pattern of neuronal deactivation

observed in NREM sleep relative to wakefulness suggests that NREM is an endogenous state of attenuated arousal.

During REM sleep, whole-brain glucose metabolism is increased by 16% relative to NREM sleep, and non-significantly different from wakefulness levels.³² REM sleep is characterized by increased regional cerebral metabolic activity and blood flow in the amygdala and anterior paralimbic areas, and with increased activity in the medial pons and thalamus relative to wakefulness.^{32–34} Lateral prefrontal cortices, parietal cortices, and primary sensory cortices are further deactivated relative to wakefulness and NREM sleep during REM sleep. These selective activation and deactivation patterns during REM sleep relative to wakefulness in healthy subjects have yielded the hypothesis that dreams may reflect the mental representations of high limbic activations in conjunctions with deactivation of high-order cortical regions.³⁴ The pattern of activation observed during REM sleep suggests that REM sleep is an endogenous state of heightened activity in emotional arousal brain centers.

The amygdala and medial prefrontal cortex as modulators of REM sleep and NREM sleep

It is clear from animal studies that limbic and paralimbic regions are not among the primary regulators of NREM and REM sleep.^{35–38} However, sleep neuroimaging studies in humans have shown that neuronal activity in amygdala and anterior paralimbic cortices including the medial prefrontal cortex varies across the sleep wake cycle. Although the amygdala and medial prefrontal cortex are not primary brain sites involved in the regulation of sleep *per se*, growing evidence suggests that both regions are important modulators of NREM and REM sleep.

Neuronal firing in the amygdala varies across the sleep-wake cycle, with higher firing rates during wakefulness and REM sleep compared to NREM sleep. In healthy human subjects, neuronal activity in the amygdala remains unchanged or is slightly reduced during NREM sleep relative to wakefulness,^{31,32,39} and is considerably increased during REM sleep compared to both NREM sleep and wakefulness. The amygdala shares interconnections with the basal forebrain, hypothalamus, preoptic area of the anterior hypothalamus, brainstem reticular formation, and solitary tract nucleus. It also shares reciprocal connections with the REM-on

and REM-off centers. Thus, the amygdala is anatomically positioned to influence sleep via its connection to wakefulness-promoting and sleep-promoting areas. Stimulation of the amygdala during REM sleep increases PGO waves in REM and NREM sleep,⁴⁰ whereas inactivation of the amygdala with tetrodotoxin decreases sleep latency, and increases slow-wave activity during wakefulness, REM sleep, NREM sleep.^{41,42} Lesions of the amygdala in rhesus monkeys are associated with increased sleep consolidation and total sleep time, and sleep consolidation is proportional to lesion size.⁴³

The medial prefrontal cortex, and especially the orbitofrontal cortex (OFC), influence sleep, and more specifically NREM sleep. Anatomically, the OFC has afferent and efferent connections with sleep-promoting regions, including the solitary tract nucleus and the ventrolateral preoptic area (VLPOA). Electrical stimulation of the OFC produces EEG synchrony and behavioral sleep, whereas lesions and ablation of the OFC are associated with reduced slow-wave sleep and reductions in behavioral sleep (see Ref. 35 for review). Neurons of the subgenual cingulate cortex, another region of the medial frontal cortex, increase their firing rate during NREM sleep in rhesus monkeys.⁴⁴

The role of the amygdala and of the medial prefrontal cortex in modulating REM and NREM sleep in humans remains incompletely explored. However, and as described below, **functioning** and structural abnormalities of the amygdala and medial prefrontal cortex that are suspected to subserve the pathophysiology of PTSD may also directly affect sleep NREM and REM sleep regulation via interconnections between the amygdala, medial frontal cortex, and sleep- and arousal-promoting brain regions.

Neurobiological correlates of fear conditioning, fear extinction, and PTSD

Pavlovian fear conditioning and fear extinction paradigms have been proposed as animal models of PTSD.⁴⁵ Fear conditioning arises when a neutral stimulus (e.g., light, tone) closely precedes in time the occurrence of an aversive, emotionally significant event (e.g., shock) that will elicit a fear response (e.g., freezing). The neutral stimulus is termed the conditioned stimulus (CS), and the aversive event is termed the unconditioned stimulus (UCS). With repetition of the association, the neutral stimulus (CS) alone can elicit the fear response, now termed as the conditioned response

(CR). With repeated presentation of the CS alone, the conditioned fear response is attenuated and eliminated. This process is called extinction.

During acquisition of fear conditioning, sensory information is transmitted to the lateral amygdala via sensory cortices and thalamus. Information is then transmitted from the lateral amygdala to the central nucleus of the amygdala, which sends projections to hypothalamic and brainstem regions that subserve autonomic and visceral fear responses. Rodent models of fear conditioning, using single-cell and multiunit recordings, c-fos activity, electrical or pharmacological stimulation, lesions, or temporary deactivation methods have shown that the amygdala and medial prefrontal cortex play critical roles in both the acquisition fear conditioning and in fear extinction (see Ref. 46 for review). Extinction does not replace or erase the fear CR, but rather reflects new learning, which competes with the CR. Recall of fear extinction relies heavily on an intact infralimbic cortex in animals,⁴⁷ which corresponds to the rostral anterior cingulate cortex, medial OFC, and subcallosal cortex (including the subgenual ACC) in humans. In healthy human subjects, functional neuroimaging studies have confirmed the role of the amygdala in fear conditioning (e.g., Refs. 48,49), as well as in fear extinction, and increased activation of the medial prefrontal cortex during fear extinction training and during fear extinction recall.⁵⁰

Functional neuroimaging findings in PTSD patients are also consistent with animal models and preclinical studies of fear conditioning and fear extinction in humans. Specifically, waking brain imaging studies indicate that PTSD is characterized by hyper-responsiveness of the amygdala to threat-related stimuli,^{51–56} and/or blunted responsiveness of the medial prefrontal cortex, which exerts inhibitory control over the amygdala.^{57,58} Altered perfusion in limbic and frontal regions has also been observed in the absence of trauma reminders. Reduced volume of the anterior cingulate has been reported in PTSD subjects compared to non-PTSD subjects.^{59,60} Thus, reduced functional activity and reduced volume of the ventromedial prefrontal cortex may both yield reduced inhibition of hyperresponsive amygdala in PTSD. Medication-free PTSD subjects show increased fear conditioning and deficits in fear extinction compared to non-PTSD subjects,⁶¹ as well as increased amygdalar activation during fear conditioning, and attenuated activation of the medial prefrontal cortex during extinction compared non-PTSD subjects.⁶²

Effects of fear conditioning and PTSD on sleep

Animal studies have investigated the acute effects of fear conditioning on sleep as a model of the physiological underpinnings of sleep in PTSD. While this model does not closely reflect the persistence of sleep disturbances long after exposure to the original trauma seen in human PTSD, it nevertheless provides insights into the effects of fear conditioning on sleep and their physiological substrates. In rats and mice, fear conditioning increases REM sleep latency, decreases REM sleep duration^{63–65} and number of REM bouts,⁶⁶ and increases ponto-geniculo-occipital (PGO) waves, a marker of alerting mechanisms during sleep and wakefulness analogous to REMs in humans.^{63,65} Alternatively, safety conditioning, where animals learn that they will not be exposed to aversive stimuli in a given environment or given a specific cue never paired with the aversive stimulus, is associated with increased REM sleep duration and percent.⁶⁶

The effects of cued fear conditioning on sleep in animals are mediated by amygdala projections to brainstem regions involved in alerting and REM sleep generation.⁶⁵ In addition, the effects of fear conditioning on sleep appear to be related to heightened neuronal activity of the brainstem reticular activating system during sleep. In mice, fear conditioning is associated with increased c-fos expression in amygdala, locus coeruleus, and dorsal raphe nucleus, but not in the pontopedunculopontine tegmentum (PPT), and laterodorsal tegmentum (LDT).⁶⁷ The sustained and increased neural activity of amygdala, the locus coeruleus, and dorsal raphe during sleep after fear conditioning disrupts REM sleep, via maintained inhibition of the cholinergic activity responsible for REM sleep generation by increased activity of the LC and dorsal raphe nucleus.

There are no studies on the effects of fear extinction on sleep in animal models. However, the relationship between sleep and fear extinction is highlighted by the effects of sleep deprivation on fear extinction in rats and mice. Specifically, sleep deprivation impairs the acquisition of fear extinction.⁶⁸ Given that fear extinction relies heavily on an intact medial prefrontal cortex, it seems plausible that sleep deprivation impairs fear extinction via its effects on the prefrontal cortex. In an analogous manner, chronic sleep disruption in PTSD interferes with fear extinction by further impairing or exacerbating impairments of the medial prefrontal cortex.

No study has yet investigated the neurobiological correlates of the effects of fear conditioning or fear extinction on NREM and REM sleep in humans. Multiple polysomnographic studies that compared PTSD and non-PTSD samples have been conducted. Overall, there are discrepancies regarding the presence and nature of objective sleep disturbance. Some PSG studies in PTSD patients have reported REM sleep anomalies, e.g.,^{69–74}, whereas other did not, e.g.,^{75–77} NREM sleep anomalies such as reduced slow-wave sleep have also been reported in some.⁷⁵ A recent meta-analysis found small-medium effect size for increased REM density and increased percentage of stage 1 sleep, and reduced slow-wave sleep in PTSD compared to non-PTSD groups.⁷⁸ It has been hypothesized that REM sleep and NREM sleep mechanisms can underlie the production of posttraumatic nightmares, and contribute to the pathogenesis and maintenance of PTSD.^{12,72,79} Heightened activity of REM sleep regulation centers and of the amygdala during sleep have also been suggested as neurobiological correlates of REM sleep anomalies in PTSD subjects.^{79–81} Consistent with Revonsuo's hypothesis that a function of dreaming is threat simulation and rehearsal of motor patterns involved in escaping threats,⁸² heightened activation of the amygdala may also subserve in the occurrence of PTSD- and non-PTSD-related nightmares.⁸¹ However, the neurobiological correlates of REM sleep and NREM sleep in PTSD, as well as the neurobiological correlates of PTSD-related nightmares remain unexplored.

In summary, the amygdala and the medial prefrontal cortex are involved in the neurobiology of PTSD and of the effects of fear conditioning on sleep in animals, in addition to the role they play in modulation of NREM and REM sleep. Heightened amygdala activity, and/or impaired medial prefrontal cortex function observed in PTSD patients may adversely affect the regulation of NREM and REM sleep via their interconnections with arousal- and sleep-promoting brain. Both REM sleep and NREM sleep are disrupted in PTSD, but the neurobiology of these sleep disturbances in PTSD have not been elucidated by polysomnographic studies.

Neurobiological hypotheses of PTSD during sleep

The study of the neurobiological correlates of PTSD during NREM and REM sleep offers a unique paradigm to observe natural activation and deactivation patterns in endogenous states of attenu-

ated central arousal and heightened limbic activity, respectively.

To further the prior hypothesis that sleep mechanisms contribute to the pathophysiology of PTSD, we propose that REM sleep amplifies altered function of the amygdala and medial frontal cortex in PTSD patients; amplification of abnormal amygdala activation in combination with reduced activation of the medial prefrontal cortex

nightmares. Figure 1a depicts a preliminary model regarding neurobiological correlates of REM sleep in PTSD subjects compared to healthy subjects, and relative to wakefulness. It is first hypothesized that heightened amygdala activity (Figure 1b) and blunted increase in activity of the medial prefrontal cortex (Figure 1c) characterize PTSD subjects compared to non-PTSD healthy subjects during REM sleep. These changes have direct impact on

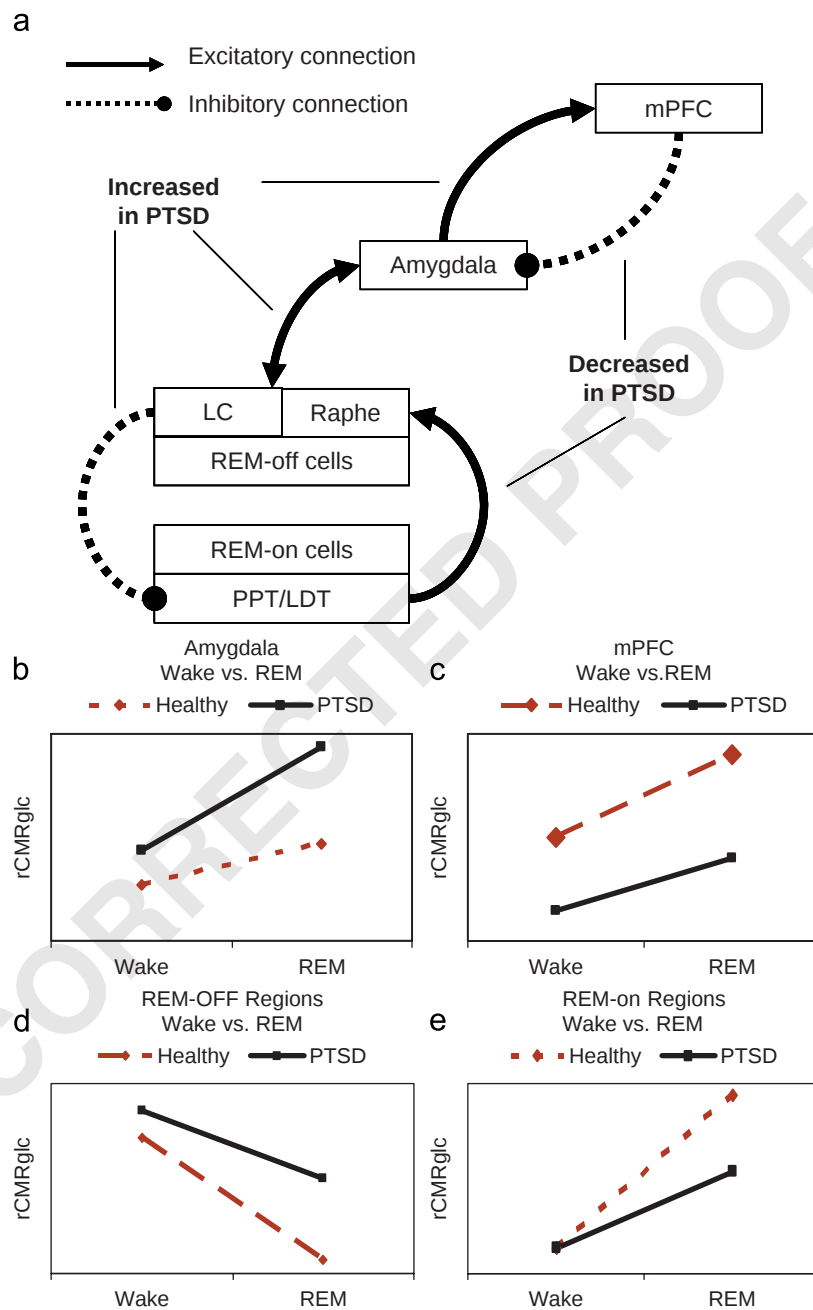


Figure 1 Proposed neurobiological model and hypotheses of PTSD during REM sleep. (a) Proposed model of PTSD in the neurobiological underpinnings of PTSD during REM sleep. (b–e) Relative to wakefulness, PTSD patients (black lines) will show increased activity of the amygdala and brainstem REM-off regions, and decreased activity of the medial prefrontal cortex (mPFC) and of brainstem REM-on regions compared to healthy subjects (dashed lines).

brainstem REM sleep regulation mechanisms, such as increased activity of brainstem REM-off regions (Figure 1d; LC, raphe), and attenuated activity of the brainstem REM-on nuclei (Figure 1e) PPT/LDG). Persistent activity of the LC and raphe and related inhibition of the PPT and LDT would be expected in PTSD subjects, and may directly relate to REM sleep disruption.

During NREM sleep, we propose that the hyperactivity of the amygdala and attenuated activity of the medial prefrontal cortex contribute to heightened whole-brain neuronal activity. Specifically,

these changes may maintain or increase activity in arousal-promoting brain centers, and reduce activity in sleep-promoting centers. The resulting pattern of persistent arousal could directly contribute to complaints of insomnia. Figure 2 depicts the preliminary NREM sleep model and hypotheses regarding neurobiological correlates of NREM sleep relative to wakefulness in PTSD patients compared to healthy subjects. Specifically, it is hypothesized that the relative persistence of amygdala activity (Figure 2b) and blunted activity of the medial prefrontal cortex (Figure 2c) during NREM sleep

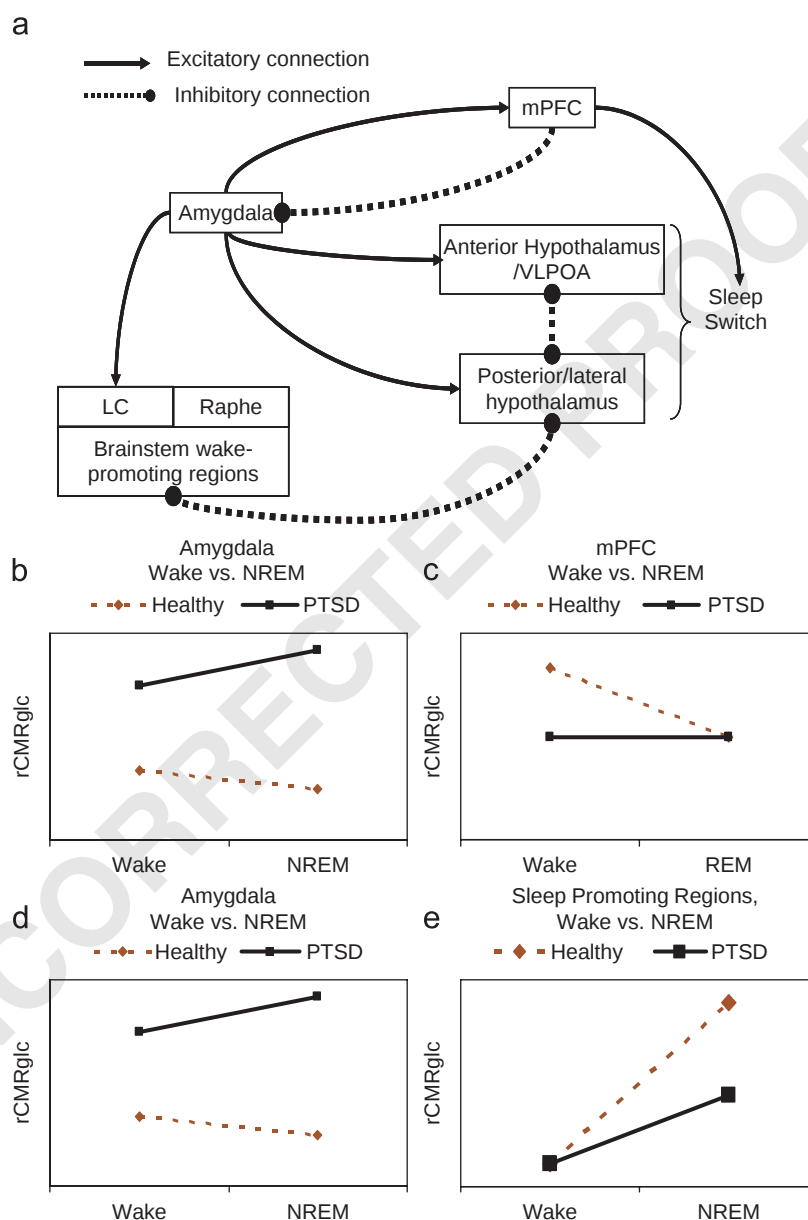


Figure 2 Proposed neurobiological correlates of PTSD during NREM sleep. (a) Proposed model of the neurobiological underpinnings of PTSD during NREM sleep. (b–e) Relative to wakefulness, PTSD patients (black lines) will show increased activity of the amygdala and wakefulness-promoting brainstem and forebrain regions, and decreased activity of the medial prefrontal cortex (mPFC) and anterior hypothalamus compared to healthy subjects (dashed lines).

would be associated with less deactivation of brainstem and forebrain wakefulness-promoting areas (Figure 2d; LC, raphe, posterior hypothalamus, thalamus), and a blunted increase in activation of the anterior hypothalamus, and blunted activation in sleep-promoting regions (Figure 2e), such as the anterior hypothalamus (which includes the VLPOA) and solitary tract nucleus (although it may not be possible to directly observe changes in activity of small or diffuse nuclei given the limits of spatial resolution of current neuroimaging methods).

Discussion

PTSD is a prevalent disorder that is often resistant to recommended treatments, and is associated with enormous health care costs. Sleep disturbances are a core feature of PTSD that are often resistant to recommended first-line treatments, and independently contribute to poor clinical outcomes. The contribution of sleep disturbances to long-term health outcomes and costs in PTSD is not currently known, but is likely to be substantial. Emerging evidence suggests that sleep-specific mechanisms underlie the neurobiology of PTSD. However, the neurobiological underpinnings of PTSD, as it persists across the sleep-wake cycle, remain unexplored using sleep neuroimaging methods.

Sleep research in PTSD samples (as well as in other stress-related disorders such as acute stress disorder, adjustment disorders, prolonged grief disorder) is ripe for the broader use of state-of-the-science sleep neuroimaging methods required to identify the sleep-specific neurobiological underpinnings of PTSD, the correlates of resistance to first-line PTSD treatments, the predictors of response to sleep-focused treatments, and the mechanisms that are normalized by effective sleep treatments.

Future research directions have direct clinical implications in PTSD and sleep research. For instance, little is known about the effects of sleep deprivation and disruption on fear conditioning and fear extinction in healthy human subjects and in patients with stress-related disorders. Understanding the sleep-specific mechanisms that may facilitate fear conditioning and/or impeded fear extinction may be especially important in samples where trauma exposure is a likely event, such as during military deployment, combat exposure, and all emergency responders. Further investigating the role of sleep in the consolidation of traumatic memories as well as in processing emotional and

traumatic material also provides an ecologically valid paradigm to further expand cognitive neuroscience models of sleep and memory. More in-depth models of the sleep-specific pathophysiological and neurobiological underpinnings of the relationship between trauma exposure, sleep, and PTSD can also guide the development and refinement of innovative prevention and intervention strategies targeting sleep disturbances in trauma-exposed and PTSD samples. For instance, an in-depth understanding of the sleep-related brain mechanisms susceptible to disruption following trauma exposure and in PTSD may facilitate treatment optimization by combining treatments that restore affected neural networks, and/or that enhance compensatory mechanisms. Identifying sleep-specific markers of vulnerability and resilience to chronic, maladaptive stress response and of sleep-focused treatment response may create new venues to prevent PTSD in high-risk samples (e.g., combat veterans, emergency workers). Finally, the nature of sleep-specific predictors of treatment response or failure to first-line PTSD treatments, or the underpinnings of effective sleep-focused pharmacological or behavioral interventions have not yet been explored.

In summary, the study of the neurobiological correlates of PTSD during sleep by using state-of-the-science sleep neuroimaging methods opens multiple opportunities to identify the sleep-specific underpinnings of this pervasive disorder, which in turn can inform the development of evidence-based interventions that normalize the underpinnings of PTSD across the sleep-wake cycle.

Practice points

1. Sleep disturbances often develop into independent, comorbid sleep disorders in adults with PTSD.
2. Complaints of sleep disturbances in adults with PTSD contribute to mental and physical health outcomes, including exacerbation of daytime PTSD symptom severity, anxiety, depression, irritability, cognitive functioning, and disability. Sleep disturbances, and potentially their more distal consequences, can be significant ameliorated with sleep-focused treatment.
3. A thorough evaluation of the nature and adverse impacts of sleep disturbances on daytime symptoms and overall functioning should be integral to PTSD evaluation.
4. Sleep disturbances comorbid to PTSD require targeted interventions.

5. Randomized controlled trials indicate that prazosin and nefazodone can effectively reduce nightmares and insomnia in PTSD. Other pharmacological interventions such as cyproheptadine, trazodone, zaleplon, and zolpidem may also reduce nightmares and insomnia, but formal clinical trials are required to fully assess their efficacy, safety, and durability in military and civilians PTSD samples.
6. Behavioral interventions for PTSD-related sleep disturbances such as imagery rehearsal, and behavioral insomnia treatments have received most empirical evidence for efficacy to date in both military and civilian PTSD samples.

Research agenda

In order to further refine our understanding of the pathophysiology of PTSD during sleep and to translate these findings into clinical practice, we need to:

1. Employ available sleep neuroimaging techniques to identify and probe the pathophysiological and neurobiological underpinnings of PTSD across the sleep–wake cycle.
2. Investigate the neurophysiological and neurobiological mechanisms that underlie sleep-focused treatment response and resistance in PTSD patients.
3. Develop and test innovative pharmacological and cognitive-behavioral interventions that specifically target and normalize altered physiological and neurobiological systems that subserve sleep disturbances in PTSD.
4. Conduct mechanistic, longitudinal studies to assess the independent effects of sleep disturbances on health outcomes in PTSD.

Acknowledgments

This manuscript was supported by the Department of Defense Peer Reviewed Medical Research Program (PR054093), and the National Institutes of Health (MH60473; MH24652; MH061566; MH066227).

References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-IV)*, 4th ed. Washington, DC: American Psychiatric Association; 1994.
- *2. Breslau N, Kessler RC, Chilcoat HD, Schultz LR, Davis GC, Andreski P. Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma. *Arch Gen Psychiatry* 1998;**55**(7):626–32.
3. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 1995;**52**(12):1048–60.
4. Resnick HS, Kilpatrick DG, Dansky BS, Saunders BE, Best CL. Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. *J Consult Clin Psychol* 1993;**61**(6):984–91.
5. Weiss DS, Marmar CR, Schlenger WE, Fairbank JA, Jordan BK, Hough RL, et al. The prevalence of lifetime and partial posttraumatic stress disorder in Vietnam theater veterans. *J Trauma Stress* 1992;**5**:365–76.
- *6. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med* 2004;**351**(1):13–22.
7. Kang HK. VA health care utilization among Operation Iraqi Freedom /Operation Enduring Freedom veterans. <www.iom.edu>; 2006.
8. Walker EA, Katon W, Russo J, Ciechanowski P, Newman E, Wagner AW. Health care costs associated with posttraumatic stress disorder symptoms in women. *Arch Gen Psychiatry* 2003;**60**(4):369–74.
9. Ballenger JC, Davidson JR, Lecrubier Y, Nutt DJ, Foa EB, Kessler RC, et al. Consensus statement on posttraumatic stress disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry* 2000;**61**(Suppl. 5):60–6.
10. The Expert Consensus Guideline Series. Treatment of posttraumatic stress disorder. The Expert Consensus Panels for PTSD. *J Clin Psychiatry* 1999;**60**(Suppl. 16):3–76.
11. Koren D, Arnon I, Lavie P, Klein E. Sleep complaints as early predictors of posttraumatic stress disorder: a 1-year prospective study of injured survivors of motor vehicle accidents. *Am J Psychiatry* 2002;**159**(5):855–7.
12. Mellman TA, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. *Am J Psychiatry* 2002;**159**(10):1696–701.
13. Mellman TA, Knorr BR, Pigeon WR, Leiter JC, Akay M. Heart rate variability during sleep and the early development of posttraumatic stress disorder. *Biol Psychiatry* 2004;**55**(9):953–6.
- *14. Germain A, Hall M, Krakow B, Shear MK, Buysse DJ. A brief sleep scale for posttraumatic stress disorder: Pittsburgh Sleep Quality Index Addendum for PTSD. *J Anxiety Disord* 2005;**19**(2):233–44.
15. Krakow B, Melendrez D, Pedersen B, Johnston L, Hollifield M, Germain A, et al. Complex insomnia: insomnia and sleep-disordered breathing in a consecutive series of crime victims with nightmares and PTSD. *Biol Psychiatry* 2001;**49**(11):948–53.
16. Krakow B, Artar A, Warner TD, Melendrez D, Johnston L, Hollifield M, et al. Sleep disorder, depression, and suicidality in female sexual assault survivors. *Crisis* 2000;**21**(4):163–70.
17. Krakow B, Melendrez D, Johnston L, Warner TD, Clark JO, Pacheco M, et al. Sleep-disordered breathing, psychiatric distress, and quality of life impairment in sexual assault survivors. *J Nerv Ment Dis* 2002;**190**(7):442–52.

18. Clum GA, Nishith P, Resick PA. Trauma-related sleep disturbance and self-reported physical health symptoms in treatment-seeking female rape victims. *J Nerv Ment Dis* 2001;**189**(9):618–22.
19. Saladin ME, Brady KT, Dansky BS, Kilpatrick DG. Understanding comorbidity between PTSD and substance use disorders: two preliminary investigations. *Addict Behav* 1995;**20**(5):643–55.
20. Nishith P, Resick PA, Mueser KT. Sleep difficulties and alcohol use motives in female rape victims with posttraumatic stress disorder. *J Trauma Stress* 2001;**14**(3):469–79.
21. Zayfert C, DeViva JC. Residual insomnia following cognitive behavioral therapy for PTSD. *J Trauma Stress* 2004;**17**(1):69–73.
22. Davidson JR, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. *Arch Gen Psychiatry* 2001;**58**(5):485–92.
23. Krakow B, Hollifield M, Johnston L, Koss M, Schrader R, Warner TD, et al. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. *JAMA* 2001;**286**(5):537–45.
- *24. Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry* 2003;**160**(2):371–3.
25. Mellman TA, Clark RE, Peacock WJ. Prescribing patterns for patients with posttraumatic stress disorder. *Psychiatr Serv* 2003;**54**(12):1618–21.
26. Cates ME, Bishop MH, Davis LL, Lowe JS, Woolley TW. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. *Ann Pharmacother* 2004;**38**(9):1395–9.
27. Germain A, Shear MK, Hall M, Buysse DJ. Effects of a brief behavioral treatment for PTSD-related sleep disturbances: a pilot study. *Behav Res Ther* 2007;**45**:627–32.
- *28. Maher MJ, Rego SA, Asnis GM. Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact and approaches to management. *CNS Drugs* 2006;**20**(7):567–90.
29. Harvey AG, Jones C, Schmidt DA. Sleep and posttraumatic stress disorder: a review. *Clin Psychol Rev* 2003;**23**(3):377–407.
30. Pillar G, Malhotra A, Lavie P. Post-traumatic stress disorder and sleep—what a nightmare!. *Sleep Med Rev* 2000;**4**(2):183–200.
31. Nofzinger EA, Buysse DJ, Miewald JM, Meltzer CC, Price JC, Sembrat RC, et al. Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. *Brain* 2002;**125**:1105–15.
32. Braun AR, Balkin TJ, Wesenten NJ, Carson RE, Varga M, Baldwin P, et al. Regional cerebral blood flow throughout the sleep–wake cycle. An H₂(15)O PET study. *Brain* 1997;**120**(Pt. 7):1173–97.
33. Nofzinger EA, Mintun MA, Wiseman MB, Kupfer DJ, Moore RY. Forebrain activation in REM sleep: an FDG PET study. *Brain Res* 1997;**770**:192–201.
34. Maquet P, Peters J, Aerts J, Delfiore G, Degueldre C, Luxen A, et al. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. *Nature* 1996;**383**(6596):163–6.
35. Jones BE. Basic mechanisms of sleep–wake states. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*; 2005. p. 136–53.
36. Sinton CM, McCarley RW. Neuroanatomical and neurophysiological aspects of sleep: basic science and clinical relevance. *Semin Clin Neuropsychiatry* 2000;**5**(1):6–19.
37. Siegel JM. Mechanisms of sleep control. *J Clin Neurophysiol* 1990;**7**(1):49–65.
38. Szymusiak R, Alam N, McGinty D. Discharge patterns of neurons in cholinergic regions of the basal forebrain during waking and sleep. *Behav Brain Res* 2000;**115**(2):171–82.
39. Maquet P, Degueldre C, Delfiore G, Aerts J, Peters JM, Luxen A, et al. Functional neuroanatomy of human slow wave sleep. *J Neurosci* 1997;**17**(8):2807–12.
40. Deboer T, Sanford LD, Ross RJ, Morrison AR. Effects of electrical stimulation in the amygdala on ponto-geniculo-occipital waves in rats. *Brain Res* 1998;**793**(1/2):305–10.
41. Sanford LD, Yang L, Liu X, Tang X. Effects of tetrodotoxin (TTX) inactivation of the central nucleus of the amygdala (CNA) on dark period sleep and activity. *Brain Res* 2006;**1084**(1):80–8.
42. Tang X, Yang L, Liu X, Sanford LD. Influence of tetrodotoxin inactivation of the central nucleus of the amygdala on sleep and arousal. *Sleep* 2005;**28**(8):923–30.
43. Benca RM, Obermeyer WH, Shelton SE, Droster J, Kalin NH. Effects of amygdala lesions on sleep in rhesus monkeys. *Brain Res* 2000;**879**(1/2):130–8.
44. Rolls ET, Inoue K, Browning A. Activity of primate subgenual cingulate cortex neurons is related to sleep. *J Neurophysiol* 2003;**90**(1):134–42.
45. Grillon C, Southwick SM, Charney DS. The psychobiological basis of posttraumatic stress disorder. *Mol Psychiatry* 1996;**1**(4):278–97.
46. Kim JJ, Jung MW. Neural circuits and mechanisms involved in Pavlovian fear conditioning: a critical review. *Neurosci Biobehav Rev* 2006;**30**(2):188–202.
- *47. Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature* 2002;**420**(6911):70–4.
48. LaBar KS, Gatenby JC, Gore JC, LeDoux JE, Phelps EA. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron* 1998;**20**(5):937–45.
49. Cheng DT, Knight DC, Smith CN, Stein EA, Helmstetter FJ. Functional MRI of human amygdala activity during Pavlovian fear conditioning: stimulus processing versus response expression. *Behav Neurosci* 2003;**117**(1):3–10.
- *50. Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: role of the amygdala and vmPFC. *Neuron* 2004;**43**(6):897–905.
51. Lanius RA, Williamson PC, Boksman K, Densmore M, Gupta M, Neufeld RW, et al. Brain activation during script-driven imagery induced dissociative responses in PTSD: a functional magnetic resonance imaging investigation. *Biol Psychiatry* 2002;**52**(4):305–11.
52. Lanius RA, Williamson PC, Densmore M, Boksman K, Gupta MA, Neufeld RW, et al. Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. *Am J Psychiatry* 2001;**158**(11):1920–2.
53. Lanius RA, Williamson PC, Hopper J, Densmore M, Boksman K, Gupta MA, et al. Recall of emotional states in posttraumatic stress disorder: an fMRI investigation. *Biol Psychiatry* 2003;**53**(3):204–10.
54. Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, et al. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psychiatry* 2000;**47**(9):769–76.
55. Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, et al. A symptom provocation study of posttrau-

- matic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry* 1996;**53**(5):380–7.
56. Shin LM, Wright CI, Cannistraro PA, Wedig MM, McMullin K, Martis B, et al. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Arch Gen Psychiatry* 2005;**62**(3):273–81.
57. Bremner JD, Staib LH, Kaloupek D, Southwick SM, Soufer R, Charney DS. Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. *Biol Psychiatry* 1999;**45**(7):806–16.
58. Shin LM, Whalen PJ, Pitman RK, Bush G, Macklin ML, Lasko NB, et al. An fMRI study of anterior cingulate function in posttraumatic stress disorder. *Biol Psychiatry* 2001;**50**(12):932–42.
59. Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaer M, Eliez S. Decreased anterior cingulate volume in combat-related PTSD. *Biol Psychiatry* 2006;**59**(7):582–7.
60. Kitayama N, Quinn S, Bremner JD. Smaller volume of anterior cingulate cortex in abuse-related posttraumatic stress disorder. *J Affect Disord* 2006;**90**(2/3):171–4.
61. Orr SP, Metzger LJ, Lasko NB, Macklin ML, Peri T, Pitman RK. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. *J Abnorm Psychol* 2000;**109**(2):290–8.
62. Bremner JD, Vermetten E, Schmahl C, Vaccarino V, Vythilingam M, Afzal N, et al. Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. *Psychol Med* 2005;**35**(6):791–806.
- *63. Jha SK, Brennan FX, Pawlyk AC, Ross RJ, Morrison AR. REM sleep: a sensitive index of fear conditioning in rats. *Eur J Neurosci* 2005;**21**(4):1077–80.
64. Sanford LD, Yang L, Tang X. Influence of contextual fear on sleep in mice: a strain comparison. *Sleep* 2003;**26**(5):527–40.
65. Sanford LD, Silvestri AJ, Ross RJ, Morrison AR. Influence of fear conditioning on elicited ponto-geniculo-occipital waves and rapid eye movement sleep. *Arch Ital Biol* 2001;**139**(3):169–83.
- *66. Pawlyk AC, Jha SK, Brennan FX, Morrison AR, Ross RJ. A rodent model of sleep disturbances in posttraumatic stress disorder: the role of context after fear conditioning. *Biol Psychiatry* 2005;**57**(3):268–77.
67. Liu X, Tang X, Sanford LD. Fear-conditioned suppression of REM sleep: relationship to Fos expression patterns in limbic and brainstem regions in BALB/cJ mice. *Brain Res* 2003;**991**(1/2):1–17.
68. Silvestri AJ. REM sleep deprivation affects extinction of cued but not contextual fear conditioning. *Physiol Behav* 2005;**84**(3):343–9.
69. Ross RJ, Ball WA, Dinges DF, Kribbs NB, Morrison AR, Silver SM, et al. Motor dysfunction during sleep in posttraumatic stress disorder. *Sleep* 1994;**17**(8):723–32.
70. Riemann D, Hohagen F, König A, Schwarz B, Gomme J, Voderholzer U, et al. Advanced vs. normal sleep timing: effects on depressed mood after response to sleep deprivation in patients with a major depressive disorder. *J Affect Disord* 1996;**37**:121–8.
71. Mellman TA, Nolan B, Hebding J, Kulick-Bell R, Dominguez R. A polysomnographic comparison of veterans with combat-related PTSD, depressed men, and non-ill controls. *Sleep* 1997;**20**(1):46–51.
72. Mellman TA, Kumar A, Kulick-Bell R, Kumar M, Nolan B. Nocturnal/daytime urine noradrenergic measures and sleep in combat-related PTSD. *Biol Psychiatry* 1995;**38**(3):174–9.
73. Greenberg R, Pearlman CA, Gampel D. War neuroses and the adaptive function of REM sleep. *Br J Med Psychol* 1972;**45**(1):27–33.
74. Engdahl BE, Eberly RE, Hurwitz TD, Mahowald MW, Blake J. Sleep in a community sample of elderly war veterans with and without posttraumatic stress disorder. *Biol Psychiatry* 2000;**47**(6):520–5.
75. Woodward SH, Bliwise DL, Friedman MJ, Gusman DF. Subjective versus objective sleep in Vietnam combat veterans hospitalized for PTSD. *J Trauma Stress* 1996;**9**(1):137–43.
76. Hurwitz TD, Mahowald MW, Kuskowski M, Engdahl BE. Polysomnographic sleep is not clinically impaired in Vietnam combat veterans with chronic posttraumatic stress disorder. *Biol Psychiatry* 1998;**44**(10):1066–73.
77. Lavie P, Katz N, Pillar G, Zinger Y. Elevated awakening thresholds during sleep: characteristics of chronic war-related posttraumatic stress disorder patients. *Biol Psychiatry* 1998;**44**(10):1060–5.
78. Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. *Psychophysiology* 2007;**44**(4):660–9.
- *79. Ross RJ, Ball WA, Sullivan KA, Caroff SN. Sleep disturbance as the hallmark of post-traumatic stress disorder. *Am J Psychiatry* 1989;**146**(6):697–707.
80. Woodward SH, Leskin GA, Sheikh JI. Movement during sleep: associations with posttraumatic stress disorder, nightmares, and comorbid panic disorder. *Sleep* 2002;**25**(6):681–8.
81. Levin R, Nielsen TA. Disturbed dreaming, posttraumatic stress disorder, and affect distress: a review and neurocognitive model. *Psychol Bull* 2007;**133**(3):482–528.
82. Revonsuo A. The reinterpretation of dreams: an evolutionary hypothesis of the function of dreaming. *Behav Brain Sci* 2000;**23**(6):877–901.

Available online at www.sciencedirect.com



Appendix III

Data Safety and Monitoring Board Report



University of Pittsburgh

School of Arts and Sciences
Department of Statistics

2717 Cathedral of Learning
Pittsburgh, PA 15260
412-624-8368
Fax: 412-648-8814

Minutes, Data Safety and Monitoring Board
Efficacy of Adjunctive Sleep Interventions for PTSD (PR054093)
April 25, 2007

DSMB Members Present: Wesley Thompson (DSMB Chair), Ellen Frank, Terrence Keane (via telephone conference).

Others Present: Anne Germain, Douglas Moul, Abdul Hakim, and Colleen Walsh.

There have been no adverse events (AEs) or serious adverse events (SEs) to date. However, Dr. Germain cited a specific example of concern: one subject's withdrawal of self from the randomized medical treatment of the study. Dr. Moul presented the subject's case. This subject had symptoms including dizziness, headaches, and self-reported tachycardia. Though this subject experienced the symptoms of the prazosin medication, he was in fact randomized to placebo. There were multiple unsuccessful attempts to contact the patient for official study termination procedures by Dr. Germain and Abdul Hakim. Dr. Frank raised the issue of how to prevent this type of situation in the future. It was decided that there is a need to stress to the subjects that it is important to return to the study in order to assess alternative explanations for symptoms, other than from placebo or study medication.

Dr. Thompson questioned if there were any problems with the other (3) randomized subjects. Dr. Germain presented that there have been no AEs or SEs. Dr. Germain cited the second subject randomized to the medical treatment of the study.

Dr. Frank raised the issue of why recruitment has been difficult for EASIP thus far, leading to a discussion of the modification to protocol inclusion and exclusion criteria. These criteria have currently been modified as follows:

A. SSRI criterion changed from the initial requirement of having to be taking a prescribed SSRI in order to be included in the study **to** there being no requirement of being on a prescribed SSRI. However, currently, if the subject is taking an SSRI, then he/she must have been taking that particular dose of the SSRI for at least 2 months prior to study enrollment.

B. Subjects' current medications prescribed by PCP/psychiatrist changed from having to be taking that particular dose of the medication up until at least 2 months prior to study enrollment **to** having to be taking that particular dose for 3

weeks prior to enrollment in the study, as determined by Drs. Germain and Moul. The reasoning is that some medications do not interfere with the treatment medication as much as others.

Dr. Thompson raised the issue of what the course of action will be when subject medications are changed by their PCPs *during* the course of the study, as opposed to prior to subjects' study enrollment.. Dr. Germain agreed that this situation is expected to occur and there will be attempts to educate the subjects on the importance of reporting these changes to the study as soon as possible. Course of action will be determined on a case by case basis.

Dr. Thompson questioned how many VAPHS subjects versus non-VAPHS subjects are expected to be recruited. Dr. Germain explained that there are about 3-4 per month, less than the 10 per month that was originally anticipated.

Consequently, Dr. Frank raised the issue of the removal of meeting the requirement for PTSD as an inclusion criterion for the study and focusing more on meeting criteria for sleep disturbances. Dr. Frank suggested that the protocol should require trauma exposure, not a PTSD diagnosis, but that a careful assessment of PTSD should be included.

The advisory board concluded that changing the protocol's focus from PTSD to sleep disturbances is the best option at this time, since:

- A. Criteria for PTSD are difficult to meet.
- B. There is a stigma in the military about having mental illnesses, so focusing on sleep will be easier for subjects to seek help.
- C. The cohort may not meet criteria for PTSD yet, but may have meaningful sleep disturbances at this time.
- D. Dr. Frank pointed out that the symptoms of PTSD are mostly the same symptoms as sleep deprivation.
- E. Dr. Germain raised the point that if the sleep problems get under control, then there can be a better idea of what the PTSD will look like down the road.

The next advisory board meeting was tentatively scheduled for October 2007. The next meeting will focus more on DSMB aspects. It was determined that the following be made available to the DSMB members at the next meeting:

- A. Written clinical information about each participant blind and unblind.
- B. Include copies of the side effect scale being used (Asberg).
- C. Detailed information on any adverse events or serious events.

Recommendation of the Chair, Wes Thompson: Continue the study with relaxation of entry criteria to include patients exposed to trauma but not necessarily diagnosed with PTSD.

A handwritten signature in black ink, appearing to read 'Wes Thompson', with a stylized, cursive script.

Wes Thompson
DSMB Chair
Assistant Professor of Statistics and Psychiatry
University of Pittsburgh