COGNITIVE-BEHAVIORAL THERAPY FOR OBSTRUCTIVE SLEEP-APNEA

TAPS STUDY PROTOCOL

NCT02641496

April 30, 2024

INTRODUCTION

The purpose of this study is to test a novel cognitive-behavioral therapy (CBT) intervention to increase continuous positive airway pressure (CPAP) treatment adherence for PTSD Veterans with a new diagnosis of obstructive sleep apnea (OSA). PTSD is a common, debilitating psychiatric consequence of exposure to trauma and a source of significant disability among U.S. war Veterans. The largest epidemiologic study of PTSD in Vietnam Veterans estimates that 15% of Vietnam Veterans suffer from PTSD [1]. Our research on OSA in Vietnam era Veterans found that 69% of the veterans in the sample had an AHI ≥ 10 [2]. OSA is likely present in 50% of middle-aged and older VA patients [2, 3]. The recurrent hypoxemia and sleep fragmentation associated with OSA can lead to neural injury and functional impairment. Efficacious treatments are available for OSA (e.g., CPAP); however, Veterans with OSA frequently fail to use them [2, 4, 5], leaving these Veterans at risk for cognitive dysfunction [6], deterioration of physical health [7], and negative functional outcomes [8]. Our long-term goal is to improve Veterans' functional outcomes by improving adherence to CPAP. If this intervention proves successful, it may represent an approach that could be applied to the rehabilitation of other chronic conditions with similar barriers to care.

The reasons for low CPAP adherence include barriers related to discomfort in using CPAP and psychological barriers to behavior change [9]. A CBT treatment to improve CPAP adherence, CBT-OSA, has been successfully applied in civilian randomized controlled trials (RCTs) [10, 11]. Our VA intervention would involve delivery of CBT-OSA to PTSD Veterans to foster long-term CPAP adherence. The CBT-OSA treatment builds on the VISN 21 MIRECC's expertise in CBT interventions [e.g., VA rollout of CBT-Insomnia] as well as on our current research on PTSD Veterans with OSA. In this sample, the vast majority were not diagnosed with OSA prior to study entry; however, 69% of the participants had an AHI ≥ 10 [2]. Of the Veterans previously diagnosed with OSA, 63% were not using their CPAP. Specifically, this will be a 1-year parallel-group RCT involving 120 PTSD Veterans with a diagnosis of OSA. All participants will receive treatment as usual in VA Pulmonary Service. Participants in the active arm will receive CBT-OSA from a trained Clinical Psychologist (CP). The other arm will receive individual participant education from an Educator (ED), but not CBT-OSA. Participants in both arms will receive weekly, individual sessions during the first 4 weeks of CPAP treatment and 3 booster sessions during the 1-year protocol. These two arms will be referred to hereafter as the CBT-OSA and the Education groups.

OBJECTIVES AND END POINTS

Objective 1. (Primary) Effect of CBT on CPAP usage. We hypothesize that the CBT-OSA group will use CPAP more hours per night on average than the Education Group. ANOVA will be used to test group differences over time in hours of "mask-on" CPAP usage per night. Primary endpoint: mean of Days 335-365.
Objective 2. (Secondary) Effect of CBT on Self-reported Everyday Activities, Mood and Quality of Life. We hypothesize that after initiating CPAP treatment, Veterans in the CBT-OSA group will report more improvement in the ease of performing everyday activities compared to that reported by those in the Education group. ANOVA will be used to test group differences over time in the total score on the Functional Outcomes of Sleep Questionnaire (FOSQ; [12], at Days 365 (endpoint).
Objective 3. (Secondary) Effect of CBT on Cognitive Outcomes. We hypothesize that the CBT-OSA group will have better cognitive outcomes than the Education group over time. ANOVA will be applied to the California Verbal Learning Test, Delayed Free Recall Score with the primary endpoint at Day 365.
Objective 4. (Secondary) Effect of CBT on PTSD. We hypothesize that the CBT-OSA group will have fewer PTSD symptoms than the Education group over time. ANOVA will be used to

test group differences over time in the total score on the PTSD Checklist for DSM-5 (PCL-5), measured at Days 0, 21, 365. Primary endpoint is Day 365.

Table 1: Description of Measures

Primary Outcome Measure:	
Hypothesis 1 Effect of CBT on CPAP adherence	
Objectively Measured CPAP Usage. The times when the mask is on the face are recorded and stored by the CPAP device ResScan™ data card.	The primary outcome measure is an objective measure: the average of CPAP mask-on time for the last 30 days of the 1-year RCT (Days 335-365).
Secondary Outcome Measures:	
Hypothesis 2 Effect of CBT on Self-reported Everyday Activities, Mood and Quality of Life	
The Functional Outcomes of Sleep Questionnaire (FOSQ) [12] is a self-report measure of how much sleepiness impacts everyday activities and quality of life in multiple domains of function.	The FOSQ is designed to be given to individuals with a sleep disorder. In a 2011 VA clinical trial, FOSQ scores improved significantly in Veterans randomly allocated to APAP (n=105) and those allocated to CPAP (n=96), p's < .0001.
Hypothesis 3. Effect of CBT on Cognitive Outcomes.	
A cognitive battery known to be sensitive to OSA, and relevant to long-term CPAP adherence [9] will include our primary outcome measure, the California Verbal Learning Test [13], Long Delay Free Recall.	The purpose of the battery is to assess if changes in cognitive function occur, dependent on intervention group status. Baseline scores will also be used in supplementary data analyses on Moderators of treatment response to identify characteristics of patients who are best served by a CBT approach.
Hypothesis 4. Effect of CBT on PTSD.	
PTSD Checklist for DSM-5 (PCL-5) [14]. PCL-5 is a 20-item self-report measure for PTSD based on DSM-5.	The PCL-5 is designed to assess if the proposed treatment has any effects on PTSD symptoms.

RESEARCH DESIGN AND METHODS

PROCEDURES INVOLVING ELIGIBLE PARTICIPANTS

Study Timeline
Schedule of Visits and Key Assessments

	Consent	Screen	BL*	Pre-Intervention Phase		Early Intervention Phase			Booster Session Phase			Final Booster Session
Treatment Session				1	Start CPAP	2	3	4	5	6	7	8
Procedure Day		-28 to -14		0		7	14	21	90	180	270	365
Consent	X	X*										
Med Hx review		X	X*									X
Blood Sample				X								
Self-reports		X	X*					X	X	X	X	X
Semi-structured Clinical Interview		X	X*									X
Cognitive Battery		X	X*									X
Self-Efficacy Measure for Sleep Apnea				X				X	X	X	X	X
Working Alliance Inventory SAT**				X		X	X	X	X	X	X	X
In-clinic treatment sessions				X		X	X	X	X	X	X	X
CPAP Usage (Measurement Periods)					X →	→	→	→	→	→	→	

**If Baseline (BL) visit is needed, it will include the activities that were not completed during the screening visit*

**WAI modified to apply to Sleep Apnea Treatment (SAT).

After Session 1 (Day 0), participants will be called by their CP or ED daily for one week to provide early and consistent intervention.

OVERVIEW

Aims and Design of the Study. To test the efficacy of CBT-OSA in improving CPAP usage, the design will be a 2-arm RCT: 120 PTSD Veterans who are recently diagnosed with OSA and newly initiating CPAP will be allocated by 1:1 random assignment to either the 'CBT-OSA' group *or* the Education group. All Veterans will participate in usual care in VAPAHCS Pulmonary Service which is considered standard of care. During the 1-year study, the CBT-OSA arm will include seven individual, in-clinic intervention sessions with a CBT-trained Clinical Psychologist (CP): one session prior to starting CPAP (Session 1-Day 0), followed by three in-clinic sessions within the first four weeks of initiating CPAP (Session 2-Day 7; Session 3-Day 14; Session 4-Day 21) and 3 booster sessions (Session 5-Day 90; Session 6-Day 180; Session 7-Day 365). Education participants will receive equivalent amounts of contact with a trained Educator. All participants will receive the same CPAP devices and appropriate follow-up as usual care at the VAPAHCS.

To test the efficacy of CBT-OSA, the two groups will be compared for differences in average hrs/day of CPAP use. We are particularly interested in the difference between the groups in CPAP usage during the final 3 months of this 1-year study. Group differences in average hrs/day of CPAP use during Weeks 0-4 will be examined as a secondary outcome.

To determine if CBT-OSA therapy translates to better participant functional outcomes than those in the Education group, each participant will be asked to fill out the Functional Outcomes of Sleep Questionnaire [FOSQ; 12] on 3 occasions: before the first and final weekly CBT-OSA treatment sessions (Day 0, 21) and before the final booster session (Day 365) after initiating CPAP treatment. Each participant will also undergo a cognitive battery on 2 occasions: at Baseline (BL; before initiating CPAP) and 1 year later (Day 365). The entire project is expected to take 4 years).

PARTICIPANTS

Veterans will be recruited from the VAPAHCS weekly 1 hour outpatient OSA Group Clinic. The majority of attendees are newly diagnosed with OSA by a Board Certified Sleep Medicine Physician. During the group appointment, Veterans receive education about OSA and treatment from a sleep medicine physician (using a PowerPoint presentation). A Q&A session follows the physician's presentation. At the conclusion of Q&A, Veterans will be introduced to the study. The study will be described as research that could help improve the participant's ability to use CPAP. Interested Veterans will participate in a confidential screen for eligibility within 4 weeks of starting CPAP. Veterans can choose to initiate or decline CPAP treatment. While participating in the proposed project, they will continue to have access to their usual care.

Inclusion and Exclusion Criteria

Overview. The inclusion/exclusion criteria are designed to select PTSD Veterans who have a diagnosis of mild to severe OSA. Patients with dementia or severe psychiatric illness will be excluded because they may be less likely to complete the study or follow the protocol procedures. Veterans with mild comorbid conditions will not be excluded because comorbidities are common in Veterans, and we want to obtain results that would be generalizable to typical VA PTSD patients.

In accordance with AASM's Practice Parameters for the use of portable monitoring devices for titrating pressures and treating adults with OSA, Veterans with clinically significant comorbid cardiac, pulmonary or neurologic disease will be excluded [15]. In general, OSA patients with significant comorbid cardiorespiratory disease or known/suspected nocturnal hypoventilation (e.g. neuromuscular disease, spinal cord injury, morbid obesity, chronic opioid use) are prescribed BPAP [16]. Thus, we plan to exclude these patients to standardize the administration of CPAP therapy and focus our research efforts on improving adherence to CPAP.

Inclusion Criteria – Each participant must meet the following criteria for inclusion in the study:

- Male or Female Veterans of any racial or ethnic group
- Age 18 years old and older
- OSA diagnosis by a board-certified Sleep Medicine physician, described below in OSA Work-up and Diagnosis section
- AHI ≥ 5 events per hour
- PTSD participants will be positive for lifetime and/or current PTSD, related to combat experience and have a diagnosis of chronic current and/or lifetime PTSD as measured by the Clinician Administered PTSD Scale (CAPS)
- Capable of giving informed consent for the study; able to read and write English; willing and able to comply with study requirements and restrictions
- Nondemented by screening assessment of global cognitive function
- Sufficient visual and auditory acuity for cognitive testing

Exclusion Criteria – Participants will be excluded from the study if any of the following criteria apply:

Sleep

- Diagnosis of Central Sleep Apnea (CSA) (CAI ≥ 5 per hour) or Complex/Treatment Emergent CSA.
- Comorbid sleep disorder (e.g. narcolepsy, restless leg syndrome, periodic limb movement disorder, idiopathic hypersomnia or REM Behavior disorder) (excluding insomnia)
- Working night, rotating or split [period of work, followed by break, and then return to work]; shift work within 1-month of screening or plan to work these shifts during study; Occupations where participants regularly experience jet lag or have irregular work schedules.

Other Medical

- Unstable or moderate to severe chronic illness including systolic congestive heart failure (LVEF <45%), COPD (FEV1<80% predicted), uncontrolled asthma, severe liver disease (modified Child-Pugh score >6), end stage renal disease requiring hemodialysis or history of systemic illness affecting CNS function (e.g. liver failure, kidney failure, congestive heart failure, systemic cancer).
- Any current clinically significant cardiovascular, respiratory, neurologic, hepatic, hematopoietic, renal, gastrointestinal or metabolic dysfunction unless currently controlled and stable. Any solid organ transplantation.
- Known or suspected neuromuscular disease (e.g. amyotrophic lateral sclerosis, spinal cord injury)
- History of head injury within past year, or history of loss of consciousness > 24 hours
- History of other neurological disease (e.g., history of stroke, transient ischemic attacks, multiple sclerosis, Parkinson's disease)
- Current or recent (prior 3-months) use of systemic steroid medication, supplemental oxygen, opioid medication, stimulant medication (e.g. modafinil, methylphenidate, amphetamine), hypnotic medication (e.g. zolpidem, eszopiclone), sedating antihistamine medication, dopamine agonists (e.g. ropinirole), excessive caffeine intake (>800 mg/day or >8 cups of coffee/day) or toxicology evidence of illicit substance use in the prior month. Such medications could add variability to behavioral outcomes such as the FOSQ, and diminish the clarity of results.
- Judged by the investigators to be unable or unlikely to follow the study protocol (e.g., dementia).

Psychiatric

- Current or lifetime history of a psychiatric disorder with primary psychotic features
- Current or lifetime bipolar disorder; Prominent suicidal or homicidal ideation

- Current exposure to trauma, or exposure to trauma in the past 3 months
- Current or within the past 30 days drug abuse or dependence (except nicotine).
- Presence of acute or unstable psychiatric condition(s) that requires referral for treatment.
- Current or expected cognitive behavior therapy for another condition (e.g. insomnia, anxiety).

Other
- A clinical history or participation in other research that would interfere with the objectives of this study.
- Any other medical, social, or geographical factor that would make it unlikely that the participant would comply with the study procedures (e.g. lack of permanent residence or history of noncompliance).

OSA Work-up and Diagnosis. Consultations are triaged, such that, a decision is made regarding the level of sleep work-up recommended for that patient within 2 days of receiving a consult. Typically, a 'Level 3' sleep study is recommended (i.e., an unattended cardiopulmonary sleep study with a portable monitor) to be performed overnight at the VAPAHCS. Prior to the sleep study, the Veteran is mailed a packet that includes information about sleep problems, an explanation of the diagnostic procedures recommended, and relevant questionnaires (e.g., Epworth Sleepiness Scale, Beck Depression Inventory-II). Apneas and hypopneas are defined using the American Academy of Sleep Medicine's recommended criteria [17]. Also, as is the case in many large VHA facilities, there are not resources to perform an in-laboratory titration of the pressure setting. Veterans that are prescribed CPAP treatment will receive a Resmed model PAP device.

SCREENING PROCEDURES AND DETERMINATION OF STUDY ELIGIBILITY

Initial contact with prospective participants will occur at the OSA Group Clinic where interested Veterans will receive an IRB approved study flyer and consent form to review. The text of the consent form and phone screen provides permission to review medical records in CPRS and mentions that a member of the research team will telephone participants to review their medical history. Screening will proceed in two phases: 1) a brief telephone interview to determine if the veteran is likely to meet inclusion and exclusion criteria, 2) followed by a comprehensive in-clinic screening visit. After the brief telephone screening interview, if the medical and psychiatric criteria appear to be met, an in-clinic screening (SC) visit with the Study Coordinator will be scheduled.

Measure	Description
MMSE	Cognitive Screen
SCID	Psychiatric Screen
CAPS-5 [18]	PTSD Screen

At the screening visit, the participant's medical record and list of medications will be reviewed for evidence of exclusionary medical (e.g., hepatic, renal, congestive heart failure) and neurologic disorders. Unstable or clinically significant conditions will receive prompt clinical follow-up by psychologists and physicians of the VAPAHCS Memory Clinic.

The results of all of the screening assessments will be reviewed with Key Personnel. After consensus determination for study eligibility, the Study Coordinator will contact the participant to schedule a Baseline visit (if eligible), or provide appropriate referral and explanation (if deemed ineligible).

Enrollment, Randomization, and Baseline Measures

RCT Enrollment and Randomization. After the two-phase screening, eligible participants will be invited to participate and, if willing, scheduled to begin within 3 to 4 weeks of the completion of the screening visit. The Baseline visit and Session 1 (Day 0) will be carefully coordinated with Pulmonary staff for the participants who will receive their CPAP on the day of Session 1 (before the start of Session 1). All eligible participants will be randomized by the Data Manager to one of the two intervention arms: "CBT-OSA" or "Education" and notify the treating CP or ED, respectively.

Baseline Measures. The Coordinator will administer a cognitive battery

Adherence Intervention: CBT-OSA vs. Education

All CBT-OSA treatment will be done by a CBT-trained Clinical Psychologist and aimed at changing a participant's behaviors and cognitions related to CPAP use. These cognitive and behavioral interventions will be taught in the initial four weekly clinic sessions and reinforced in three booster sessions. To increase motivation and positive expectations, CBT-OSA will also include treatment goals relevant to the particular participant's condition.

The treating CP will work closely with the PI for clinical supervision and protocol adherence. The CP will learn the CBT-OSA intervention and will be practiced in achieving treatment fidelity. The CP will work with the participant individually (during certain sessions with the participant and bed partner).

The Education arm will focus on educational material (e.g., sleep health, sleep disorders, PTSD, cardiovascular health) over four weekly sessions and reinforced in three booster sessions. All participants will have equal opportunities for contact time with research staff. Participants will bring their CPAP to all sessions to use for exposure intervention (if in CBT-OSA) and to allow study staff to download CPAP data.

Pre-CPAP Intervention Phase

On Day 0, prior to starting or reinitiating CPAP (Pre-CPAP Intervention Phase), the Veteran will complete the following self-report measures: FOSQ, ESS, PCL-5, BDI-II, SEMSA and WAI-SAT. Then, participants in both arms, will have one individual in-clinic session (Session 1-Day 0) with their assigned CP or ED.

MEASURES

Consented Veterans who have been determined eligible and are willing to enter the RCT will be administered the measures described in Table 1 above.

DATA ANALYTIC PLAN

Hypothesis 1. (Primary Outcome) Effect of CBT on CPAP usage. We hypothesize that the CBT-OSA group will use CPAP more hours per night on average than the Education group. An ANCOVA will be used to compare performance on the primary measure [(the average of CPAP mask-on time for the last 30 days of the 1-year RCT (Days 335-365); a continuous variable)] by Group (CBT-OSA versus Education). The analyses will be an intention to treat design using multiple imputation for missing data [19]. We will perform multiple regression analyses to identify potential covariates (e.g., AHI prior to treatmen1, daytime sleepiness) which will be considered in the analysis. In a RCT, we assume that the groups will be apportioned relatively equally on relevant background variables, but we will verify this by analyzing specific baseline

variables (e.g., gender, age, education). We do not propose to enter all possible background variables as covariates into this analysis; however, we will perform multiple regression analyses to identify significant covariates. We will then include those variables in the ANOVA as covariates.

Hypothesis 2-4. (Secondary Outcomes) Effect of CBT on Self-reported Everyday Activities, Mood and Quality of Life, Cognitive Outcomes and PTSD. Secondary analyses will be conducted to compare performance between groups at Day 365 on relevant measures listed in Table 4 using the same statistical approach as Hypothesis 1.

Hypothesis 2. Effect of CBT on Self-reported Everyday Activities, Mood and Quality of Life. We hypothesize that after initiating CPAP treatment, Veterans in the CBT-OSA group will report more improvement in the ease of performing everyday activities compared to that reported by those in the Education group. An ANOVA will be used to compare performance on the FOSQ Total Score (continuous variable) by Group at Day 365.

Hypothesis 3. Effect of CBT on Cognitive Outcomes. We hypothesize that the CBT-OSA group will have better cognitive outcomes than the Education group over time. An ANOVA will be used to compare performance on CVLT Delayed Free Recall Score (continuous variable) by Group at Day 365.

Hypothesis 4. Effect of CBT on PTSD. We hypothesize that the CBT-OSA group will have fewer PTSD symptoms than the Education group over time. An ANOVA will be used to compare the PCL-5 Total Score (continuous variable) by Group at Day 365. Potential covariates relevant to Hypotheses 2-4 will be treated as for Hypothesis 1.

REFERENCES

1. Kulka RA, Schlenger WE, Fairbanks JA, Hough RL, Jordan BK, Marmar CR, Weiss DS: **Trauma and the Vietnam War Generation: Report of findings for the Natioinal Vietnam Veterans Readustment Study** New York: Brunner/Mazel; 1990.
2. Yesavage JA, Kinoshita LM, Kimball T, Zeitzer J, Friedman L, Noda A, David R, Hernandez B, Lee T, Cheng J: **Sleep-disordered breathing in Vietnam veterans with posttraumatic stress disorder**. *The American Journal of Geriatric Psychiatry* 2012, **20**(3):199-204.
3. Mustafa M, Erokwu N, Ebose I, Strohl K: **Sleep problems and the risk for sleep disorders in an outpatient veteran population**. *Sleep & breathing = Schlaf & Atmung* 2005, **9**(2):57-63.
4. Kuna ST, Gurubhagavatula I, Maislin G, Hin S, Hartwig KC, McCloskey S, Hachadoorian R, Hurley S, Gupta R, Staley B *et al*: **Noninferiority of functional outcome in ambulatory management of obstructive sleep apnea**. *American journal of respiratory and critical care medicine* 2011, **183**(9):1238-1244.
5. Platt AB, Field SH, Asch DA, Chen Z, Patel NP, Gupta R, Roche DF, Gurubhagavatula I, Christie JD, Kuna ST: **Neighborhood of residence is associated with daily adherence to CPAP therapy**. *Sleep* 2009, **32**(6):799-806.
6. Hrubos-Strom H, Randby A, Namtvedt SK, Kristiansen HA, Einvik G, Benth J, Somers VK, Nordhus IH, Russell MB, Dammen T *et al*: **A Norwegian population-based study on the risk and prevalence of obstructive sleep apnea. The Akershus Sleep Apnea Project (ASAP)**. *Journal of sleep research* 2011, **20**(1 Pt 2):162-170.
7. Marin JM, Carrizo SJ, Vicente E, Agusti AG: **Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study**. *Lancet* 2005, **365**(9464):1046-1053.
8. Sassani A, Findley LJ, Kryger M, Goldlust E, George C, Davidson TM: **Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome**. *Sleep* 2004, **27**(3):453-458.
9. Matthews EE, Aloia MS: **Cognitive recovery following positive airway pressure (PAP) in sleep apnea**. *Progress in brain research* 2011, **190**:71-88.
10. Aloia MS, Di Dio L, Ilniczky N, Perlis ML, Greenblatt DW, Giles DE: **Improving compliance with nasal CPAP and vigilance in older adults with OAHS**. *Sleep & breathing = Schlaf & Atmung* 2001, **5**(1):13-21.
11. Richards D, Bartlett DJ, Wong K, Malouff J, Grunstein RR: **Increased adherence to CPAP with a group cognitive behavioral treatment intervention: a randomized trial**. *Sleep* 2007, **30**(5):635-640.
12. Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, Smith PL, Schwartz AR, Redline S, Pack AI *et al*: **An instrument to measure functional status outcomes for disorders of excessive sleepiness**. *Sleep* 1997, **20**(10):835-843.
13. Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987-2000). *California Verbal Learning Test--Second Edition (CVLT –II)*. APA PsycTests.
14. Weathers FW, Litz, B.T., Keane, T.M., Palmieri, P.A., Marx, B.P., & Schnurr, P.P. : **The PTSD Checklist for DSM-5 (PCL-5).** ; 2013.
15. Morgenthaler TI, Aurora RN, Brown T, Zak R, Alessi C, Boehlecke B, Chesson AL, Jr., Friedman L, Kapur V, Maganti R *et al*: **Practice parameters for the use of autotitrating continuous positive airway pressure devices for titrating pressures and treating adult patients with obstructive sleep apnea syndrome: an update for 2007. An American Academy of Sleep Medicine report**. *Sleep* 2008, **31**(1):141-147.
16. Kushida CA, Littner MR, Hirshkowitz M, Morgenthaler TI, Alessi CA, Bailey D, Boehlecke B, Brown TM, Coleman J, Jr., Friedman L *et al*: **Practice parameters for the use of**

continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. *Sleep* 2006, **29**(3):375-380.
17. Iber C, Ancoli-Israel S, Chesson AL, Quan SF: **The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications**. Westchester: American Academy of Sleep Medicine; 2007.
18. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM: **The development of a Clinician-Administered PTSD Scale**. *JTraumaStress* 1995, **8**:75-90.
19. Rubin DB: **Multiple Imputation for Nonresponse in Surveys**. New York: J. Wiley & Sons; 1987.