A pragmatic randomized comparator trial of eszopiclone and brief behavioral therapy for insomnia in CPAP non adherent Veterans with PTSD and complex insomnia

NCT03937713

June 5, 2020

RESEARCH DESIGN AND METHODS

The current application proposes to explore the comparative effectiveness of combination therapy of behavioral and pharmacological interventions with behavioral therapy alone in improving the sleep quality of life of Veterans with COMISA.

Trial design

This trial will follow the International CONSORT (Consolidated Standards of Reporting Trials) guidelines using a randomized trial design [1]. The trial will be registered at clinicaltrials.gov.

Study population

Participants will be recruited from the sleep clinics at the VA Western New York Healthcare System. The clinics operate 8 sessions per week with more than 3,500 visits per year. A written waiver of consent and partial waiver of HIPAA authorization will be requested to collect and review health information about prospective subjects prior to obtaining written informed consent**.** The waiver will not adversely affect the rights and welfare of the subjects, and the research could not be conducted without the waiver because the health information collected is necessary to ascertain which subjects are eligible to participate in the study.

Inclusion criteria: Subjects who fulfill the following criteria at screening will be included in the study:

- Age >18 years and <65 years old (the reason for limiting recruitment for combat-exposed Veterans between 18 and 65 years of age is due to the change in pharmacodynamics of eszopiclone in patients above 65 years old. Compared to nonelderly adults, a 41% increase in the AUC and a prolonged elimination ($t_{1/2}$ life) of approximately 9 hours were observed in subjects 65 years and older) [2]
- Documented obstructive sleep apnea by polysomnography (AHI≥5 or more/hour) who are non-adherent to CPAP as defined by device usage of less than 4 hours per night
- Chronic (≥3 months' duration) insomnia disorder (based on International Classification of Sleep Disorders, Second Edition (ICSD-2) criteria). The Diagnostic and Statistical Manual, 5th edition (DSM-5) defines insomnia as difficulty falling or staying asleep, or non-restorative sleep, at least 3 nights per week, with sleep-related distress or daytime dysfunction, for at least 3 months
- Psychotherapeutic treatment stable for at least 4 weeks prior to randomization
- Capable of giving informed consent

Exclusion Criteria: Subjects who meet any of the following criteria at screening will be excluded from the study Medical:

- Insomnia secondary to pain
- History of narcolepsy and/or cataplexy, central apnea, or parasomnias
- Treatment for seizure disorders
- Pregnant or lactating
- History of clinically significant hepatic impairment
- History of hypersensitivity, intolerance, or contraindication to eszopiclone
- Use of potent cytochrome p450 3A4 inhibitor medications (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole, itraconazole) and is unwilling or it is clinically contraindicated to stop the medication
- Unwilling to try or use CPAP

Psychiatric/Behavioral:

- Diagnosis of current schizophrenia or schizoaffective disorder
- Diagnosis of a substance dependence/abuse disorder
- Severe psychiatric instability or severe situational life crises, including evidence of being actively suicidal or homicidal, or any behavior which poses an immediate danger to patient or others
- Diagnosis of bipolar disorder
- Consumption of more than two alcoholic beverages per night
- Receiving behavioral or pharmacological treatment for insomnia including benzodiazepines

Baseline assessments

Eligible participants will be informed about their rights to end their participation at any time without negative consequences. Confidentiality will be maintained at all levels of the pilot study by staff members, diagnosticians, supervisors and researchers. After obtaining informed consent, demographic, anthropomorphic, and socioeconomic will be obtained from all participants, including include age, gender, height, weight, occupation, and income level. Additional information on comorbidities, coexisting psychiatric disorders, and a list of medications including the last CPAP smartcard reading will be recorded during that visit. Each participant will be asked to complete the Epworth Sleepiness Scale (ESS) [3], the Pittsburgh Sleep Quality Index (PSQI), the Beck Depression Inventory Questionnaire (BDI-II) [4], and the Insomnia Severity Index (ISI) [5].

Subjects who score < than 15 points on the Insomnia Severity Index which is the recommended cutoff to detect clinical insomnia according to the American Academy of Sleep Medicine cases will be excluded from participation [6]. Similarly, individuals who are identified by the BDI-II questionnaire or interview to have severe or extreme depression (score >30) will be also excluded from participation. In both of these instances, subjects will be considered a screen failure and will be denoted as such on the Case Report Form.

In case a potential case of severe or major depression is suspected, the Research coordinator will contact the P.I. who will determine appropriate referrals and responses. If there is any indication that a participant is in imminent danger to him/herself or others, the participant would be escorted to the nearest emergency room for evaluation by a psychiatrist.

After completing the baseline assessment visit, all participants will be asked to prospectively track their sleep/wake patterns using the Pittsburgh Sleep Diary (PSD) [7] for the seven consecutive days and nights that immediately preceded their first treatment visit. The PSD is an instrument that can be used to measure to quantify sleep and waking behaviors. It includes items on the time at which the participant went to bed, attempted to fall asleep, the number, cause, and duration of nocturnal awakenings, final time out of bed, and total estimated time spent asleep. A wrist actigraph (Minimitter Actiwatch®-64; Minimitter, Bend, Oregon) will be assigned also to all participants to monitor their sleep/wake schedule. Participants will be asked to wear it for the seven consecutive days and nights that immediately preceded their first treatment visit in tandem with the recordings of the Sleep Diary. The Actigraphy is an important adjunctive measure in the diagnosis and treatment of insomnia that can improve the reliability of self-report estimates of sleep [8]. Actigraphy data will be collected in 1-min epochs and analyzed with the validated Actiware Version 5.04 software program. Variables that will be evaluated include sleep latency (SL), wakefulness after sleep onset (WASO), sleep efficiency, and total sleep time (TST) (expressed in minutes). Data derived from actigraphy measures and sleep dairy will be used to individualize sleep schedule. Discrepancies between sleep diary and actigraphy measures will be queried and resolved with participants' input.

6.4 *Randomization*

Participants who complete all baseline assessments will be randomized in a 1:1 fashion to either BBTI plus eszopiclone or BBTI using a stratified permuted block randomization scheme. The proposed assignment method has been shown to effectively create similar groups of participants across treatment conditions [9]. The randomization list will be generated by the study biostatistician. Subjects will be included in data analyses according to their randomized assignment irrespective of the treatment received (intent-to-treat).

6.5 *Intervention*

Prior to initiating treatment, patients will be studied for the fitting of a nasal or oronasal facemask using a custom fitting chart. The appropriate sized facemask and head strap will be used that provides maximum patient comfort and minimizes leaks around the mask. All patients will be taught how to properly fit the mask and head strap and remove it and maintaining its care. Sleep hygiene education will be provided about the effects of caffeine, alcohol, and exercise on sleep, and the effects of noise, light, and excessive temperature. All participants will receive a standardized education session with their bed partner (if possible) designed to improve their CPAP adherence. They will also receive an educational brochure, which is reviewed by the respiratory therapist. In addition to motivational content to promote adherence, the brochure will cover what CPAP is, why regular use is important, care and daily cleaning of the mask, how to troubleshoot mask-related problems, how to perform weekly cleaning of the mask and the device, care, and cleaning of the humidifier, and general care of the device. The respiratory therapist will also demonstrate the described techniques using an unpowered unit. At each telephone call and follow up visit, participants will be prompted for any CPAP-related problem using the CPAP troubleshoot checklist. In case a problem is identified, the respiratory therapist will contact the participant to address the problem.

A. Brief Behavior Treatment of Insomnia-Military Version

Detailed descriptions of BBTI efficacy data and therapeutic guidelines have been previously reported [10-12]. BBTI is adapted from a manualized behavioral treatment as described previously [11]. BBTI will be delivered over four consecutive weeks, and includes one individual in-person visit (45 min) at week 1, a second in-person visit at week 3 (<30 min), and brief telephone appointments during weeks 2 and 4 (<20 min each).

The content of the first BBTI session will be focused on providing accurate and concise information about military-specific factors that adversely affect sleep before and during deployment, and about behaviors that contribute to the persistence of insomnia post-deployment. The session is designed to be both educational and interactive. “Customized sleep schedule” or recommended bedtime and rise time will be determined based on data gathered from the baseline sleep diary and actigraphy measures. The technical implementation of this approach has been described previously by Troxel et al. [11]. Briefly, the average total sleep time reported on the sleep diary and actigraphy recordings will be first computed for each participant. By adopting the principles of sleep restriction [13], 30 min will be added to the average total sleep time, in order to account for normal time to fall asleep and nocturnal awakenings. A minimum bedtime is set at 6 hours for safety reasons even if the patient reports sleeping fewer than 6 hours. Then, the participant and the research coordinator agree on a fixed wake-up time of the day, every day even after a poor night of sleep. The rationale for that approach is three folded: 1) wakeup time is the single most important cue for “setting” the biological clock; 2) wakeup time regulates exposure to morning light—another powerful cue to set the biological clock and prevent phase delay; and 3) maintaining a consistent wakeup time even after a poor night of sleep increases homeostatic sleep drive for the subsequent night. Finally, instructions on how to avoid going to bed unless sleepiness has set in and to get out of bed if awake for more than 30 minutes. Over time, being in bed while awake can lead to conditioning effects such that the bed becomes a conditioned stimulus for arousal. By limiting the amount of time in bed to approximately the amount of time spent sleeping, the bed becomes a conditioned stimulus for sleep. Just getting in bed can then elicit sleep rather than arousal. In addition, to facilitate successful implementation of stimulus control recommendations, the research coordinator will work with the patient on specific activities that he/she can do in the middle of the night if not sleeping. At the end of the session, participants will receive a new 14-day sleep/wake diary to track adherence and progress until the following in-person visit. Participants will be reminded not to remove or turn off the wrist actigraph during this period.

The second in-person visit (Week 3) is used to review and reinforce adherence to the prescribed sleep-wake schedule, and to determine whether changes in the prescribed time in bed are required. Specifically, participants who showed a diary- and actigraphy-based average sleep latency and average duration of wake-time after sleep onset of less than 30 min, with an average sleep efficiency greater than 85% on the previous week's sleep diary/actigraphy recordings will be allowed to increase the total time spent in bed by 15 min for the subsequent three or four nights, by either advancing bedtime by 15 min or delaying the rise time by 15 min. If sleep consolidation is maintained over these nights, they are instructed to extend their allotted time in bed by another 15 minutes. Conversely, if sleep latency and the duration of wake time after sleep onset exceeded 30 min, or if sleep efficiency was less than 85%, they are instructed to restrict their time in bed by 15 min. The critical feature of this session is that the patient understands that time in bed should be decreased when sleep is poor and can be increased when sleep is good.

The two phone contacts scheduled for week 2 and 4 are designed to provide support and to troubleshoot any emerging issues regarding treatment adherence. The research coordinator will go over the previous week sleep diary with the participant. The session generally does not require a night-by-night review of the sleep diaries. The sessions are used to review the rules for better sleep, including the instructions for stimulus control and sleep restriction, and to review the instructions for increasing or decreasing time in bed.

To ensure attendance, reminders will be sent to the participants at each contact/visit and the day prior to the next scheduled encounter. A makeup session/call will be provided at the next convenient time agreeable between the participant and the research coordinator.

B. Combined CBT-I plus eszopiclone

In addition to CBT-I, participants randomized to the combination therapy will receive eszopiclone 2 mg orally at bedtime or placebo starting with the CBT-I sessions for a period of 2 weeks. A brief in person (20-30 minutes) consultation session during the enrollment visit will be provided to review potential side effects that could arise from the medication. The Patient Monitoring Checklist will be obtained at baseline (enrollment), week 1, and at week 2. The study pharmacist will review the Patient Monitoring Checklist to assess for serious adverse events. Patients will be encouraged to comply with the medication regimen. Medication adherence will be determined by self-report and pill counts at end of treatment.

C. CPAP device

Participants will be instructed to adhere to CPAP utilization (at least 4 hours per night) on the first night after treatment is initiated. All participants will be provided with a REMstar Pro CPAP (Respironics Inc., Murrysville PA) device operated in automatic mode with a data-storage SmartCard at no cost. The data card records time while the mask is on the face. The returned data cards will be downloaded by staff who will be blinded to the treatment arms and automatically analyzed using the Encore Pro software (Respironics Inc., Murrysville PA).

6.6 *Follow-up Study visits*

Follow up visits for all participants will be scheduled at EOT and at 6-month. At each of the scheduled follow-up visit, participants will be asked to complete the PSQI, ESS, PCL-5, ISI, and BDI-II. The list of medications will be reviewed and any changes in prescribed and non-prescribed medicines will be recorded. Potential adverse events will be assessed including hospitalization, and extreme sleepiness (such as while driving, operating machinery, cooking, or in other unsafe situations). A random urine toxicology testing will be conducted. During these follow-up visits, adherence to CPAP will be assessed by downloading the SmartCard data by a respiratory therapist blinded to the treatment intervention. At the end of 6-month follow-up interview, all participants will complete the Client Satisfaction Questionnaire (CSQ) [14] to assess satisfaction with and acceptability of the intervention. The CSQ is an 8-item, easily scored and administered measurement that is designed to measure client satisfaction with services. The items for the CSQ-8 were selected on the basis of ratings by mental health professionals of a number of items that could be related to client satisfaction and by subsequent factor analysis. The CSQ has demonstrated adequate reliability and validity (Cronbach's alpha 0.90) in various samples [15,16]. Two additional open questions will be included to assess the participants' perception of therapist competence and offer the opportunity to make any other comments regarding the treatment. The practicalities of recruitment will be assessed descriptively. Refusal and dropout from the study protocol will be recorded. Rates of withdrawal from treatment will be calculated as a percentage of those randomized. A schedule of study visits is displayed in Table 2.

Table 2. Scheduled visits

	Enrollment	**BBTI + eszopiclone**		**BBTI**	
		EOT	6-month	EOT	6-month
Procedure & Assessment					
Informed Consent	•				
Demographics	•				
ESS	•	•	•	•	•
PCL-5	•	•	•	•	•
PSQI	•	•	•	•	•
ASI-Lite	•	•	•	•	•
Insomnia Severity Index (ISI)	•	•	•	•	•
Beck's Depression Inventory	•	•	•	•	•
CSQ			•		•
CPAP adherence		•	•	•	•
Medication Review	•	•	•	•	•
Actigraphy	•	•	•	•	•

6.7 *Training and Monitoring of treatment delivery*

6.7.1 BBTI training: The behavioral intervention will be delivered by the Research coordinator who has a master's level degree with more than 8 years of prior clinical research experience. The Research coordinator will receive a total of 20 hours of training that consists of didactic explanation of the principles of BBTI intervention, followed by topic-by-topic reviews of the manual, several role-play and feedback exercises, discussion of case examples, and rehearsing strategies for difficult or challenging cases. These training sessions will be overseen by a licensed psychologist. The training focuses on developing a formalized structure of the planned sessions (e.g., setting

the agenda, conducting behavioral rehearsal of coping skills, checking homework, assigning homework). After training, the research coordinator will be assigned a minimum of 3 practice/training cases. These sessions will be taped and rated for adherence to manual guidelines, level of skillfulness, and appropriate structure and focus. Acceptable levels of adherence and competence ratings (>80%) are needed for both treatment protocols. Strategies for maintaining focus, redirecting tangential discussions, helping patients set aside time in a private part of the home, and scheduling time for the intervention appointments will be reviewed on regular basis during the course of the study.

Treatment fidelity: To ensure treatment fidelity, the PI will randomly select 20% of the audiotapes and forward to Dr. El Solh for adherence and competence ratings, using a modified version of the Competence and Adherence Scale for cognitive behavioral therapy [17]. In case it is determined that the research coordinator has deviated significantly from the protocol, he/she will be assigned to 3 practice/training cases/week under close supervision with intensified tape rating until the original certification level has been reestablished. In addition, ongoing supervision and the provision of corrective feedback are critical to avoid therapist "drift" and ensure continued fidelity of treatment. The therapeutic value of CBT in randomized controlled trials appears particularly dependent on the quality of supervision. Controlled trials that have incorporated more intensive supervision have yielded stronger outcome data [18]. Proper supervision would include two components: 1) continuous monitoring of treatment delivery and 2) provision of corrective action. We will adopt the supervisory model of a well administered multicenter trial (the Enhancing Recovery in Coronary Heart Disease) that featured CBT for depression and low social support for post MI-patients [18]. The model would include biweekly meetings of the research coordinator with the PI, review of audiotapes, and self-monitoring of the administered therapy through checklists.

Outcome measures

The Pittsburgh Sleep Quality Index (PSQI)[19] The PSQI is a 19-item, self-rated questionnaire, assessed various aspects of sleep, sleep quality, and sleep disturbances over the previous month. Psychometric evaluation of the scale supports its internal consistency reliability and construct validity, and the scale is highly sensitive and specific for the identification of sleep disturbances in a variety of clinical populations[20]. The PSQI is composed of 7 components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these 7 components yields 1 global score. Total PSQI scores > 5 have yielded a diagnostic sensitivity of 89.6% and a specificity of 86.5% in distinguishing poor sleepers from good sleepers.

Insomnia Severity Index (ISI)[5] The ISI is a 7-item patient-reported outcome assessing the severity of initial, middle, and late insomnia; sleep satisfaction; interference of insomnia with daytime functioning; noticeability of sleep problems by others; and distress about sleep difficulties. A 5-point scale is used to rate each item, yielding a total score ranging from 0 to 28. A higher score indicates more severe insomnia within the following 4 severity categories of absence of insomnia (score of 0-7); subthreshold insomnia (score of 8-14); moderate insomnia (score of 15-21); and severe insomnia (score of 22-28). The ISI has adequate psychometric properties and is sensitive to measure treatment response [5]. Patients are considered treatment responders if their ISI change score compared with baseline is greater than 7 and treatment remitters if their absolute ISI score is less than 8.

Beck Depression Inventory (BDI-II) [4]: The BDI-II is a 21-item questionnaire in which respondents indicate on a four-point Likert-type scale (0=minimal to 3=severe) the presence and severity of depressive symptoms during the past 2 weeks. Items are scored on a 4-point scale ranging from 0 to 3, with higher scores indicating the presence of more depressive symptoms. The BDI-II has demonstrated good validity, reliability, test-retest reliability, and high internal consistency (Cronbach's alpha .92) in patients with chronic pain [21]. The BDI-II score is derived by summing all responses, with total scores ranging from 0 to 63.

Actigraphy: The wrist actigraphy provides continuous activity data using a battery-operated wristwatch-size microprocessor that records physical movement using an accelerometer-microprocessor link. High-resolution data will be down-sampled to one-minute sample intervals for conventional actigraphic sleep-wake estimation and analyzed using the validated Actiware Version 5.04 software. Sleep efficiency, sleep maintenance, total sleep time and wake after sleep onset will be calculated as secondary objective measures of sleep.

CPAP adherence: CPAP adherence will be obtained by downloading the data stored on the SmartCard. CPAP adherence will be defined as the percentage use of CPAP for ≥ 4h/night during a 28 consecutive day period.

Other (secondary) measures of CPAP adherence will include also average hours of use per night and usage index which will be calculated as the number of days the CPAP was used for more than 4 hours divided by the total number of days studied.

Statistical and Analytical Plans

Data analysis will consist of descriptive statistics of all variables and constructs. These will include counts and percentages for binary and categorical variables and means and standard deviations, or medians with lower and upper quartiles, for continuous variables, along with minimum and maximum values and counts of missing values. Data distributions and all model assumptions will be checked for all analyses. If model assumptions are not met, data will either be transformed or analyzed using a non-parametric test, as appropriate. The descriptive statistics will ensure that our randomization process is effective and that no statistical differences exist between the study population. In the event that key differences emerge, weighting procedures will be used in the analysis to control for these baseline differences. The intent-to-treat (ITT) protocol will be followed for these analysis [22]. We plan also on following up all participants enrolled in the study independent of whether they complete treatment so that we can perform both per protocol (PP) as well as intent-to-treat analyses. Per protocol analyses focus evaluation only on those individuals who complete treatment. The logic is that to evaluate the effectiveness of a treatment protocol, analyses should be conducted on those who received "full dose" of the treatment. By contrast, ITT analyses place greater emphasis on external validity and focuses on the real world impact of the treatment taking into account that individuals may choose to drop out of treatment because of the nature of the treatment itself. In ITT analyses, all respondents who are initially randomly assigned to the various experimental conditions are analyzed to the posttests [23] whereas in PP analyses, only those who complete the treatment protocol are analyzed. Both forms of analyses are informative, and we will approach the data from each perspective.

Analysis plan for the primary outcome

Our primary strategy is to compare BBTI plus eszopiclone versus BBTI using analyses that are straightforward and highly interpretable while still accounting for other important covariates. Within-subject changes in the PSQI from baseline will be **the primary outcome**. The primary analyses involve the statistical assessment of group differences with regards to this outcome and will be based on a linear model. In taking this approach, we fit the dependent variable as a linear function of independent variables treatment regimen, and baseline outcome level. Rather than utilizing the null distribution associated with the classic F-test for treatment differences within this framework which is dependent on the validity of distributional assumptions, an exact permutation testing approach will be utilized. The randomization mechanism at work is a crucial component in this study in that it will be used to create the randomization distribution by which statistical significance will be determined. For more on this approach see Gail, Tan, and Piantadosi (1988)[24]. Reported p-values will be obtained from the permutation distributions of the test statistics based on 10,000 Monte Carlo simulations. As secondary analyses, additional subject covariates will be included as independent variables. The interaction of the treatment group and subject covariates may also be examined in a secondary fashion in order to identify possible differential effects of treatment. All statistical tests will be two-sided and tested at a 0.05 nominal significance level.

Analysis plan for the secondary outcomes

Analyses of secondary outcomes will proceed in a similar fashion. For actigraphy outcomes, data will be averaged over one-week periods. Alpha level will be adjusted using the Bonferroni correction when indicated. All analyses will be carried out using SAS version 9.4 (or higher) statistical software (Cary, NC).

8.0 Sample size

The sample size selected for this study is based on the analysis of the primary outcome. For the sake of simplicity, calculations corresponding to the test based on the proposed approach are approximated by those of a simple two-sample t-test for mean differences. The estimate of the variability used for sample size calculations was derived from a randomized controlled trial of BBTI for the treatment of insomnia in military Veterans where an approximate standard deviation of 3.5 was found[12]. A correlation between baseline and post-randomization measurements of the outcome of 0.7 was obtained from our data presented in the section of preliminary findings. Calculations show a sample size of 21 per group (42 total) will allow us to detect differences as small as 3 units (a minimal clinically important difference)[25] with approximately 80% power. The actual analysis is based on a model with additional independent variables that will account for some of the unexplained variability in the

dependent variable. These calculations may be viewed as conservative. Since we expect a 25% dropout rate, 52 patients will be enrolled in this study.