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PSYCHIATRICS • ORIGINAL ARTICLE

Predictors of cognitive behavioral therapy outcomes for insomnia in veterans with post-traumatic stress disorder

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Abstract

Background Insomnia is a well-recognized co-morbid condition in veterans with post-traumatic stress disorder (PTSD) with negative personal and social consequences. Cognitive behavioral therapy (CBT) is considered an efficacious treatment, yet little attention has been devoted to treatment response in this population. The aim of this study was to identify factors that may predict clinical response to CBT for insomnia (CBT-I) in veterans with PTSD.

Methods A retrospective chart review of 136 veterans with PTSD-related insomnia was conducted. Epworth Sleepiness Score (ESS), PTSD Checklist (PCL), and Insomnia Severity Index (ISI) were assessed at baseline. We converted prescribed antidepressant and hypnotic dosages before and after CBT-I to dose equivalent of fluoxetine diazepam, respectively. A 6-point reduction or greater in ISI scores at 6-month follow-up visit was defined as CBT-I responsiveness.

Results CBT-I responsiveness was observed in 47% of veterans with PTSD. Seventy-seven percent completed treatment. Lack of perceived benefit was the most given reason for failure to return for follow-up. In contrast to hypnotics, antidepressants usage decreased in those who had experienced benefit from CBT-I ($p = 0.001$). Younger age, non-white race, and use of hypnotics prior to behavioral therapy were independently associated with lack of response to CBT-I.

Conclusions While CBT-I ameliorates insomnia in veterans with PTSD, the use of hypnotics prior to instituting behavioral therapy may negatively affect the response rate to CBT-I. Future studies should examine whether racial and cultural influences on the generation of insomnia in veterans with PTSD affects the response to CBT-I.

Keywords Insomnia · Cognitive behavioral therapy · Post-traumatic stress disorder · Race · Hypnotics

Introduction

Sleep disturbances are considered a hallmark of combat-related post-traumatic stress disorder (PTSD) [1, 2]. Nearly two-thirds of the 2.5 million U.S. military personnel who served in Afghanistan (Operation Enduring Freedom, OEF) and Iraq (Operation Iraqi Freedom, OIF) reported insomnia problems after returning home [3, 4]. The consequences of insomnia in veterans with PTSD have been highlighted in several investigations [5]. In addition to its social and financial toll, insomnia is associated with serious health conditions, greater healthcare utilization, and worsening psychiatric ailments including PTSD, alcohol abuse or dependence, depression, and suicidality [6–9].

With the increased awareness of PTSD-related insomnia and its complications, national guidelines recommend the use of cognitive behavioral therapy for insomnia (CBT-I) as the standard treatment approach for managing this sleep disorder [10]. CBT-I targets specific behaviors and thoughts by combining stimulus control (associating the bed and bedroom with sleep), sleep restriction (increasing the homeostatic drive to sleep by reducing time in bed), and cognitive therapy (addressing maladaptive beliefs about sleep, and reducing anxiety

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about sleep and the consequences of not sleeping). CBT-I has been shown to be a successful and a cost-effective treatment for insomnia in veterans with PTSD [11]. From baseline- to post-treatment, CBT-I yields improved sleep architecture, attenuates insomnia severity, and ameliorates depression. Its effects are also maintained past the conclusion of the treatment period which offers a significant advantage over long-term pharmacotherapy, where the risk of side effects and potential drug interactions can complicate the management of other coexisting conditions [11].

Whereas standard CBT-I may enhance sleep quality, evidence suggests that as many of 50% of patients with PTSD who achieve remission following treatment continue to experience residual insomnia [11]. Earlier studies in patients with primary insomnia without PTSD found that demographic variables have not been consistent predictors of favorable outcomes of CBT-I [12, 13] while baseline usage of sleep medications is associated with reduced treatment gains [14]. Given that the vast majority of insomnia patients with PTSD can be characterized as comorbid cases, further investigation on predictors of treatment response in a sample more characteristic of trauma-associated insomnia is warranted. The study objectives are to determine the fraction of veterans with PTSD who showed reliable improvement in sleep following treatment outside a controlled environment (i.e., clinical trials) and to identify pretreatment characteristics that may predict reliable change.

Methods

Participants

The study was approved by the Institutional Review Board of the VA Western New York Healthcare System (VA WNYHS). Participants' records of eligible veterans at the VA Western New York Healthcare System were reviewed between January 2013 and September of 2017. Inclusion criteria included veterans between the ages of 18 and 75 years who (1) had chronic PTSD of at least 3 months' duration based on Diagnostic and Statistical Manual of Mental Disorders (DSM), fourth and fifth edition diagnostic criteria (because of the study time frame that spanned the transition from DSM-IV to DSM-5); (2) have been on stable psychotropic medications for at least 3 months prior to baseline assessment if they were receiving psychotropic agents; (3) had persistent DSM-IV or DSM-5 defined insomnia for at least 3 months prior to presentation; and (4) received at least one session of CBT-I. Exclusion criteria included history of obstructive sleep apnea defined as apnea hypopnea index ≥ 5 by polysomnography, restless leg syndrome, any hospitalization in the previous 3 months, and current night shift work. Both PTSD and insomnia diagnoses were assessed by a psychologist and a sleep specialist, respectively.

Descriptive characteristics (e.g., age, sex, race and ethnicity, marital status, and combat history), DSM-IV/5-based insomnia classification, comorbid medical and psychiatric conditions were collected at the time of referral to the sleep clinic. We extracted also pre-treatment polysomnographic data from all selected cases including sleep onset latency (SOL), total sleep time (TST), sleep efficiency (SE), and arousal index. A list of prescribed medications for sleep was compiled at baseline and at the date of the last visit. These were sorted into four categories: hypnotics, antidepressants, antipsychotics, and others. To evaluate the prescribed dosages, we converted the antidepressant/antipsychotic dosages to dose equivalent of fluoxetine [15] and the hypnotic dosages to dose equivalent of diazepam [16]. The conversion calculation approximates a reasonable equipotent dose between two oral agents based on published equipotent estimates whereby we multiply the milligram of drug that the patient is taking per day by the fluoxetine or diazepam conversion constant.

Procedures

The specific protocol for CBT-I used by the Insomnia clinic at the VA WNYHS was developed in accordance with standardized manuals for the treatment of insomnia [17]. Treatment plan comprised four sessions delivered individually with each session lasting between 30 and 45 min. As with traditional CBT approaches, CBT-I comprises techniques that involve self-monitoring, behavior modifications, and cognitive restructuring. The behavioral components of CBT-I included sleep restriction therapy, modified stimulus control, and relaxation training. Sleep restriction therapy consisted of curtailing time in bed to more closely approximate actual sleep time. Participants were also instructed to maintain a consistent arising time, even after a poor night's sleep, to synchronize the endogenous circadian rhythm that regulates sleep and wakefulness. Modified stimulus control techniques were designed to teach participants to associate the bed and bedtime with sleep as opposed to frustrating wakefulness and "trying" to sleep. Participants were instructed to (1) use the bedroom primarily for sleep and sex; (2) go to bed only when drowsy; (3) if unable to fall asleep within 20 to 30 min, get out of bed and go to another room to engage in a quiet, relaxing activity until drowsy except when getting out of bed may prove to be uncomfortable (during winter months) or raise concerns about fear of falling due to underlying medical conditions. Instead, patients were asked to engage in worry-incompatible activity (e.g., reading) until drowsy; and (4) repeat this step as often as necessary and use for middle-of-the-night awakenings. Relaxation techniques involved muscle relaxation, breathing, and mental focusing techniques that were practiced during the day and at bedtime. Treatment was delivered by clinical

graduate trainees and supervised by a behavioral sleep specialist. Once treatment sessions were completed, follow-up visits were made at the discretion of the treating physician but a 6-month follow-up visit was scheduled for all participants.

Measurements

The Epworth Sleepiness Scale (ESS) [18], the PTSD Checklist (PCL) [19], and the Insomnia Severity Index (ISI) [20] were administered prior to initiating CBT-I. The ESS is a self-administered 8-item questionnaire used index to measure sleep propensity. Scores range from 0 to 24, with a cutoff of > 10 representing clinically significant sleepiness. The PCL is a 17-item self-report questionnaire that is widely used in military and civilian population to assess the severity of PTSD symptoms. A total symptom severity score (range 17–85) can be obtained by summing the scores from each of the 17 items that have response options from 0 "not at all" to 4 "extremely." Psychometric evaluations of PCL scores have found them to have high internal consistency in samples of war veterans ($\alpha = .95$) [21] as well as civilians ($\alpha = .95$) [22]. The ISI is a 7-item measure of perceived insomnia severity. The ISI assesses sleep difficulties and distress, and impairment related to the sleep disturbance. Total scores range from 0 to 28, with a higher score indicative of greater insomnia severity. The ISI has excellent internal consistency (Cronbach $\alpha = 0.74$) and temporal stability ($r = 0.80$) [20]. Based on prior studies, we have considered a 6-point reduction or greater in ISI scores from baseline to 6-month follow-up was used to define a CBT-I responsive group [23]. Failure to complete CBT-I sessions was coded as CBT-I non responsive. Those who did not show up for the 6-month visit were coded based on the ISI scores obtained at the last visit to the clinic.

Statistical analysis

Continuous variables were reported as mean ± standard deviation. Means were compared using the Student's t test when normally distributed and the Mann-Whitney test otherwise. Proportions were compared using the chi-square test with Yates correction or Fisher exact test. A total of 34 multiple imputations by using the Markov Monte Carlo method was used to impute missing values for variables entered in the analyses based on the average missing data rate [24]. A logistic regression was performed to ascertain independent factors responsible for failure to benefit from CBT-I. Only significant clinical and demographic variables from the initial group comparisons ($p \leq 0.1$) were entered as confounders in the logistic regression analyses. All potential explanatory variables included in the multivariable analyses were subjected to correlation matrix for analysis of collinearity. Variables with association among each other were not included in the multivariable model. Results are presented as odds ratios (OR) with 95%confidence intervals (CI). All tests were two-tailed with a 0.05 significance level. All analyses were performed with STATA software, version 13 (StataCorp, College Station, TX).

Results

Study population

From March 2016 to September 2018, 221 veterans with PTSD were evaluated at the VA Western New York Healthcare sleep clinic for insomnia (Fig. 1). As part of the initial workup, a polysomnogram was conducted to exclude the presence of coexistent sleep disorders. One hundred eighty-eight patients were referred for CBT-I. Thirty-seven declined behavioral therapy and 15 did not show up for their initial appointment leaving 136 cases for analyses. Patients included 105 men and 31 women between 20 and 74 years old with an average of 46.9 years. The majority were identified as white (74%). African-American and Hispanic veterans represented 21% and 5% of the sample, respectively.

Of all the records reviewed, 91% of the insomnia were attributed to co-existing psychiatric conditions including depression and PTSD. Only 9% were labeled as primary insomnia. In 87% of the cases, insomnia either preceded or developed within 6 months of PTSD diagnosis. The majority of patients (72%) described their insomnia as both sleep-onset and sleep-maintenance. Sleep-onset insomnia alone accounted for 6% while sleep-maintenance insomnia alone represented 21%. The average ISI score for participants prior to CBT-I was 20.2 ± 3.3. The use of hypnotics was reported in 61 patients out of 136 (44%) of the study population and consisted of benzodiazepines ($n = 53$) and non-benzodiazepine gamma aminobutyric acid (GABA) receptor agonists ($n = 8$). Sixty-two percent of the patients were also receiving psychotropic medications at the time CBT-I was delivered. Among those, half were prescribed antidepressants and 35% were taking antipsychotic agents. Within the antidepressants, selective serotonin reuptake inhibitors (SSRIs) were the predominant choice while quetiapine and mirtazapine accounted for the most frequently prescribed antipsychotics.

CBT-I attendance and follow-up

Twenty-four patients (18%) completed only one CBT-I session and thirty-one (23%) did not return for follow-up visit at the 6-month appointment. Although the reasons for failing to complete the treatment sessions were not provided, 26 of the 31 patients who failed to return for the 6-month appointment had reported lack of perceived benefit. The remaining five

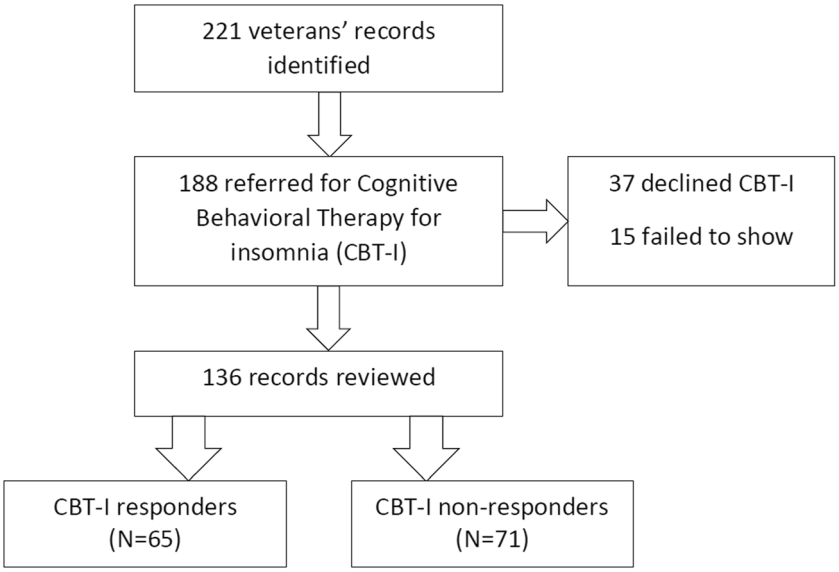

Fig. 1 Study flow diagram

either were hospitalized for worsening of their psychiatric conditions ($n = 3$) or were unable to attend due to time constraints ($n = 2$). Neither the demographic characteristics nor the number of sessions attended differed in terms of age, sex, or race, from those who had returned for their 6-month follow-up.

CBT-I treatment outcomes

Out of the 136 cases, 65 (47%) patients had a drop of six points or greater in ISI. Table 1 displays the demographic and baseline clinical characteristics of those who had a clinically meaningful response to CBT-I and those who did not. The group who experienced improvement in insomnia was older and predominantly white. African-Americans and Hispanic veterans had significantly lower CBT-I response rate compared to White veterans (6% versus 19%, $p = 0.001$). Sex distribution and combat experience were comparable in both groups. Similarly, the severity of insomnia and the severity of PTSD were no different at baseline between responders and non-responders to CBT-I ($p = 0.78$ and $p = 0.31$, respectively). On diagnostic polysomnography, sleep onset latency was

Table 1 Characteristics of the patient population at baseline

	CBT-I responsive ($n = 65$)	CBT-I non responsive ($n = 71$)	p value
Age, years	50.2 ± 13.3	43.9 ± 40.8	0.007
Sex, (M/F)	52/13	51/20	0.39
Race, *n* (%)			0.001
Whites	57 (88)	44 (62)	
Non-Whites	8 (12)	27 (38)	
Combat PTSD, *n* (%)	28 (43)	35 (49)	0.47
Nightmares, *n* (%)	32 (49)	35 (49)	0.99
Depression, *n* (%)	29 (45)	33 (46)	0.64
ESS	8.4 ± 3.9	8.1 ± 5.1	0.8
ISI	20.8 ± 3.3	20.2 ± 3.3	0.78
PCL	46.8 ± 10.2	48.5 ± 7.9	0.31
Polysomnography			
SOL, min	21.6 ± 24.0	34.2 ± 25.25	< 0.001
TST, min	301.2 ± 110.4	295.2 ± 92.4	0.79
SE, %	79.2 ± 6.4	76.8 ± 7.1	0.62
REM, %	0.19 ± 0.16	0.13 ± 0.13	0.04
Arousal index, 1/h	24.3 ± 12.8	29.1 ± 13.5	0.74

ESS, Epworth Sleepiness Scale; *ISI*, Insomnia Severity Index; *PCL*, PTSD Checklist; *SOL*, sleep onset latency; *TST*, total sleep time; *SE*, sleep efficiency

longer for veterans who failed to respond to CBT-I compared to those who had a favorable response ($p < 0.001$). Similarly, the percentage of total sleep time spent in REM was higher in CBT-I responders than CBT-I non-responders ($p = 0.04$). However, there was no difference in the total sleep time, sleep efficiency, or arousal index between the two groups.

Table 2 shows the list of psychotropic medications prescribed to veterans at the time CBT-I was initiated. There was no difference in the prescription rate of antidepressants or antipsychotics between CBT-I responders and CBT-I non-responders at baseline. However, 25% of veterans who had a favorable response to CBT-I were receiving a combination of trazodone and SSRI at baseline compared to 6% who had no improvement after CBT-I ($p = 0.002$). Conversely, the prescription rate of benzodiazepines and non-benzodiazepine GABA receptor agonists were significantly higher at baseline in the CBT-I non-responders group than the CBT-I responders ($p = 0.005$). Benzodiazepines and non-benzodiazepine GABA receptor agonists accounted for 87% and 13% of the total hypnotics respectively. The listed indications for the use of hypnotics included insomnia (68%), anxiety (24%), and PTSD (8%). Of interest, there was no significant difference in prazosin use between CBT-I responders and CBT-I non-responders (12% versus 6%, $p = 0.34$; respectively).

The dose equivalent of antidepressants/antipsychotics prior to CBT-I was comparable between the CBT-I responders and non-responders (27.3 ± 20.8 mg and 21.1 ± 20.7 mg, respectively; $p = 0.11$). Following CBT-I, the dose equivalent of antidepressants/anti-psychotics decreased in both groups but the difference was statistically significant only for those who had improvement in their insomnia scores (21.1 ± 19.8 mg and 17.4 ± 15.1, respectively; $p = 0.001$) (Fig. 2). As for hypnotics use, the diazepam equivalent dose was higher in the non-responders in comparison to responders both prior and after CBT-I ($p = 0.01$ and $p = 0.002$, respectively) but there was no change in the dose equivalent of hypnotics following CBT-I in either CBT-I responders or CBT-I non-responders compared to baseline ($p = 0.60$ and $p = 0.28$, respectively) (Fig. 3).

Using a multivariate analysis, younger age, non-White, and use of hypnotics prior to behavioral therapy were independently associated with lack of response to CBT-I (Table 3).

Discussion

The findings of the current study show that less than half of veterans with PTSD experience clinical improvement in insomnia 6-month after CBT-I. Although the rate of CBT-I attendance was comparable among responders and non-responders, age, race, and prior use of hypnotics were independently associated with CBT-I treatment response in veterans with PTSD.

The preponderance of insomnia research treatment outcome to date examining race and ethnicity has focused on broad patterns of mental health usage and its efficacy in the general population. Despite the evidence that CBT-I is an efficacious intervention for reducing insomnia, the majority of PTSD participants in these efficacy trials were identified as Caucasians [11, 25] leading to questions about whether these findings can be extrapolated to ethnical minorities. Our CBT-I protocol was based on established norms that have not been validated among veterans with diverse ethnic and racial background. In essence, there are no studies to our knowledge that have been designed to assess whether there is any difference in treatment effectiveness of CBT-I between Whites, ethnic or racial minorities. Recent meta-analyses revealed that individuals who are categorized as African Americans (AA) show consistently shorter sleep duration, poorer sleep efficiency, greater onset latency, and worse overall sleep quality relative to Whites [26, 27]. In particular, studies indicate shorter sleep duration, poorer sleep efficiency, greater onset latency, and worse overall sleep quality among AAs relative to Whites [26, 28]. However, it is unknown whether these sleep derangements are replicated in veterans with PTSD. More importantly, we have no data to assess whether the constructs of CBT-I in veterans with PTSD are affected by race and ethnical diversities. Previous studies examining depression in low-income

Table 2 Prescribed treatment for insomnia at presentation

	CBT-I responsive ($n = 65$)	CBT-I non responsive ($n = 71$)	p value
Antidepressants	29 (21)	39 (28)	0.23
SSRIs, *n* (%)	25 (38)	32 (45)	0.44
Trazodone, *n* (%)	20 (31)	11 (15)	0.03
Antipsychotics, *n* (%)	20 (31)	28 (39)	0.29
Quetiapine, *n* (%)	8 (12)	12 (17)	0.45
Mirtazapine, *n* (%)	4 (6)	4 (5)	0.89
Others, *n* (%)	8 (12)	12 (17)	0.45
Hypnotics*, *n* (%)	21 (32)	40 (56)	0.005

SSRI, selective serotonin reuptake inhibitors

*Hypnotics refer to benzodiazepines and non-benzodiazepine GABA receptor agonists

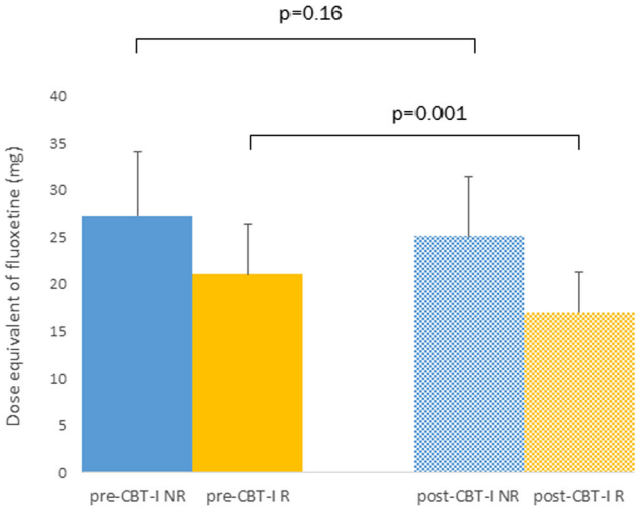

Fig. 2 Comparison of changes in fluoxetine dose equivalent between responders (R) and non-responders (NR) at baseline and at follow up. The graph also depicts the changes in each group of the fluoxetine dose equivalent from baseline to post intervention

African-American women found that interventions which relied on culturally adapted forms of CBT are more effective than non-adapted forms of CBT in terms of dropout rates and improvement in symptoms and functioning [29]. Hence, culturally adapted behavioral interventions may be more effective when these adaptations are specific or targeted to a particular racial/ethnic group [30]. However, in order to cross-culturally adapt survey instruments, a conceptual framework should be established based on the following milestones: (1) translation (backward, forward, and comparison), (2) qualitative analysis to assess the cultural competence or content validity of the translated survey instrument, and (3) field test and analyses to determine reliability and validity. Future studies also should examine, through mediational analyses and dismantling studies, whether the model of the cultural influences on the generation of insomnia in veterans with PTSD is accurate, and whether the interventions identified in the model lead to improvement.

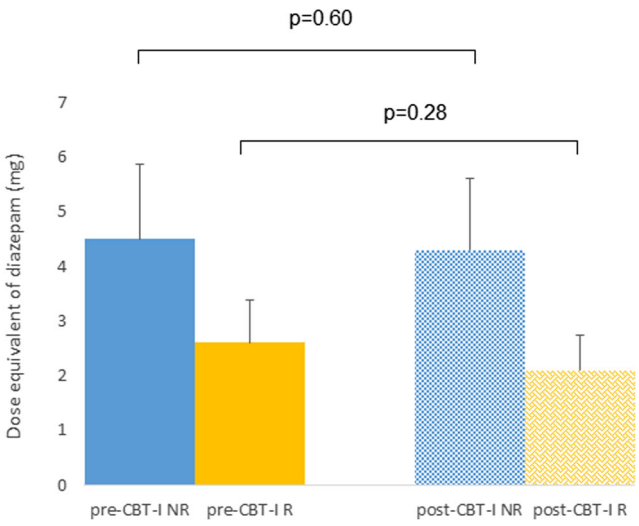

Fig. 3 Comparison of changes in diazepam dose equivalent between responders (R) and non-responders (NR) at baseline and at follow up. The graph also depicts the changes in each group of the fluoxetine dose equivalent from baseline to post intervention

In line with other investigations, we found that benzodiazepines and non-benzodiazepine GABA receptor agonists remain commonly prescribed in this population [31, 32]. Benzodiazepines and non-benzodiazepine GABA receptor agonists have historically been used as effective treatment for anxiety, irritability, and/or insomnia associated with PTSD. However, several randomized controlled trials have concluded that these agents, notably the benzodiazepines, are unlikely to be effective long-term hypnotics or anxiolytics [33, 34]. There is evidence to suggest that benzodiazepines may in fact increase posttraumatic behaviors upon subsequent exposure to stress, indicating that the fear-sensitizing effects of benzodiazepines may act synergistically with trauma-related fear, creating a generalized fear response to subsequent stressors [35, 36]. The most recent VA/DoD Clinical Practice Guideline for Management of Post-Traumatic Stress specifically recommended against long-term use of these drugs [37]. The findings of this study add to the significance of the VA/DoD guidelines by showing that benzodiazepines may also prohibit substantial benefit from CBT-I. Rather than augmenting psychotherapy, benzodiazepines seem to reduce or even inhibit recovery. Benzodiazepines can impair that experience by dulling emotions, decreasing learning efficiency, and inhibiting memory processing of material learned in therapy [38]. As such, benzodiazepines-induced emotional numbness directly interferes with the therapeutic effects of exposure to anxiety-provoking stimuli by inhibiting fear activation, a necessary step for effective behavioral therapy [39]. By hampering the ability to process these distressing events, resurgence of maladaptive behaviors serves only to perpetuate the cycle of insomnia. Accordingly, prescriptions of hypnotics in this population ought not to be considered unless behavioral therapy is deemed to be ineffective or unless the benefits of hypnotics outweigh their serious adverse effects. This recommendation, however, may not be applicable in cases where hypnotic agents are used as adjunct treatment with CBT-I. There is evidence to suggest that the addition of a hypnotic agent to CBT-I may produce incremental improvements of sleep latency, time awake after sleep onset, and sleep efficiency during initial therapy [40].

In our experience, veterans with PTSD are often resistant to attempts of reducing or withdrawing their hypnotic prescriptions [41] because the perception of loss of sleep quality with drug withdrawal produces a kind of dependence that overrides the long-term consequences of chronic benzodiazepine use. This hypothesis is further substantiated by the fact that we have not observed a reduction in the use of hypnotics among veterans with PTSD after completion of CBT-I despite

Table 3 Results of the logistic regression analysis identifying factors associated with lack of response to CBT-I

	Coefficient	Standard error	OR (95% CI)	*p* value
Age	− 0.043	0.016	0.95 (0.92–0.98)	0.001
Non-White	1.71	0.47	5.52 (2.19–13.95)	< 0.001
Use of hypnotics	1.25	0.40	3.49 (1.58–7.66)	0.002

amelioration in the severity of their insomnia. A prior randomized trial of CBT-I in chronic psychiatric conditions showed similarly no change in hypnotics use among hypnotic-dependent patients [42]. In contrast, we found a significant change in antidepressants use after CBT-I. Given that depression was a frequent diagnosis in our population, it is plausible that amelioration of insomnia in those who responded to CBT-I may have reduced the severity of depression, and thus the dosage of antidepressants. Although no quantifiable assessment of depression severity was recorded pre- or post-CBT-I in this study, a randomized controlled study of 30 patients with both major depression disorder and insomnia showed that augmenting an antidepressant with a brief, symptom focused, CBT-I in patients with major depressive disorder produced higher remission rates for both depression and insomnia [43].

It has been alluded recently that the impact of cognitive processes on subjective sleep parameters may be dependent on objective sleep duration. A short sleep duration of 6 h or less was associated with a blunted response to CBT-I compared to individuals with insomnia and objective normal sleep duration above 6 h [44]. We were not able to ascertain any difference in insomnia severity outcome based on PSG-measured sleep duration between CBT-I responders and CBT-I non responders. This inconsistency may be attributed to the fact that the distinction between short and normal sleep duration has been established in patients with primary insomnia, a condition representing less than 10% of our study sample.

Admittedly, this study had several limitations that merit consideration. First, the overall sample size is relatively small and this may limit the generalizability of our results. Because of the retrospective design of the study, we may have missed a number of factors that could influence the treatment outcome. Second, the CBT-I model administered in our sleep clinics was delivered via individual therapy sessions. We might have obtained different findings with group treatment models or individual treatment sessions supplemented by programmed self-help or interactive internet-based interventions. Third, the participants in our study were recruited and selected based on insomnia defining criteria according to the DSM-IV and DSM-5 which may introduce heterogeneity into the study population. In DSM-5, the criteria to meet insomnia disorder require that the sleep problems have to occur at least 3 days per week and be present for at least 3 months [45], while for DSM-IV, symptoms had to be present for at least 1 month with no set minimum amount of days per week specified, although in clinical practice, a minimum of 3 days per week was conventional. From the chart reviews, all of the participants in our study suffered from self-reported insomnia at least 3 days a week and for 3 or more months thus satisfying the criteria for insomnia disorder according to the DSM-5 hence reducing any significant differences in the diagnostic criteria for insomnia between DSM-IV and DSM-5. Fourth, the findings in this study were mostly related to patients with insomnia predominantly related to other mental disorders and may not be applicable to veterans with primary insomnia. Further evaluation may be warranted when it comes to other types of insomnia. Fifth, prior studies have established that insomnia in subjects with PTSD may be driven by the frequency and intensity of nightmares common in PTSD [11, 46]. Despite the comparable nightmare prevalence between CBT-I responders and CBT-I non-responders in our population, a complete assessment of the severity of nightmares was not available in the medical records. In addition, we cannot exclude the possibility that nightmare severity may have contributed to lack of CBT-I response. Lastly, we have used the last observation carried forward for missing values. This assumption may introduce biased treatment effects when this assumption is not justified [47].

In conclusion, our results indicate that in veterans with PTSD and insomnia, variation in the clinical response to CBT-I may be accounted for by differences in age and ethnocultural factors. Although it may be tempting to treat PTSD-associated insomnia with hypnotics, benzodiazepines, and non-benzodiazepines GABA receptor agonists may blunt the benefits of CBT-I, and are best to be avoided due to evidence of long-term risks outweighing evidence of any short-term benefits.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. Funding: The study was partially supported by the US VA Office of Research and Development, Department of Veterans Affairs, Clinical Service Research and Development (CX001656)

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the

institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A waiver of informed consent was granted by the Institutional Review Board because of the retrospective study design.

Disclaimer The contents of this paper do not represent the views of the Department of Veterans Affairs or the United States Government.

References

1. Baird T, McLeay S, Harvey W, Theal R, Law D, O'Sullivan R, Initiative P (2018) Sleep disturbances in Australian Vietnam veterans with and without posttraumatic stress disorder. J Clin Sleep Med 14(5):745–752. https://doi.org/10.5664/jcsm.7096
2. Maher MJ, Rego SA, Asnis GM (2006) Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact and approaches to management. CNS drugs 20(7):567–590. https://doi.org/10.2165/00023210-200620070-00003
3. Amin MM, Parisi JA, Gold MS, Gold AR (2010) War-related illness symptoms among operation Iraqi freedom/operation enduring freedom returnees. Mil Med 175(3):155–157
4. Seelig AD, Jacobson IG, Smith B, Hooper TI, Boyko EJ, Gackstetter GD, Gehrman P, Macera CA, Smith TC, Millennium Cohort Study T (2010) Sleep patterns before, during, and after deployment to Iraq and Afghanistan. Sleep 33(12):1615–1622
5. Hughes JM, Ulmer CS, Gierisch JM, Nicole Hastings S, Howard MO (2018) Insomnia in United States military veterans: an integrated theoretical model. Clin Psychol Rev 59:118–125. https://doi.org/10.1016/j.cpr.2017.11.005
6. Applewhite L, Keller N, Borah A (2012) Mental health care use by soldiers conducting counterinsurgency operations. Mil Med 177(5):501–506
7. Wright KM, Britt TW, Bliese PD, Adler AB, Picchioni D, Moore D (2011) Insomnia as predictor versus outcome of PTSD and depression among Iraq combat veterans. J Clin Psychol 67(12):1240–1258. https://doi.org/10.1002/jclp.20845
8. McLay RN, Klam WP, Volkert SL (2010) Insomnia is the most commonly reported symptom and predicts other symptoms of post-traumatic stress disorder in U.S. service members returning from military deployments. Mil Med 175(10):759–762
9. Hoge EA, Austin ED, Pollack MH (2007) Resilience: research evidence and conceptual considerations for posttraumatic stress disorder. Depress Anxiety 24(2):139–152. https://doi.org/10.1002/da.20175
10. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Clinical Guidelines Committee of the American College of P (2016) Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med 165(2):125–133. https://doi.org/10.7326/M15-2175
11. Talbot LS, Maguen S, Metzler TJ, Schmitz M, McCaslin SE, Richards A, Perlis ML, Posner DA, Weiss B, Ruoff L, Varbel J, Neylan TC (2014) Cognitive behavioral therapy for insomnia in posttraumatic stress disorder: a randomized controlled trial. Sleep 37(2):327–341. https://doi.org/10.5665/sleep.3408
12. Espie CA, Inglis SJ, Harvey L (2001) Predicting clinically significant response to cognitive behavior therapy for chronic insomnia in general medical practice: analysis of outcome data at 12 months posttreatment. J Consult Clin Psychol 69(1):58–66
13. Troxel WM, Conrad TS, Germain A, Buysse DJ (2013) Predictors of treatment response to brief behavioral treatment of insomnia (BBTI) in older adults. J Clin Sleep Med 9(12):1281–1289. https://doi.org/10.5664/jcsm.3270
14. Gagne A, Morin C (2001) Predicting treatment response in older adults with insomnia. J Clin Geropsychol 7:131–143
15. Hayasaka Y, Purgato M, Magni LR, Ogawa Y, Takeshima N, Cipriani A, Barbui C, Leucht S, Furukawa TA (2015) Dose equivalents of antidepressants: evidence-based recommendations from randomized controlled trials. J Affect Disord 180:179–184. https://doi.org/10.1016/j.jad.2015.03.021
16. Lieberman JA, Tasman, A. (2006) Handbook of psychiatric drugs. John Wiley & Sons Incorporated,
17. Perlis M, Jungquist C, Smith M, Posner D (2005) The cognitive behavioral treatment of insomnia: a treatment manual. Springer Verlag, New York
18. Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14(6):540–545
19. Weathers F, Litz B, Herman D, Huska J, Keane T (1993) The PTSD checklist: reliability, validity, & diagnostic utility. Paper presented at the Annual Meeting of the Internation Society of Traumatic Stress Studies, San Antonio, TX,
20. Bastien CH, Vallieres A, Morin CM (2001) Validation of the insomnia severity index as an outcome measure for insomnia research. Sleep Med 2(4):297–307
21. Pietrzak RH, Tsai J, Armour C, Mota N, Harpaz-Rotem I, Southwick SM (2015) Functional significance of a novel 7-factor model of DSM-5 PTSD symptoms: results from the National Health and resilience in veterans study. J Affect Disord 174:522–526. https://doi.org/10.1016/j.jad.2014.12.007
22. Armour C, Tsai J, Durham TA, Charak R, Biehn TL, Elhai JD, Pietrzak RH (2015) Dimensional structure of DSM-5 posttraumatic stress symptoms: support for a hybrid anhedonia and externalizing behaviors model. J Psychiatr Res 61:106–113. https://doi.org/10.1016/j.jpsychires.2014.10.012
23. Yang M, Morin CM, Schaefer K, Wallenstein GV (2009) Interpreting score differences in the insomnia severity index: using health-related outcomes to define the minimally important difference. Curr Med Res Opin 25(10):2487–2494. https://doi.org/10.1185/03007990903167415
24. Baraldi AN, Enders CK (2010) An introduction to modern missing data analyses. J Sch Psychol 48(1):5–37. https://doi.org/10.1016/j.jsp.2009.10.001
25. DeViva JC, Zayfert C, Pigeon WR, Mellman TA (2005) Treatment of residual insomnia after CBT for PTSD: case studies. J Trauma Stress 18(2):155–159. https://doi.org/10.1002/jts.20015
26. Petrov ME, Lichstein KL (2016) Differences in sleep between black and white adults: an update and future directions. Sleep Med 18:74–81. https://doi.org/10.1016/j.sleep.2015.01.011
27. Ruiter ME, DeCoster J, Jacobs L, Lichstein KL (2010) Sleep disorders in African Americans and Caucasian Americans: a meta-analysis. Behav Sleep Med 8(4):246–259. https://doi.org/10.1080/15402002.2010.509251
28. Ruiter ME, Decoster J, Jacobs L, Lichstein KL (2011) Normal sleep in African-Americans and Caucasian-Americans: a meta-analysis. Sleep Med 12(3):209–214. https://doi.org/10.1016/j.sleep.2010.12.010
29. Kohn LP, Oden T, Munoz RF, Robinson A, Leavitt D (2002) Adapted cognitive behavioral group therapy for depressed low-income African American women. Community Ment Health J 38(6):497–504
30. Benish SG, Quintana S, Wampold BE (2011) Culturally adapted psychotherapy and the legitimacy of myth: a direct-comparison meta-analysis. J Couns Psychol 58(3):279–289. https://doi.org/10.1037/a0023626
31. Lund BC, Abrams TE, Bernardy NC, Alexander B, Friedman MJ (2013) Benzodiazepine prescribing variation and clinical uncertainty in treating posttraumatic stress disorder. Psychiatr Serv 64(1):21–27. https://doi.org/10.1176/appi.ps.201100544

32. Lund BC, Bernardy NC, Vaughan-Sarrazin M, Alexander B, Friedman MJ (2013) Patient and facility characteristics associated with benzodiazepine prescribing for veterans with PTSD. Psychiatr Serv 64(2):149–155. https://doi.org/10.1176/appi.ps.201200267
33. Cates ME, Bishop MH, Davis LL, Lowe JS, Woolley TW (2004) Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. Ann Pharmacother 38(9):1395–1399. https://doi.org/10.1345/aph.1E043
34. Guina J, Rossetter SR, De RB, Nahhas RW, Welton RS (2015) Benzodiazepines for PTSD: a systematic review and meta-analysis. J Psychiatr Pract 21(4):281–303. https://doi.org/10.1097/PRA.0000000000000091
35. Matar MA, Zohar J, Kaplan Z, Cohen H (2009) Alprazolam treatment immediately after stress exposure interferes with the normal HPA-stress response and increases vulnerability to subsequent stress in an animal model of PTSD. Eur Neuropsychopharmacol 19(4):283–295. https://doi.org/10.1016/j.euroneuro.2008.12.004
36. Li S, Murakami Y, Wang M, Maeda K, Matsumoto K (2006) The effects of chronic valproate and diazepam in a mouse model of posttraumatic stress disorder. Pharmacol Biochem Behav 85(2):324–331. https://doi.org/10.1016/j.pbb.2006.08.015
37. Group MoP-TSW (2017) VA/DoD clinical practice guidelines for management of post-traumatic stress. Washington, DC
38. Rosen CS, Greenbaum MA, Schnurr PP, Holmes TH, Brennan PL, Friedman MJ (2013) Do benzodiazepines reduce the effectiveness of exposure therapy for posttraumatic stress disorder? J Clin Psychiatry 74(12):1241–1248. https://doi.org/10.4088/JCP.13m08592
39. van Minnen A, Arntz A, Keijsers GP (2002) Prolonged exposure in patients with chronic PTSD: predictors of treatment outcome and dropout. Behav Res Ther 40(4):439–457
40. Morin CM, Vallieres A, Guay B, Ivers H, Savard J, Merette C, Bastien C, Baillargeon L (2009) Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. JAMA 301(19):2005–2015. https://doi.org/10.1001/jama.2009.682
41. Park K, Kim T, Kim W, An S, Lee E (2018) Cognitive behavioral therapy for insomnia reduces hypnotic prescriptions. Psychiatry Investig 2018:499–504
42. Taylor HL, Rybarczyk BD, Nay W, Leszczyszyn D (2015) Effectiveness of a CBT intervention for persistent insomnia and hypnotic dependency in an outpatient psychiatry clinic. J Clin Psychol 71(7):666–683. https://doi.org/10.1002/jclp.22186
43. Manber R, Edinger JD, Gress JL, San Pedro-Salcedo MG, Kuo TF, Kalista T (2008) Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. Sleep 31(4):489–495
44. Bathgate CJ, Edinger JD, Krystal AD (2017) Insomnia patients with objective Short sleep duration have a blunted response to cognitive behavioral therapy for insomnia. Sleep 40(1). https://doi.org/10.1093/sleep/zsw012
45. Association AP (2013) Diagnostic and statistical manual of mental disorders. 5th edition edn., Washington, DC
46. Short NA, Allan NP, Stentz L, Portero AK, Schmidt NB (2018) Predictors of insomnia symptoms and nightmares among individuals with post-traumatic stress disorder: an ecological momentary assessment study. J Sleep Res 27(1):64–72. https://doi.org/10.1111/jsr.12589
47. Molnar F, Man-Son-Hing M, Hutton B, Fergusson D (2009) Have last-observation-carried-forward analyses caused us to favour more toxic dementia therapies over less toxic alternatives? A systematic review. Open Med 3:e31–e50