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## “Posttraumatic stress disorder risk and benzodiazepine dependence in older veterans with insomnia symptoms”

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### Abstract

**Objectives:** To measure the rate of benzodiazepine receptor agonist (BZA) dependence in older veterans with insomnia symptoms chronically using BZAs and to assess for associations between high posttraumatic stress disorder (PTSD) risk and BZA dependence.

**Methods:** Cross-sectional study conducted among veterans aged 55 years and older with insomnia symptoms (current or historical) and chronic use of BZAs (> 3 months). Measurements included the Primary Care-PTSD screen (score > 2 indicates high PTSD risk) and Benzodiazepine Dependence Questionnaire. Logistic regression was used to test for associations between PTSD risk and BZA dependence.

**Results:** High PTSD risk was observed in 40% of participants (N=33). One-fifth (21.7%, N=18) of participants met the criteria for benzodiazepine dependence (score ≥ 3 on Benzodiazepine

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- Sara Ghadimi: interpretation of data, drafting of manuscript, final approval, accountable for all aspects
- Alexandra Krall, BA: conception/design of work, acquisition of data, revision of manuscript, final approval, accountable for all aspects
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- Constance H. Fung, MD, MSHS: analysis, interpretation of data, drafting of manuscript, final approval of manuscript, accountable for all aspects

Data availability statement: This data set is part of an ongoing clinical trial and resides at the institutions affiliated with the clinical trial.

Dependence Questionnaire). Veterans with high PTSD risk were significantly more likely to have BZA dependence (odds ratio 10.09, 95% CI [2.39, 42.54],  $p=.002$ ).

**Conclusions:** In older veterans with insomnia symptoms and chronic use of BZAs, high PTSD risk is associated with elevated risk for BZA dependence, which may make discontinuation of these medications difficult.

**Clinical Implications:** Clinicians should consider the strong association between PTSD symptoms and benzodiazepine dependence when developing plans to taper a BZA in veterans with these symptoms.

### Keywords

benzodiazepines; posttraumatic stress disorder; substance use

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### Introduction

Posttraumatic stress disorder (PTSD) affects 2–15% of primary care and 25% of Veterans Affairs (VA) clinic patients (Greene et al., 2016). PTSD is characterized by intrusive symptoms (e.g., nightmares, flashbacks), avoidance behaviors, negative cognitions and mood, and hyperarousal that continues for more than one month after a significant traumatic event. Benzodiazepines and benzodiazepine receptor agonists (BZAs) are often used to address PTSD symptoms such as anxiety and nightmares. Although BZA prescriptions may provide some benefit, limits to their usefulness are well-documented. In a meta-analysis, patients taking BZAs reported better sleep on the first night, but not on subsequent nights (Guina et al., 2015). Some studies have found that BZAs are no better than placebos in helping with PTSD-related insomnia and may even interrupt natural fear extinction after a traumatic event (Lipinska et al., 2016). Despite these limitations and the availability of excellent treatments for PTSD (Cook et al., 2017) (as well as for insomnia (Martin et al., 2017)), BZAs are still some of the most prescribed drugs in the United States.

BZA use is especially common in older adults and veterans, with individuals aged 50 years receiving the highest number of BZA prescriptions (Cook et al., 2018). This is concerning given the possibility of serious adverse effects (e.g., cognitive impairment & hip fractures), the high prevalence of polypharmacy, and potential for drug-drug interactions with BZAs in older adults. Among veterans, factors associated with receiving BZA prescriptions include time since their first PTSD diagnosis (where 36% of those with 3 year history of PTSD used a BZA), service-connected disability, and serving during the Vietnam War era (Lund et al., 2013). Additional predictors of receiving a BZA prescription are white race and higher education level (Cook et al., 2018).

Given the risks associated with BZAs in older adults and veterans, researchers have examined predictors of BZA dependence. A study conducted in adults who receive care from an urban healthcare system found that predictors of BZA dependence include use of pain medication and concurrent PTSD, bipolar disorder, psychosis, anxiety, or sleep disturbance (Cook et al., 2018). In this same study, White and Asian individuals who have

a BZA prescription are at a greater risk of becoming dependent than Black and Latino individuals, but age and sex are not predictors of dependence.

With the aging of the Vietnam-era Veterans, there are now high rates of PTSD among older veterans. Given the numerous concerns associated with BZA use in late-life, our study goal was to measure rates of BZA dependence in older veterans with insomnia symptoms who endorsed chronic hypnotic use and to assess whether high PTSD risk is associated with BZA dependence in older veterans. We hypothesized that high PTSD risk would be associated with high risk of BZA dependence.

## Methods

Veterans aged  $\geq 55$  years who receive healthcare through one VA facility in a large urban area and endorse chronic hypnotic use ( $\geq 3$  months) and insomnia symptoms (current or historical) were recruited for participation in an ongoing comparative effectiveness trial ([NCT03687086](#)) testing two methods of tapering BZAs. This clinical trial has been approved by the local institutional review board. For the analysis presented in this paper, we used baseline data that were collected from February 2019 to September 2020 to determine eligibility for the aforementioned trial. Demographic characteristics (age, gender, education, race/ethnicity) were collected, along with other variables pertaining to trial eligibility, including but not limited to PTSD symptoms, BZA dependence, and sleep quality.

PTSD risk was assessed using the Primary Care-PTSD Screen (PC-PTSD). This tool uses 4 questions based on Diagnostic and Statistical Manual-IV PTSD symptoms to assess whether the participant has experienced any PTSD symptoms related to exposures to traumatic events. Participants received a total score ranging from 0 to 4 based on the number of questions they endorsed (1 point for each “yes” answer to the 4 questions). Participants with a score  $> 2$  were classified as high risk for PTSD, based on prior evidence that this cut-off score is optimally sensitive for identifying veterans who meet diagnostic criteria for PTSD (Prins et al., 2016).

BZA dependence was assessed using the Benzodiazepine Dependence Questionnaire (BDEPQ) (Baillie & Mattick, 1996), a 30-item self-reported questionnaire that measures dependence on benzodiazepines, tranquilizers, sedatives and hypnotics. For the current study, we used a previously reported cut-off score of 23 or higher to define positive BZA dependence, with 23 being an accepted value for differentiating between patients with and without benzodiazepine dependence (Minaya et al., 2011).

Sleep quality, which is a predictor of BZA dependence (Cook et al., 2018), was assessed using the Pittsburgh Sleep Quality Index (PSQI) total score (Buysse et al., 1989), a 19-item questionnaire that assesses sleep quality and disturbances over a 1-month time period (0–21 range, with higher scores [i.e., scores  $> 5$ ] indicating worse sleep quality).

Chi-square analyses were used to evaluate group differences (PTSD risk and BZA dependence), and logistic regression was used to test for associations between PTSD risk (predictor of interest) and BZA dependence (dependent variable), adjusting for sleep quality,

age, gender, ethnicity and years of education. All statistical analyses were conducted using Stata v.15.1 (StataCorp, College Station, Texas).

## Results

Participants (N = 83) were mostly male (95%). The mean age was 70 years (SD = 9.1). Most participants were Non-Hispanic White (60.2%), with 24.1% of the sample identifying as African American/Black and 12.1% as Hispanic/Latino. Most participants were retired (69.9%) and married (49.4%). The mean years of education was 15.3 years (SD= 2.9). The mean PSQI total score was 9.2 (SD=2.6).

A PC-PTSD score > 2 was observed in 39.8% of participants (N=33). One-fifth (21.7% of participants) scored 23 or higher on the BDEP (N=18).

Pearson chi-squared analyses showed significant differences between participants with a PC-PTSD > 2 (high PTSD risk) versus ≤ 2 (low PTSD risk) in dichotomized BDEP (≥ 23 versus < 23), with 66.7% of participants with a high risk PC-PTSD scoring positive on the BDEP versus 33.3% of participants with a low risk PC-PTSD score (chi-squared = 6.95, p=.008).

In a logistic regression model (Table 1), a PC-PTSD score > 2 was associated with increased odds for scoring 23 or higher on the BDEP (odds ratio 10.09, 95% CI [2.39, 42.54]; p=.002), after adjusting for PSQI total score, gender, age, race/ethnicity, and years of education.

## Discussion

In this sample of older Veterans, we found that nearly 40% of the sample had probable PTSD, and over 20% of the sample had BZA dependence on a validated scale. Veterans scoring as high risk for PTSD had 10 times the odds as those with low risk for scoring above the clinical cutoff for BZA dependence. Given that prescribing BZAs to individuals for PTSD-related symptoms is a common yet controversial practice, this finding further highlights the potential hazards associated with this approach. The VA Practice Guideline for the Management of PTSD strongly recommends against the routine use of benzodiazepines in veterans with PTSD, citing the unproven efficacy of benzodiazepine treatment and the risks for abuse and dependence. Our findings also provide important implications for deprescribing efforts, which are increasingly recommended, considering the associations between BZA use and adverse outcomes in older adults. Based on this study's findings, deprescribing efforts may need to consider concomitant PTSD symptoms and BZA dependence, in addition to approaches that result in patients valuing the greater treatment benefits and longevity offered by non-BZA treatments over the immediate symptom relief associated with BZAs.

Our study did not find evidence of statistically significant associations between demographics (e.g., age, race, gender, years of education) or sleep quality and screening positive for BZA dependence, in contrast to other studies. While this finding may not align with the findings of previous research (Cook et al., 2018), the scope of previous research on BZA dependence has not focused solely on older veterans. American military veterans

are a unique population, and older veterans are now comprised primarily of individuals who served during the Vietnam conflict. As a result, the older veteran population includes individuals with a host of physical and mental health conditions dating back to their years of service in the 1960's and 1970's coupled with common diseases that emerge with age such as hypertension, diabetes, and cognitive disorders..

Limitations of this study include the cross-sectional study design which does not allow for inference of causality, and a relatively small sample size which may have resulted in reduced power to detect statistical significance. Additionally, most participants are male as typical in the veteran population, limiting generalizability to older female veterans. Also, this study used a screening tool for PTSD that was designed for use in a primary care setting to indicate probable PTSD, rather than a formal diagnostic assessment of or assessment of PTSD symptom severity. The screening tool does not account for medication use, substance use, and other medical or mental health disorders that may mirror the symptoms of PTSD. Because our study utilized baseline data collected for a clinical trial, the information and variables we had available for analysis were limited. We were unable to account for other variables that may help further explain the findings (e.g., length of time spent in the service, frequency of exposure to traumatic events, duration of BZA use).

Future research that focuses on BZA dependence in older adults and veterans, particularly those with mental health comorbidities, is needed. This information may not only inform prescribing practices for those who work with and treat older adults and veterans with PTSD, but it may also enhance BZA deprescribing efforts in those with mental health conditions.

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### Clinical Implications

- Clinicians caring for older veterans who have insomnia symptoms and use a BZA should consider assessing for BZA dependence.
- Clinicians should consider the strong association between PTSD symptoms and benzodiazepine dependence when developing plans to taper a BZA in veterans with these symptoms.



**Table 1.**

Logistic regression model: benzodiazepine dependence screen positivity (N=83)

Variable	Odds Ratio (95% Confidence Interval)	P-value
PC-PTSD score > 2	10.09 (2.39, 42.54)	.002*
PSQI Total Score	0.82 (0.63, 1.05)	.11
Male	1.87 (0.11, 32.56)	.67
Age (55–65 years old)	0.52 (0.41, 9.05)	.41
Non-Hispanic White	2.20 (0.54, 9)	.27
Years of Education	0.96 (0.77, 1.18)	.67

\*p<.05; PC-PTSD=Primary Care-Posttraumatic Stress Disorder; PSQI=Pittsburgh Sleep Quality Index

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