Hospitalization Risk With Benzodiazepine and Opioid Use in Veterans With Posttraumatic Stress Disorder

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Combat veterans with PTSD who are prescribed benzodiazepines and/or opioids in addition to first-line pharmacotherapy are at significantly increased risk for hospitalization.

Posttraumatic stress disorder (PTSD) is a mental health condition that may develop in response to a traumatic event, such as that experienced by a soldier during active combat duty. In 2009, more than 495,000 veterans within the VA health care system were treated for PTSD—nearly triple the number a decade earlier.[1] Core symptoms of PTSD include alterations in arousal and reactivity, avoidant behaviors, negative alterations in mood and cognition, and intrusive thoughts and nightmares. All of the symptoms can be debilitating. First-line pharmacotherapy options that target these core symptoms include selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).[2]

The anxiolytic and sedative effects of benzodiazepines may provide quick relief from many of the secondary symptoms of PTSD, including sleep disturbances, irritability, and panic attacks. However, benzodiazepines potentially interfere with the extinction of conditioned fear—a goal integral to certain types of psychotherapy, such as exposure therapy.[3,4] In addition, the systematic review and meta-analysis by Guina and colleagues revealed that benzodiazepines are ineffective in the treatment of PTSD.[5] The majority of the evaluated studies that used PTSD-specific measures (eg, Clinician-Administered PTSD Scale [CAPS]) found increased PTSD severity and worse prognosis with use of these medications.[5] In 2010, the VA and the DoD released a joint guideline for PTSD management.[2] According to the guideline, benzodiazepines cause harm when used in PTSD and are relatively contraindicated in combat veterans because of the higher incidence of comorbid substance use disorders (SUDs) in these veterans relative to the general population.[2,6]

Opioid use also has been linked to poor functional and clinical outcomes in veterans with PTSD. Among patients being treated for opioid use disorder, those with PTSD were less likely to endorse employment as a main source of income and had a higher incidence of recent attempted suicide.[7] In a large retrospective cohort study, Operation Iraqi Freedom and Operation Enduring Freedom veterans with PTSD who were prescribed opioids were more likely to present to the emergency department (ED) and to be hospitalized for overdoses and injuries.[8]

Despite the risks of benzodiazepine and opioid use in this patient population, these medications are still often prescribed to veterans with PTSD for symptomatic relief. In fiscal year 2009, across the VHA system 37% of veterans diagnosed with PTSD were prescribed a benzodiazepine, 69% of the time by a mental health provider.[9] Among Iraq and Afghanistan veterans, those with PTSD were significantly more likely to be prescribed an opioid for diagnosed pain—relative to those with a mental health disorder other than PTSD and those without a mental

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Table 1. Baseline Characteristics

Characteristics	SSRI/SNRI (n = 456)	SSRI/SNRI + Benzodiazepine (n = 81)	SSRI/SNRI + Opioid (n = 62)	SSRI/SNRI + Benzodiazepine + Opioid (n = 14)
Mean age, y	49	46	51	49
Female, n (%)	29 (6)	8 (10)	7 (11)	5 (36)[a]
Mental health disorder, n (%)				
Depression	258 (57)	45 (56)	31 (50)	6 (43)
Anxiety	66 (15)	34 (42)[a]	6 (10)	5 (36)
Bipolar disorder	11 (2)	5 (6)	1 (2)	2 (14)[b]
Schizophrenia	0 (0)	1 (1)	0 (0)	0 (0)
Substance use disorder, n (%)	147 (32)	21 (26)	16 (26)	4 (29)
Insomnia, n (%)	210 (46)	52 (65)[a]	12 (19)[a]	5 (36)
Pain, n (%)	170 (37)	28 (35)	57 (92)[a]	13 (93)[a]
Psychotropic medications, n (%)				
Other Antidepressant	28 (6)	9 (11)	1 (2)	1 (7)
Mood stabilizer	15 (3)	6 (7)	2 (3)	1 (7)
Anxiolytic	10 (2)	3 (4)	6 (10)[a]	1 (7)
Antipsychotic	28 (6)	6 (7)	7 (11)	4 (29)[a]
Sedative/hypnotic	107 (24)	17 (21)	19 (31)	1 (7)

Abbreviations: SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitors.
[a]$P < .01$ compared with SSRI/SNRI group.
[b]$P < .05$ compared with SSRI/SNRI group.

health disorder.[8] Thus, there seems to be a disconnect between guideline recommendations and current practice.

The authors conducted a study to assess the potential risk of hospitalization for veterans with PTSD prescribed first-line pharmacotherapy and those also prescribed concurrent benzodiazepine and/or opioid therapy since the release of the PTSD guideline in 2010.[2]

METHODS

In this retrospective cohort study, conducted at the Southern Arizona VA Health Care System (SAVAHCS), the authors analyzed electronic medical record data from November 1, 2009 to August 1, 2015. Study inclusion criteria were veteran, aged 18 to 89 years, diagnosis of PTSD (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 309.81), and SSRI or SNRI newly prescribed between November 1, 2010 and August 1, 2013.

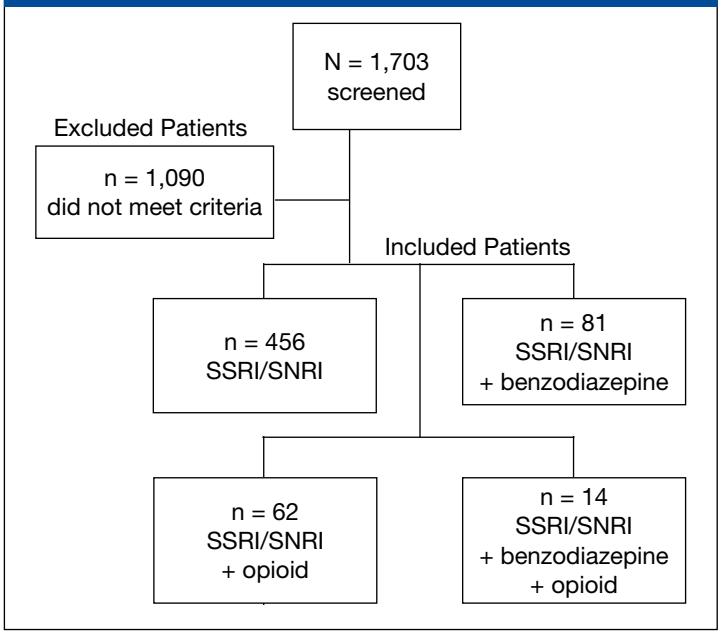
Any veteran prescribed at least one 30-day or longer supply of any benzodiazepine or opioid within 1 year before the SSRI/SNRI initial prescription date was excluded from the study. Also excluded was any patient treated for PTSD at a facility outside SAVAHCS or whose 2-year evaluation period extended past August 1, 2015.

Study Groups

An outpatient prescription was determined to be the initial SSRI/SNRI prescription for a patient who received less than a 30-day cumulative supply of any SSRI or SNRI within 1 year before that prescription date. Citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, paroxetine, sertraline, venlafaxine, vilazodone, and vortioxetine were the prespecified SSRI/SNRIs included in the study.

Patients who received at least 1 outpatient prescription for any benzodiazepine (minimum 30-day supply) within

Figure 1. Patient Flowchart



Abbreviations: SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

1 year after the initial SSRI/SNRI prescription date were determined to be on concurrent SSRI/SNRI and benzodiazepine therapy. Alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam were the prespecified benzodiazepines included in the study.

Patients who received at least 1 outpatient prescription for any opioid (minimum 30-day supply) within 1 year after the initial SSRI/SNRI prescription date were determined to be on concurrent SSRI/SNRI and opioid therapy. Codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxymorphone, pentazocine, propoxyphene, and tramadol were the prespecified opioids included in this study.

Patients who received at least 1 outpatient prescription for any benzodiazepine and any opioid (minimum 30-day supply) within 1 year after the initial SSRI/SNRI prescription date were determined to be on concurrent SSRI/SNRI, benzodiazepine, and opioid therapy.

The index date was defined as the first date of prescription overlap. If there was no benzodiazepine or opioid prescription within 1 year after the initial SSRI/SNRI prescription date, the patient was categorized as being on SSRI/SNRI monotherapy, and the index date was the date of the initial SSRI/SNRI prescription. For each patient, hospitalization data from the 2-year period after the index date were evaluated.

Outcomes and Data Collection

For evaluation of the primary outcome (2-year overall hospitalization risk), the number of unique mental health and medical/surgical hospitalizations was identified by the number of discharge summaries documented in the patient chart during the evaluation period. Time to first hospitalization was recorded for the survival data analysis. Secondary outcomes were mental health hospitalization risk, medical/surgical hospitalization risk, and all-cause mortality within 2 years.

Demographic data that were collected included age, sex, comorbid mental health disorders, comorbid SUDs, and concomitant use of psychotropic medications at index date (baseline). Select comorbid mental health disorders (anxiety, schizophrenia, depression, bipolar disorder) and substance use disorders (alcohol, opioid, illicit drug) also were identified. Data on insomnia and pain comorbidities (headaches or migraines; neuropathy; head, neck, back, arthritis, or joint pain) were collected, as these comorbidities could be indications for prescribing benzodiazepines and opioids. Concomitant baseline use of classes of psychotropic medications (antipsychotics, non-SSRI/SNRI antidepressants, mood stabilizers, anxiolytics, nonbenzodiazepine sedatives/hypnotics) also were documented. Last, hospitalizations within 6 months before the initial SSRI/SNRI prescription date were noted.

Statistical Analysis

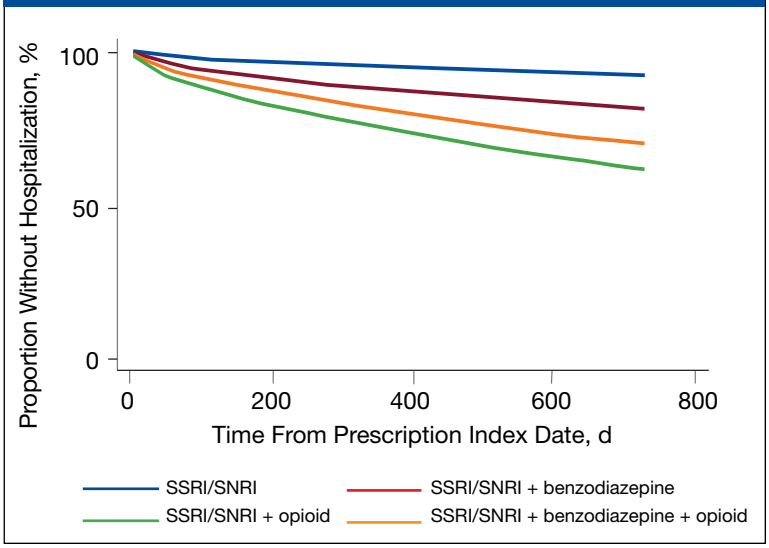
Descriptive statistics were used to analyze all baseline demographic data. Continuous measures were evaluated with 1-way analyses of variance and post hoc Bonferroni-corrected pairwise comparisons, and categorical measures with contingency tables and χ^2 tests or Fisher exact tests. When the overall χ^2 test was significant across all 4 study groups, post hoc comparisons were performed between the SSRI/SNRI monotherapy group and each other group with Bonferroni adjusted for 3 comparisons.

Unadjusted and adjusted Weibull proportional hazard regression models were used to estimate hospitalization risk within 2 years after the index date for the different study groups with the SSRI/SNRI monotherapy group as the referent. Robust standard errors were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

The Weibull model (and not the Cox model) was used because it does not assume hazard remains constant over time, which is appropriate in this instance, as the risk of an adverse event (AE) may be higher when first starting a medication or combination of medications relative to when doses are stabilized. Models were adjusted for age, sex, baseline mental health disorders, and baseline psychotropic medications. As earlier hospitalizations showed evidence of effect modification when this covariate was tested, hazard analyses were limited to patients not previously hospitalized.

The effect size of differences in hospitalization risk meeting statistical significance was assessed by estimating the number needed to harm (NNH) and 95% CIs (not shown) to observe 1 additional hospitalization in each medication group relative to the SSRI/SNRI monotherapy group over a 90-day period. A 95% CI for NNH that did not include 0 indicated the NNH was significant at the .05 level.[10] All-cause mortality was evaluated with the Fisher exact test with post hoc Bonferroni-corrected comparisons as appropriate.

Figure 2. Survival Curve for Overall Hospitalizations Within 2 Years[a]



Abbreviations: SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]Excludes patients hospitalized within 6 months before index date.

RESULTS

Of 1,703 patients screened, 613 met all study inclusion criteria (Figure 1). Most excluded patients had been prescribed an SSRI or SNRI by a non-VA provider or another VA facility and were transferring care to SAVAHCS; they were not true "new starts" on an SSRI or SNRI for PTSD.

Baseline characteristics revealed no significant differences between groups in age or comorbid depression, schizophrenia, or SUDs (Table 1). Concomitant use of a non-SSRI/SNRI antidepressant and a mood stabilizer was also similar across groups. Rates of anxiety and insomnia were higher in the SSRI/SNRI and benzodiazepine therapy group than in the SSRI/SNRI monotherapy group. As expected, rates of comorbid pain were higher in the 2 groups on concurrent opioid therapy. The proportion of female patients and the incidence of bipolar disorder and antipsychotic use were higher in the SSRI/SNRI, benzodiazepine, and opioid therapy group. One-fourth to one-third of patients across all study groups had an active diagnosis of a select SUD.

With the SSRI/SNRI monotherapy group as the referent, all concurrent therapy groups were at significantly increased risk for overall hospitalization within 2 years after the index date (Tables 2 & 3, Figure 2). The SSRI/SNRI and benzodiazepine therapy group had an adjusted HR (AHR) of 2.6 (95% CI, 1.1-5.7) and an NNH of 46; the SSRI/SNRI and opioid therapy group had an AHR of 6.1 (95% CI, 2.6-14.0) and an NNH of 15; and the SSRI/SNRI, benzodiazepine, and opioid therapy group had an AHR of 3.9 (95% CI, 1.1-14.6) and an NNH of 25.

Risk for mental health hospitalization was significantly increased in all concurrent therapy groups relative to the referent group. The SSRI/SNRI and benzodiazepine therapy group had an AHR of 5.5 (95% CI, 1.6-18.7) and an NNH of 32; the SSRI/SNRI and opioid therapy group had an AHR of 12.3 (95% CI, 3.3-46.2) and an NNH of 13; and the SSRI/SNRI, benzodiazepine, and opioid therapy group had an AHR of 20.0 (95% CI, 4.0-101) and an NNH of 8.

Although the risk for medical/surgical hospitalization was not significantly increased in the SSRI/SNRI and benzodiazepine therapy group (AHR, 1.9; 95% CI, 0.67-5.6), a significant difference was found in the SSRI/SNRI and opioid therapy group (AHR, 4.4; 95% CI, 1.6-12.0; NNH, 42). After the patients who were hospitalized within 6 months before the index date in the SSRI/SNRI, benzodiazepine, and opioid therapy group were excluded, there were no medical/surgical hospitalizations. The

Table 2. Hazard Ratios of Overall, Mental Health, and Medical/Surgical Hospitalizations[a]

Hospitalization Type	SSRI/SNRI (n = 425)	SSRI/SNRI + Benzodiazepine (n = 72)			SSRI/SNRI + Opioid (n = 43)		
	n (%)	n (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	n (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Any Hospitalization	35 (8.2)	10 (13.9)	1.8 (0.88-3.6)	2.6 (1.1-5.7)	15 (34.9)	5.1 (2.8-9.4)	6.1 (2.6-14.0)
Mental Health Hospitalization	9 (2.1)	6 (8.3)	4.1 (1.5-11.8)	5.5 (1.6-18.7)	7 (16.3)	8.2 (3.1-22.0)	12.3 (3.3-46.2)
Medical/Surgical Hospitalization	26 (6.1)	5 (6.9)	1.2 (0.44-3.0)	1.9 (0.67-5.6)	10 (23.3)	4.4 (2.1-9.2)	4.4 (1.6-12.0)

Abbreviations: CI, confidence interval; HR, hazard ratio; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]Excludes patients hospitalized within 6 months before index date; SSRI/SNRI monotherapy group used as referent.

overall cohort's 2-year all-cause mortality was significantly higher ($P < .01$) in the SSRI/SNRI, benzodiazepine and opioid therapy group (21.4%) than in the SSRI/SNRI monotherapy group (1.1%) (Table 4).

DISCUSSION

In 2013, Hawkins and colleagues evaluated hospitalization risk in veterans treated for PTSD within the Northwest VISN 20 between 2004 and 2010.[11] Compared with patients treated with only an SSRI or SNRI, those treated with 1 of those medications and a benzodiazepine were at significantly higher risk for overall hospitalization (AHR, 1.79; 95% CI, 1.38-2.32; $P < .001$) and mental health hospitalization (AHR, 1.87; 95% CI, 1.37-2.53; $P < .001$). Furthermore, those prescribed a benzodiazepine and an opioid along with an SSRI or SNRI were at higher risk for overall hospitalization (AHR, 2.98; 95% CI, 2.22-4.00; $P < .001$), mental health hospitalization (AHR, 2.00; 95% CI, 1.35-2.98; $P < .01$), medical/surgical hospitalization (AHR, 4.86; 95% CI, 3.30-7.14; $P < .001$), and ED visits (AHR, 2.01; 95% CI, 1.53-2.65; $P < .001$).

Findings from the present study, which covered a period after the newest PTSD guideline was released, support findings reported by Hawkins and colleagues in their retrospective cohort study covering an earlier period.[2,11] In the present study, compared with the monotherapy group, the SSRI/SNRI and benzodiazepine therapy group and the SSRI/SNRI, benzodiazepine, and opioid therapy group were at higher risk for both overall hospitalization and mental health hospitalization within 2 years. However, in a subset of PTSD patients prescribed opioids along with first-line pharmacotherapy, this study found that overall, mental health, and medical/surgical hospitalizations were significantly increased as well. Furthermore, this study found 2-year mortality was significantly higher for the SSRI/SNRI, benzodiazepine, and opioid therapy group than for the SSRI/SNRI monotherapy group.

Adjusted hazard ratios were higher in the present study than those in the study by Hawkins and colleagues, but CIs were wider as well.[11] These differences may be attributable to the relatively smaller sample size of the present study and may explain why the HR was higher for the SSRI/SNRI and opioid therapy group than for the SSRI/SNRI, benzodiazepine, and opioid therapy group.

Nevertheless, these results support the growing body of evidence establishing the many risks for AEs when benzodiazepines and opioids are prescribed in the setting of PTSD. Unfortunately, it seems that, against clear guideline recommendations and literature findings, these medications still are being prescribed to this vulnerable, high-risk population.

In the last few months of 2013, the VA health care system launched 2 important medication safety initiatives. The Psychotropic Drug Safety Initiative (PDSI) was established as a quality improvement initiative for evidence-based provision of psychotropic medications. One PDSI metric in particular focused on reducing the proportion of veterans with PTSD being treated with benzodiazepines. The Opioid Safety Initiative (OSI) came as

SSRI/SNRI + Benzodiazepine + Opioid (n = 27)		
n (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
2 (28.6)	3.7 (0.89-15.4)	3.9 (1.1-14.6)
2 (28.6)	14.8 (3.4-64)	20.0 (4.0-101)
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a response to a dramatic increase in the number of fatal overdoses related to prescription opioids—an increase linked to an unprecedented jump in opioid use for nonmalignant pain. As the present study's inclusion cutoff date of August 1, 2013, preceded the debut of both PDSI and OSI, the benzodiazepine and opioid prescription rates reported here might be higher than those currently being found under the 2 initiatives.

Limitations

This study had several limitations that might affect the interpretation or generalizability of findings. Requiring at least a 30-day supply for prescription eligibility was an attempt to focus on chronic use of medications rather than on, for example, onetime supplies of opioids for dental procedures. However, prescription fill history was not assessed. Therefore, patients could have been included in certain study groups even if their SSRI, SNRI, benzodiazepine, or opioid prescription was not refilled. Furthermore, only VA medical records were used; non-VA prescriptions were not captured.

In addition, this study was limited to patients who at bare minimum were prescribed an SSRI or an SNRI. Some patients may have been prescribed a benzodiazepine and/or an opioid but were not on appropriate first-line pharmacotherapy for PTSD. These patients were excluded from the study, and their relative hospitalization risk went unexplored. Therefore, the magnitude of the issue at hand might have been underestimated.

Although psychotherapy is a first-line treatment option for PTSD, the study did not assess the potential impact of psychotherapy on outcomes or the groups' relative proportions of patients undergoing psychotherapy. It is unknown whether the groups were equivalent at baseline in regards to psychotherapy participation rates.

This study did not characterize the specific reasons for hospitalization beyond whether it was for a mental health or a medical/surgical issue; thus, no distinction was made between hospitalizations for an elective procedure and hospitalizations for a drug overdose or an injury. Investigators could characterize admission diagnoses to better assess whether hospitalizations are truly associated with study medications or whether patients are being hospitalized for unrelated reasons. In addition, they could elucidate the true nature of hospitalization risk associated with SSRI/SNRI, benzodiazepine, and opioid use by comparing admission diagnoses made before and after initiation of these pharmacologic therapies.

This study also could not assess outcomes for patients who presented to the ED but were not admitted. If the hospital's floor and ED beds were at full capacity, some patients might have been transferred to an outside facility. However, this scenario is not common at SAVAHCS, where the study was conducted.

Although some comorbid conditions were noted, the study did not evaluate whether its patients had a compelling indication for benzodiazepines in particular. Opioid use is very limited to the treatment of pain, and the majority of the patients on opioid therapy in this study had a diagnosed pain syndrome.

Because of the study's sample size and power limitations, patients were eligible to be included in a concurrent therapy group if a benzodiazepine, an opioid, or both were added no later than 1 year after SSRI/SNRI initiation. This gap of up to 1 year might have introduced some variability in exposure to risk from earlier prescribed medications. However, sensitivity analyses were performed with multiple constructed Weibull models of time to hospitalization based on subsets with varying overlapping medication gaps. Analyses revealed relatively stable HRs, suggesting that potential bias did not occur.

Future Directions

Investigators could explore the higher all-cause mortality rates in the SSRI/SNRI, benzodiazepine, and opioid therapy group, as this study did not assess cause of death in these patients. Whether any patients died of reasons directly attributable to benzodiazepines or opioids is unknown.

That SSRIs and SNRIs are the only established first-line pharmacologic treatment options for PTSD symptoms

Table 3. Number Needed to Harm by Hospitalization

Hospitalization Type	SSRI/SNRI + Benzodiazepine	SSRI/SNRI + Opioid	SSRI/SNRI + Benzodiazepine + Opioid
Any	46	15	25
Mental health	32	13	8
Medical/surgical	NR[a]	42	NR[a]

Abbreviations: NR, not reported; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]Number needed to harm not reported as adjusted hazard ratio was either not significant or not defined.

Table 4. Two-Year All-Cause Mortality

	SSRI/SNRI	SSRI/SNRI + Benzodiazepine	SSRI/SNRI + Opioid	SSRI/SNRI + Benzodiazepine + Opioid
All-cause mortality, n (%)	5 (1.1)	0	3 (4.8)	3 (21.4)[a]

Abbreviations: SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]$P < .01$ compared with SSRI/SNRI group.

partly accounts for the widespread use of benzodiazepines in this population. For that reason, beyond characterizing the many risks associated with using benzodiazepines to manage these symptoms, there is a huge need to research the viability of other pharmacologic agents in treating PTSD. This is especially important given the slower onset to efficacy of the SSRIs and SNRIs; per estimates, only up to 60% of patients respond to SSRIs, and 20% to 30% achieve full remission of PTSD.[12] Furthermore, these rates likely are even lower for combat veterans than those for the general population. Several trials discussed in a 2009 guideline review of the treatment of patients with acute stress disorder and PTSD have called into question the efficacy of SSRIs for combat-related PTSD.[13] In these randomized, controlled trials, change in PTSD symptom severity as measured with CAPS was not significantly reduced with SSRIs compared with placebo.

A systematic review revealed that, of the nonantidepressants used as adjuncts in treating patients who do not achieve remission with SSRIs, the atypical antipsychotic risperidone may have the strongest supporting evidence.[12] However, the present study found high rates of antipsychotic use in the SSRI/SNRI, benzodiazepine, and opioid therapy group, which also had the highest all-cause mortality rate. The safety of risperidone as an alternative treatment needs further evaluation.

Some prospective studies have suggested that the α_1 blockers doxazosin and prazosin, the latter of which is commonly used for PTSD nightmares, also may improve PTSD symptoms as assessed by CAPS.[14,15] Although these results are promising, the trials to date have been conducted with relatively small sample sizes.

With more veterans being treated for PTSD within the VA health care system, the central treatment goal remains: Adequately address the symptoms of PTSD while minimizing the harm caused by medications. Prescribers should limit benzodiazepine and opioid use in this population and consider safer nonpharmacologic and pharmacologic treatment options when possible.

CONCLUSION

Combat veterans with PTSD who are prescribed benzodiazepines and/or opioids in addition to first-line pharmacotherapy are at significantly increased risk for overall and mental health hospitalization. ●

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