Original Research Articles

Increased Polysedative Use in Veterans with Posttraumatic Stress Disorder

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Abstract

Background. Posttraumatic stress disorder (PTSD) treatment is often complicated in veterans by co-occurring conditions including pain, insomnia, brain injury, and other mental disorders. Pharmacologic approaches to these conditions can produce an accumulation of sedating medications with potential for safety concerns.

Objective. The objective of this study was to characterize polysedative prescribing among veterans with PTSD over an 8-year period.

Design. National Department of Veterans Affairs (VA) data were used to identify veterans with PTSD using International Classification of Diseases, Ninth Revision codes among regular medication users. Prescribing of benzodiazepines, hypnotics, atypical antipsychotics, opioids, and muscle relaxants was determined annually. Prevalence and incidence rates were determined for each medication class from 2004 through 2011. Polysedative use was determined from longitudinal refill patterns that indicated concurrent use across sedative classes.

Results. In 2004, 9.8% of veterans with PTSD concurrently received medications from three or more sedative classes. By 2011, the prevalence of concurrent use involving three or more classes increased to 12.1%. Polysedative use varied across demographic subgroups, with higher rates observed among women, rural residents, younger adults, Native Americans and Whites. The most common combination was an opioid plus a benzodiazepine, taken concurrently by 15.9% of veterans with PTSD.

Conclusions. Important trends in polysedative use among veterans with PTSD illustrate the complexity of treating an intersecting cluster of symptoms managed by sedative medications. As the VA seeks to improve care by focusing on non-pharmacologic options, our findings emphasize the need for a comprehensive approach that encompasses overlapping conditions of relevance to veterans with PTSD.

Key Words. Posttraumatic Stress Disorder; Clinical Pharmacology; Coordinated Care

Introduction

Chronic pain is a common complaint among veterans returning from Iraq and Afghanistan [1], and prior studies of treatment-seeking veterans with posttraumatic stress disorder (PTSD) suggest that as many as 66–80% may be suffering from chronic pain [2–4]. In addition, approximately two thirds of PTSD patients experience sleep dysfunction [5], as well as a host of psychiatric comorbidities including depression and substance use disorders [6,7]. Management of these various conditions can lead to an accumulation of multiple sedative medications, which represents a critical patient safety issue [8].
Bernardy et al.

Unfortunately, the evidence base concerning coordinated treatment recommendations for PTSD with co-occurring pain and insomnia is quite limited. The 2010 revised Department of Veterans Affairs and Department of Defense (VA/DoD) Clinical Practice Guideline (CPG) for the management of PTSD cautions providers against the use of benzodiazepines to manage the core symptoms of PTSD [9]. The PTSD guideline also provides separate recommendations for the treatment of pain and insomnia which emphasize non-pharmacological options as first-line treatment [9]. Additional pain medication guidance is offered in the VA/DoD CPG for management of opioid therapy for chronic pain, but the issue of comorbid PTSD is not addressed [10]. Despite the prominent role that pharmacotherapy plays in the management of PTSD, chronic pain, and insomnia, and the risk for drug interactions involving opioids, benzodiazepines, and other sedatives used to treat these conditions [11], data concerning poly-sedative prescribing in veterans with PTSD are extremely inadequate. In order to fill this critical knowledge gap, the objective of this study was to characterize poly-sedative prescribing among veterans with PTSD, including an examination of recent temporal trends, use across demographic subgroups, and a description of common combinations.

Methods

Data Source

National administrative VA data were obtained for fiscal years (FY) 2003 through 2011 from the VA Austin Information Technology Center (Austin, TX) and included outpatient visits, inpatient discharges, and outpatient medication dispensing. This study was approved by the University of Iowa Institutional Review Board and the Iowa City Veterans Administration Research and Development Committee.

Participants

The target population was veterans with PTSD who were regular users of VA health care services, and individual cohorts were established annually for FY 2004–2011. PTSD was identified using the International Classification of Diseases, Ninth Revision (ICD-9) code of 309.81 and extracted from inpatient and outpatient visits. Patients were considered to have PTSD during a given year if they had at least one visit coded for PTSD as either a primary diagnosis or secondary diagnosis [12–19]. The estimated rate of false positive cases due to administrative miscoding is infrequent (<4%) using this methodology [20,21] and our prior analyses of VA prescribing trends have generally yielded similar findings across alternative PTSD case definitions [19]. Patients were considered to be regular VA health care users during a given year if they had regular VA medication use that year and the prior year. Regular medication use was defined as a history of outpatient medication fills where the day’s supply periods spanned at least 240 of 365 days, a definition used previously [15,22]. In addition to identifying a population of stable and consistent users of VA health care, the requirement for 2 consecutive years of regular VA health use was necessary to establish incident medication use. Without this requirement, a first observed medication fill among new patients transferring care to the VA could be erroneously classified as incident use.

Medication Use

Outpatient pharmacy data were used to determine prevalent and incident medication use for each year. The sedative classes of interest included benzodiazepines, hypnotics (zolpidem, eszopiclone, zaleplon, and ramelteon), atypical antipsychotics, opioid analgesics, and skeletal muscle relaxants (baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, and tizanidine). Prevalent use was defined as receiving at least 20-day supply of a given medication class during the FY [23]. Incident medication use was defined as a first fill observed in a given FY that was preceded by 365 days with no prior medications from the same class.

Concurrent use across medication classes was determined by a two-step process. First, periods of active use were established for each sedative medication class over the course of the year based on longitudinal refill histories. Overall, we employed a strict approach to establishing periods of active use in order to exclude common inter-class regimen changes from being considered concurrent use (e.g., switching a patient from lorazepam to zolpidem). Medications were considered active during an interval between two fills if the duration of the interval was less than twice the day’s supply of the first of these two fills. If the interval exceeded this threshold, the medication class was considered inactive during the entire interval. This definition was used to allow for nonadherence, but to assume that large gaps between fills represented a period of discontinuation followed by a new decision to restart medication. Active use periods were established across all intervals between fills across the year to define the period of active use. Medications were considered inactive following the date of last observed fill during the year because a medication could have been discontinued at any point after the last observed fill. The second step was to determine whether these active use periods overlapped between sedative classes. If overlap occurred at any point during the year, these classes were considered to be used concurrently.

Analysis

Annual prevalence and incidence rates were determined for each sedative medication class for 2004 through 2011. The frequency of concurrent sedative class use was determined for 2004 and 2011, and the frequency of individual concurrent class pairs was determined for 2011. Concurrent sedative use at the time of new sedative initiation was also determined for 2011. Demographic subgroup stratifications were included for the prevalence and incidence
rates for individual sedative classes and the frequency of sedative polytherapy (two or more sedative classes used concurrently). Subgroups were based on sex, age (≥65 years), rural vs urban residence, and race. In keeping with prior analyses of this complete population of veterans receiving care in VA, we did not report inferential statistics, but have included an interpretation of the clinical significance of our findings [15,17].

Results

Patients

A total of 243,767 veterans had at least one PTSD coded encounter in 2004, of which 165,391 (67.8%) were regular users of Veterans Health Administration services during 2003–2004 and comprised the 2004 cohort. Identical inclusion criteria were applied across each FY through 2011, over which time the cohort size more than doubled, to 358,992 veterans with PTSD in 2011.

Trends in Sedative Use

Longitudinal trends in sedative prescribing are found in Figure 1. Benzodiazepine and atypical antipsychotic prescribing followed similar trends with gradual declines in both incidence and prevalence. The incident prescribing of skeletal muscle relaxants remained consistent, although the prevalence increased from 16.8% in 2004 to 19.7% in 2011. The prevalence of opioid use increased from 30.3% in 2004 to 34.9% in 2011 despite a more than 25% relative decrease in incidence during this period, from 8.2% to 5.9%, suggesting a shift toward more chronic prescribing of opioids.

Sedative use varied across demographic subgroups with higher rates observed among women, rural residents, younger adults, Native Americans, and Whites (Table 1). Benzodiazepine prescribing was markedly elevated among women (44.4%) compared with men (33.8%), and somewhat lower among older adults (31.2% vs 35.5%). Rural veterans had higher benzodiazepine prevalence rates compared with urban veterans, despite similar incidence rates. Benzodiazepine prevalence varied among racial and ethnic groups, and was notably lower for Black veterans, where only 21.9% received benzodiazepines during 2011 compared with 38.4% among Whites and 36.6% among Hispanics. Demographic differences in opioid use were similar to benzodiazepines, with the exceptions of race. In contrast to benzodiazepines, opioid incidence rates were equivalent for Blacks and Whites and the difference in prevalence rates was smaller (Blacks: 32.1% vs Whites: 36.8%). In addition, the incidence and prevalence of opioid prescribing was highest among Native Americans (44%) compared with all other racial and ethnic groups.

Polysedative Use

In FY 2004, approximately 75% of veterans with PTSD received at least one sedative medication, 34.2% concurrently received medications from two or more sedative

![Figure 1](https://academic.oup.com/painmedicine/article-abstract/15/7/1083/1877154/Increased-Polysedative-Use-in-Veterans-with-PTSD/1085)

**Figure 1** Period prevalence and incidence in sedative prescribing in a national sample of veterans diagnosed with post-traumatic stress disorder (PTSD) in the Veterans Affairs (VA). **FY** = fiscal year.
classes, and 9.8% took three or more. By FY 2011, the prevalence of concurrent polysedative use involving three or more classes increased to 12.1% (Table 2). Although a small percentage (0.2%), concurrent use of all five sedative classes was observed for 757 patients, compared with only 97 patients in FY 2004.

Several important differences in concurrent polysedative use were observed across demographic subgroups (Table 3). Polysedative use was more common in 2011 among women than men; 49.7% vs 35.5% for two or more classes, and 20.8% vs 11.4% for three or more classes. Polysedative use among older adults (≥65 years) was approximately half that observed for younger patients, and rural veterans had slightly higher rates compared with urban veterans. Variation in polysedative use was observed across racial and ethnic groups, with the highest rates among Native Americans, Whites, Hispanics, and lowest among Blacks.

The prevalence rates of individual sedative pairings are found in Table 4. The most commonly observed sedative combination was opioids and benzodiazepines, taken concurrently by 15.9% of veterans with PTSD during 2011. This frequency is higher than expected based on the individual prevalence rates for these classes (benzodiazepines: 34.6%; opioids: 34.9%; expected concurrence rate: 12.1%). Two other combinations that were used more frequently than expected were opioids plus skeletal muscle relaxants, and benzodiazepines plus atypical antipsychotics.

**Conclusions**

This work is the first national study of polysedative prescribing in veterans with PTSD. Among veterans of the Afghanistan and Iraq era (Operation Enduring Freedom, Operation Iraqi Freedom, Operation New Dawn [OEF/OIF/OND]) with chronic pain, the presence of co-occurring PTSD has previously been associated with an increased likelihood of opioid prescribing, as well as high-risk behaviors and adverse clinical outcomes associated with opioid treatment [23]. This study further demonstrated that OEF/OIF/OND veterans with PTSD were more likely to receive two or more opioids concurrently, as well as sedative hypnotics and opioids concurrently. Finally, a small
cross-sectional study found that 47% of veterans with PTSD taking benzodiazepines were concurrently prescribed long-term opioids [24].

Our primary finding was an increase in polysedative use over time, from 34.2% to 36.6% for two or more sedative classes, and from 9.8% to 12.1% for three or more classes. While this may appear to be modest, the increase in polysedative use of three or more classes represents a concerning clinical trend with a relative increase of nearly 25%. More importantly, the number of veterans with PTSD represented in the denominator of these proportions more than doubled during this time period. Thus, the absolute number of veterans receiving three or more sedative medication classes increased nearly threefold, from 16,126 in 2004 to 43,374 in 2011. In this manner, our findings can be interpreted from different perspectives. For the clinicians treating individual patients, the increase from 9.8% to 12.1% may be the most relevant expression of our findings. From a national policy perspective however, the threefold increase in the number of veterans exposed to polysedative prescribing should elicit concern regarding adherence to guidelines for evidence-based treatment.

In order to understand patterns in polysedative use, we also characterized prescribing trends for individual sedative classes, both in terms of incident and prevalent prescribing (Figure 1). Declining benzodiazepine and atypical antipsychotic use are consistent with PTSD guideline recommendations, including an ongoing caution against benzodiazepine use and a recent negative clinical trial of the atypical antipsychotic risperidone for PTSD [25]. Opioid prescribing trends were particularly notable, where prevalent use increased over time despite a more than 25% increase in incident use.

### Table 3  Frequency of concurrent polysedative use stratified by demographic subgroup

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>2004 Two or More (%)</th>
<th>2004 Three or More (%)</th>
<th>2011 Two or More (%)</th>
<th>2011 Three or More (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>33.6</td>
<td>9.4</td>
<td>35.5</td>
<td>11.4</td>
</tr>
<tr>
<td>Women</td>
<td>46.7</td>
<td>15.7</td>
<td>49.7</td>
<td>20.8</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults, &lt;65 years</td>
<td>37.2</td>
<td>11.1</td>
<td>39.6</td>
<td>13.6</td>
</tr>
<tr>
<td>Older adults, ≥65 years</td>
<td>20.4</td>
<td>3.6</td>
<td>25.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>33.4</td>
<td>9.5</td>
<td>35.7</td>
<td>11.6</td>
</tr>
<tr>
<td>Rural</td>
<td>35.9</td>
<td>10.4</td>
<td>38.3</td>
<td>13.1</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>39.4</td>
<td>12.4</td>
<td>41.0</td>
<td>14.3</td>
</tr>
<tr>
<td>White</td>
<td>37.2</td>
<td>11.2</td>
<td>39.0</td>
<td>13.4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>34.6</td>
<td>8.5</td>
<td>36.2</td>
<td>11.7</td>
</tr>
<tr>
<td>Asian</td>
<td>29.7</td>
<td>7.5</td>
<td>32.5</td>
<td>10.7</td>
</tr>
<tr>
<td>Black</td>
<td>29.6</td>
<td>7.4</td>
<td>31.5</td>
<td>9.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>25.5</td>
<td>6.2</td>
<td>29.5</td>
<td>8.6</td>
</tr>
<tr>
<td>All patients</td>
<td>34.2</td>
<td>9.8</td>
<td>36.6</td>
<td>12.1</td>
</tr>
</tbody>
</table>

### Table 4  Period prevalence of any concurrent use of polysedative combinations in 2011

<table>
<thead>
<tr>
<th>Observed Prevalence % (Expected Prevalence %)*</th>
<th>Hypnotics</th>
<th>Atypical antipsychotics</th>
<th>Opioids</th>
<th>Skeletal muscle relaxants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>5.2 (5.3)</td>
<td>9.5 (8.1)</td>
<td>15.9 (12.1)</td>
<td>7.1 (6.8)</td>
</tr>
<tr>
<td>Hypnotics</td>
<td>3.3 (3.6)</td>
<td>6.1 (5.3)</td>
<td>10.8 (6.9)</td>
<td>4.7 (4.6)</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>8.9 (8.1)</td>
<td>4.7 (4.6)</td>
<td>3.0 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Expected prevalence rates determined by multiplying the individual prevalence rates of the two medication classes in 2011, as found in Figure 1. For example, the expected frequency for the concurrent use of benzodiazepines and opioids, where the individual frequencies were 34.6% and 34.9%, respectively, is 12.1%. The actual observed frequency of this combination was 15.9%.
Bernardy et al.

relative decrease in incidence. This pattern is indicative of a shift toward chronic opioid use, a well-documented trend not unique to the VA and particularly concerning given the lack of evidence supporting the sustained effectiveness of opioids for chronic pain over long periods of time (months to years) [26]. Prescribing patterns for skeletal muscle relaxants indicated stable incidence rates with increasing prevalence rates; again suggesting a trend toward more chronic use. Prescribing trends for hypnotics were driven by a dramatic increase in zolpidem use in 2008 after this medication was added to the VA national formulary [17]. Since the initial surge, incidence prescribing rates have declined and prevalence rates have leveled off at approximately 15%.

Increasing chronic opioid use stands in contrast to the VA PTSD CPG, which recommends a multidisciplinary approach that includes initial non-pharmacological modalities for pain control such as biofeedback, massage, imaging, physical therapy, and complementary alternative modalities such as yoga meditation and acupuncture [9]. It also suggests that clinicians should consider offering cognitive-behavioral therapy for pain. The CPG adds that centrally acting medications should be prescribed cautiously and at the lowest effective dose as they may cause confusion and deterioration of cognitive performance and interfere with recovery. Prescribing of opioids or other centrally acting analgesics, if required, should be restricted whenever possible to short time intervals (e.g., less than 1 week) with a transition to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as soon as possible. Although recent research has questioned the use of NSAIDs, particularly in patients on antidepressants [27], as are many patients with PTSD, the role of NSAIDs is by no means settled and changes have not been made to the recommendation of their use to address chronic noncancer related pain. In the case of opioids, complete pain relief is usually not possible [28] and it has been suggested that opioids should be considered just one modality for use in the very complicated setting of chronic pain management [29].

In addition to describing general trends, we contrasted prescribing across demographic subgroups. Polysedative use was more common among women veterans, which is consistent with recent findings in veterans with PTSD showing elevated benzodiazepine prescribing among women compared with men [12,24]. Women veterans are more likely to report more painful musculoskeletal conditions after deployment than male veterans [1], and the increase in reported pain may contribute to higher receipt of opioids but does not address their increased receipt of concurrent prescriptions for other sedative agents. Polysedative use was less common among older adults, which is encouraging given the increased susceptibility to adverse drug events and complex medication regimens in this population. Polysedative use was also more common among rural veterans, which is again consistent with recent findings in veterans with PTSD showing elevated benzodiazepine prescribing among veterans with rural residence [13]. Polysedative prescribing, and use of benzodiazepines and opioids specifically, was generally higher for Whites compared with other racial and ethnic groups. These differences may reflect varying attitudes across racial and ethnic groups toward the role of medication in the management of chronic pain, PTSD, sleep, and other indications for which sedatives are prescribed. These findings might also reflect an underlying disparity in healthcare access. However, the relative pattern of use across racial and ethnic groups varied widely between benzodiazepine, opioid, and polysedative use, suggesting that these differences are not solely explained by broad disparities in access.

There are several important limitations to our findings. First, our intent was to describe polysedative prescribing patterns, not to judge the clinical appropriateness of individual prescribing decisions. Some concurrent sedative use may be justified, but the trend toward increasing polysedative prescribing warrants additional patient-level examination. This work will be complicated by a lack of clear consensus regarding appropriate use, particularly in weighing treatment decisions in light of multiple co-occurring conditions. Second, we chose to focus on inter-class polysedative use, and did not examine trends in intra-class polysedative use. Receipt of multiple medications from a single class (e.g., two benzodiazepines) was not counted as polysedative use in our analysis. Thus, our findings could be viewed as underestimates if intra-class polytherapy were to be considered. In addition, we only observed VA medications. Medications dispensed from non-VA pharmacies, as well as drugs obtained on an illicit basis, were not represented in our analysis. This limitation also means that our findings could be considered underestimates of overall polysedative use. An additional limitation is that veterans with PTSD were identified by using the ICD-9 code 309.81. It is conceivable that some portion of the increase in PTSD diagnoses made in recent years could be due to trends in rates of overdiagnosis leading to an increased false positive rate and impacting our findings. Finally, our findings are only directly applicable to veterans with PTSD treated in the VA health care system. It is unclear whether our findings generalize to other patient groups in VA, to veterans with PTSD seeking treatment outside VA, or to nonveteran patients with PTSD.

Many veterans with PTSD suffer from an intersecting cluster of symptoms including chronic pain, anxiety, and sleep disturbances that may be directly attributable to or exacerbated by PTSD. Making appropriate risk-benefit decisions concerning the use of sedative medications that simultaneously considers these multiple factors is challenging. For example, the current VA PTSD guideline discourages benzodiazepine use and promotes nonpharmacologic treatments as first-line options for chronic pain in this population. Despite these recommendations, prevalent prescribing for both benzodiazepines and opioids are in excess of 30% individually, and nearly 16% in combination. This is particularly concerning as it is recognized that persons receiving sedative hypnotic medications and opioids are at increased risk for opioid overdose, a national epidemic [30]. An accompanying editorial
to that research noted that many overdose incidents might have been averted by changes in prescriber practices such as avoiding concurrently prescribed sedative hypnotics [31]. Looking beyond clinician decision-making, there are a number of patient and organizational factors that may contribute to polysedative prescribing. Some patients prefer the short-term symptomatic fix of taking medications to the longer term solution of engaging in evidenced-based psychotherapy and other non-pharmacological based interventions. Lack of access to these alternative treatments may also contribute to increased polysedative prescribing. Additional organizational barriers can arise from the involvement of multiple providers due to disruptions in continuity of care or from lack of communication between primary care and specialty providers. For example, in VA the majority (70–80%) of benzodiazepine prescribing among veterans with PTSD comes from mental health specialists [16]. In contrast, more than 75% of opioid prescribing comes from primary care and nonmental health specialists [23,24]. The clinical complexity of caring for veterans with PTSD creates an environment that, without careful and deliberate coordination of care, can lead to expanding use of high-risk sedative combinations. At a time when VA is making significant strides to improve the management of chronic pain in veterans with PTSD, it is imperative that we minimize the use of high-risk medications with questionable long-term benefits in the management of pain, anxiety, sleep, and other common symptoms experienced by veterans with PTSD. Instead, it is necessary to promote a more comprehensive approach to treatment that addresses these various symptom clusters and encourages guideline concordant care. VA has undertaken a number of steps to improve PTSD treatment practices that include dissemination of evidence-based psychotherapy, consultation for complex comorbid cases, and funding research to improve prescribing practices. It will be essential as we move forward to monitor the progress of these steps and their impact on clinical care.

Acknowledgment

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Bernardy et al.


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