Long-Term Benzodiazepine Use in Posttraumatic Stress Disorder and Chronic Obstructive Pulmonary Disease

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Abstract

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Objective: Examine the national prevalence and variability in long-term benzodiazepine prescriptions for patients with two comorbidities placing them at high risk for benzodiazepine-related complications, posttraumatic stress disorder (PTSD) and chronic obstructive pulmonary disease (COPD).

Methods: We identified Veterans with PTSD and COPD identified from electronic health records from Veterans Health Administration between 2010-2012. We used a mixed-effects logistic regression model with long-term benzodiazepine prescriptions (≥90 days) as the outcome to assess patient and center predictors.

Results: Of 44,949 patients diagnosed with PTSD and COPD at 130 centers, 24.3% were prescribed benzodiazepines long-term. Patients with long-term prescriptions were more likely to be white (90.1 vs. 80.8%, $p<0.001$) and have other mental health comorbidities including generalized anxiety disorder (31.0 vs. 16.5%, $p<0.001$). Substantial heterogeneity among medical centers existed, and proportional use of long-term benzodiazepine ranged from 8.6 to 56.5%. This heterogeneity persisted after accounting for patient characteristics with a random effect by medical center of 0.33 (95% CI 0.28-0.39). Accounting for patient-level factors, southern centers were more likely than centers in the northeast to prescribe benzodiazepines long-

term (OR 1.22, 95%CI 1.02-1.47), and centers with higher Veteran-reported access to mental health care were less likely to prescribe long-term benzodiazepines (OR 0.51, 95%CI 0.32-0.81).

Conclusions: Long-term benzodiazepine prescribing is common among patients at high risk for complications, although this practice varies substantially from center to center. Poor access to mental health care is a potential driver of this guideline inconsistent use.

Introduction:

Benzodiazepines are frequently prescribed on a long-term basis to patients with the common conditions of posttraumatic stress disorder (PTSD) and chronic obstructive pulmonary disease (COPD), despite considerable concerns regarding the safety of these medications in each condition.(1, 2) Among patients with PTSD, benzodiazepine use is strongly discouraged by Veterans Affairs (VA) and Department of Defense Guidelines due inadequate evidence of treatment benefit, risks related to use (e.g. substance abuse), and the potential for reduced efficacy of exposure therapies.(3, 4) Among patients with COPD, benzodiazepines are associated with a 45% increased risk of exacerbations and increased mortality, prompting guidelines to discourage use.(5-8) With symptoms of PTSD present in up to 40% of patients with COPD, the co-occurrence of these conditions is common, and of increasing concern given greater respiratory and mental health symptom burden among those with co-occurring disease.(9, 10)

In each condition, there is a heavy burden of symptoms of anxiety and insomnia, which often prompt benzodiazepine use, although alternative therapies exist.(11-13) The prescription of alternative sedating agents such as non-benzodiazepine GABA agonists, antidepressants, and antipsychotics can improve sleep continuity or reduce symptoms of anxiety otherwise treated by benzodiazepines.(14-23) With regard to PTSD, psychotherapy can also be considered as an alternative.(4) Prior analyses have found substantial variability by center related to benzodiazepine prescribing in PTSD. These studies found regional variability by center, and hypothesized lack of access to subspecialty care and psychotherapy among patients with PTSD as potential additional mediators of this variability. However, these studies did not have access to subjective or objective measures of patient access in their analyses.(2, 24)

A more thorough understanding of guideline discordant benzodiazepine use will be critical to reduce such use and its associated risks. Here, we aim to examine the prevalence of guideline discordant benzodiazepine prescribing among patients with comorbid PTSD and COPD, individuals with dual contraindications to use, and evaluate the variability by center in

this practice. We also specifically assessed the relationship of center-level mental health access to guideline discordant prescribing. Given the potential utility of careful, short-term (up to 4 week) benzodiazepine use for acute symptoms,(25) we focused on longer term or "chronic" prescriptions of benzodiazepines that we define as at least 90 days of continuous exposure.(26) We hypothesized that centers will vary in the long-term prescribing of benzodiazepines, even after accounting for patient level factors, and that centers with greater access to mental health care would have lower rates of guideline discordant benzodiazepine prescriptions.

Methods:

Using the VA Corporate Data Warehouse (CDW), we identified all patients enrolled in VA care with COPD and comorbid PTSD from 2010-12. The CDW incorporates nationwide medical record data for all Veterans seeking care within the VA and includes pharmacy records, demographics, outpatient visits and inpatient stays.(27)

To determine if benzodiazepine use was associated with access to mental health care, we used center-level data from a number of sources. We used center aggregated results from the VA Survey of Healthcare Experiences, an annual survey to randomly selected patients assessing patient experience, (28) as well as the mental health domains of the quarterly Strategic Analytics for Improvement and Learning (SAIL) reports measuring population reach, continuity of care, and care experience.(29) The VA Puget Sound Institutional Review Board approved this study IRB# 00703.

For inclusion in our cohort, we required patients to have two or more encounters with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnoses of COPD (491.xx, 492.xx, 493.2, 496.xx) during 2010-12. We required two encounters to reduce misclassification of COPD.(30) We defined the date of the second qualifying COPD diagnosis as the index date. Patients also needed at least one ICD-9-CM diagnosis of PTSD (309.81) documented in the medical record in the year prior to index. We excluded patients enrolled in hospice as the use of benzodiazepines may be indicated in this setting, (31) and also excluded those not alive 180 days after the index date, as these individuals would not have adequate opportunity to experience the outcome of interest.

Our outcome of interest was long-term benzodiazepine exposure, which we defined as filled prescriptions of 90 or more consecutive days' supply of a benzodiazepine medication in the 180-day period after index.(26) We quantified benzodiazepine dose in terms of daily diazepam equivalents.(32)

Our patient-level predictors of interest are included in Tables 1 and 2, and correspond to variables hypothesized to predispose patients to benzodiazepine use, and include demographic, medical and mental health comorbidities, markers healthcare utilization, and potential alternative medications for symptoms of anxiety, insomnia, and dyspnea.(11, 33-44)

Consistent with a Donabedian framework of quality,(45) we evaluated structural and process domains of the healthcare center. Structural domains refer to the physical facility and human resources of a healthcare system, whereas process domains include the actions a health system takes to deliver care.(45) These characteristics were hypothesized to impact Veterans access to care and alternative therapies. As most benzodiazepines prescribed to patients with PTSD in the VA are prescribed by mental health providers,(46, 47) we focused on mental health specific center level factors. In terms of structural factors, we included center rurality, complexity, quartile of volume of patients with PTSD, and region of care. We defined rurality at the medical center level as urban, rural, or highly rural as documented in the CDW. Center complexity is based on the VA complexity model that is based on number of patients, patient risk scores, research dollars and availability of services, and we obtained this measure from the CDW.(48) We estimated quartile of overall PTSD patient volume as documented in the Mental Health domain of the SAIL report.(29) Consistent with prior analyses of benzodiazepine prescribing in the VA,(24) we classified region by Veterans Integrated Service Network (VISN) as follows: Northeast VISNs 1–5; Midwest, VISNs 10–12, 15, and 23; South, VISNs 6–9, 16, and 17; and West, VISNs 18–22.

To capture care process, we included available metrics related to center utilization of psychotherapy, and Veteran reported access. Using the Mental Health SAIL program reports, we measured with the proportion of PTSD patients at a center who received psychotherapy sessions, the proportion who received longitudinal psychotherapy defined as 3 or more sessions in 6 weeks, and the proportion who received subspecialty PTSD care. We also incorporated center-averaged Veteran's ratings of overall access to care using a single item assessing the timeliness of

appointments from VA Survey of Healthcare Experiences, and mental health appointment access as obtained in a five item instrument and reported in the Mental Health SAIL program reports. The questions outlined in these instruments are described in more detail in the appendix.(28, 29) It is important to note that the earliest Mental Health SAIL program reports occurred in 2014, after the time period of this cohort. However, in analyses described in greater detail in the appendix, these variables by center were stable over time.(Appendix)

Statistical Analysis:

We first compared individual patient and center level characteristics by long-term benzodiazepine use with paired t-test and chi squared tests. We then used separate univariate logistic regression models for the association of center-level factors (structural and process factors) with long-term benzodiazepine prescribing not accounting for patient level factors, and thereafter used a mixed effects logistic regression model with patient and center level variables defined above as fixed effects and center as a random effect. Such a mixed effects model allowed us to determine the adjusted association of center level factors while simultaneously accounting for patient-level factors. To measure variability in long-term benzodiazepine prescribing between centers, we report the random effects parameters for center from the mixed effects model, which demonstrates the estimated standard deviation of the intercept by center on the logit scale. We report the random effect parameter for long-term benzodiazepine prescribing in 1) an unadjusted mixed effects logistic regression model, 2) a model incorporating only patient level variables, and 3) a model incorporating both patient and center level variables. To graphically assess center-to-center variability, we created a bar graph illustrating the proportion of Veterans prescribed long-term benzodiazepines at each center. All analyses were performed using the STATA statistical package (Version 14; College Station, TX).

Results:

Overall, 44,946 patients diagnosed with comorbid PTSD and COPD at 130 centers were alive during our time period of interest and were not currently enrolled in hospice. Of these, 10,926 (24.3%) were exposed to long-term benzodiazepines during our 180-day period of interest. Demographics, comorbidity, and medications prescribed prior to the period of interest are included in Table 1, and healthcare utilization and center level factors are included in Table 2.

We noted substantial differences among individuals with and without long-term benzodiazepine use. Compared to those who were not prescribed long-term benzodiazepines, those with long-term prescriptions were more likely to be white (90.1 vs. 80.8%), current smokers (69.3 vs. 66.8%), and have other mental health comorbidities such as generalized anxiety disorder (31.0 vs. 16.5%) and bipolar disorder (9.5 vs. 7.1%). Consistent with the mental health comorbidities above, individuals with long-term prescriptions were also more likely to be previously treated with medications such as atypical antipsychotics (34.5 vs. 23.5%), selective serotonin and serotonin-norepinephrine reuptake inhibitors (70.0 vs. 60.6%), "Z-drug" sedative hypnotics (15.2 vs 12.2%), and were more likely to have at least one mental health visit in the last year (Tables 1 and 2). Patients with long-term benzodiazepine prescriptions were also more likely to have markers of greater medication utilization for COPD, such as more frequent prescriptions of "rescue inhalers" such as albuterol (34.1 vs. 23.4% with >= 10 canister fills/year), long acting beta agonists (27.2 vs 23.2%), inhaled corticosteroids (34.7 vs 30.6%). Finally, it is of interest that patients with long-term benzodiazepine use were more likely to be prescribed opioids (54.1 vs. 32.9%; Table 1).

In models not adjusted for patient or other center level factors, center characteristics such as psychotherapy provided to a greater proportion of patients (OR 0.98, 95% CI 0.98-0.99), rural location (0.72, 95% CI 0.52-0.99), and a PTSD population in the second or third quartile (Second: 0.84,95% CI 0.78-0.91; Third: 0.81, 95% CI 0.76-0.88) were associated with reduced long term benzodiazepine use. Midwest and Southern locations were associated with greater prescribing

(Midwest: OR 1.22, 95% CI 1.15-1.31; South 1.19, 95% CI 1.13-1.27). In the unadjusted model, the random effect on the logit scale by center was 0.36 (95% CI 0.31-0.41). In analyses adjusted for patient, but not center level factors, the random effect of was slightly attenuated 0.33 (95% CI 0.28-0.39). This variability in actual center level prescribing is illustrated in Figure 1.

In models inclusive of patient and center level factors, Southern centers were associated with long-term benzodiazepine prescribing (OR 1.22, 95% CI 1.02-1.47), as were centers with a greater percentage of patients receiving subspecialty PTSD care (OR 1.01, 95% CI 1.00-1.02). Centers where Veteran surveys reported greater access to mental health services tended to have lower rates of long-term benzodiazepine prescribing (OR 0.51, 95% CI 0.32-0.81). In this fully adjusted model that incorporated center level factors, the random effect by center was further attenuated 0.28 (95% CI 0.24-0.33).

Discussion:

We observed long-term benzodiazepine prescriptions among a quarter of Veterans with comorbid PTSD and COPD, individuals with dual contraindications to such prescriptions.(3, 5) Considerable variability existed among medical centers in these prescriptions, even after accounting for a robust set of patient level factors. Consistent with our hypothesis, we found lower ratings of access to be associated with guideline discordant benzodiazepine prescriptions.

Among the center mental health access variables, lower perceived access to mental health services and greater proportional use of subspecialty PTSD care emerged as significant associations. The interpretation of greater benzodiazepine prescriptions with lower Veteran reported access is fairly intuitive, benzodiazepines may be substituted for evidence-based therapies among individuals with a real or perceived inability to access alternatives.(49) However, the association of guideline discordant benzodiazepine prescribing with greater center-level percentage use of subspecialty PTSD services is less straightforward. One possible interpretation could be that having a higher percentage of patients with PTSD being treated in PTSD subspecialty care is indicative of strain on subspecialty PTSD services (i.e. capacity of subspecialty PTSD services is overcome). In the setting of this strain on PTSD subspecialty services, the centers may not be able to provide optimal guideline concordant care, as has been observed in other settings.(50, 51) It is also possible that the greater proportion of subspecialty use is a marker of greater patient illness severity at these centers not captured in our analysis of patient level data. Future studies incorporating more in-depth measures of patient symptom severity may be better able to explain these findings.

Consistent with an analysis of benzodiazepine prescribing among Veterans with PTSD by Lund et. al.,(24) we found that prescription of benzodiazepines varied substantially by region. However, while Lund et. al. had found the regional variation had declined substantially by their last year of analysis in 2009, these regional differences emerged in our analysis just several years later (2010-2012). Similar to the earlier estimates, we observed the highest prescribing of

benzodiazepines to occur in the South.(24) This finding also tracks with greater overall benzodiazepine prescribing in the South in a non-VA sample, suggesting regional medical practices exist that transcend particular healthcare organizations or condition-specific indications.(52)

While we found several center-level variables associated with benzodiazepine prescriptions, a substantial degree of variation remained even after accounting for these factors. Prior work has found that barriers to guideline consistent prescribing for opioids and benzodiazepines include institutional culture, individual provider beliefs regarding comparative medication safety, and the emotional burden on providers associated with the de-implementation of these medications.(53, 54) Future studies involving a qualitative approach in low and high prescribers of long-term benzodiazepines will be necessary to better understand sources of unmeasured variability in this practice.

Our work has several limitations. First, as an analysis of administrative data, we are limited in our capacity to directly ascertain severity of PTSD and COPD. For instance, we did not have patient symptom questionnaires related to PTSD, and we did not have access to spirometry to grade the severity of airflow limitation related to COPD. As noted above, this may limit our ability to fully control for patient level symptom severity at each center. We mitigate this limitation by incorporating a large number of patient level variables related to medication and healthcare utilization hypothesized to reflect illness severity, but residual unmeasured confounding by illness severity remains a concern. Another potential limitation concerns our inability to determine the reason for benzodiazepine prescription, and it is possible that in relatively rare cases, long-term benzodiazepine use may be warranted for certain neurologic, sleep, and mental health disorders such as REM sleep behavior disorder(55) and severe panic disorder.(56) Although it would be incorrect to assume that patients with PTSD and COPD should never be prescribed long-term benzodiazepines, the proportion of patients with such treatment far exceeds what would be expected from these relatively rare indications.

Guideline discordant long-term benzodiazepine prescriptions are common among Veterans with comorbid PTSD and COPD, and prescribing practices vary substantially by center. This variability, in turn, is at least partially explained by access to mental health services. Our findings suggest that patient access to high quality mental health care will need to be incorporated into future strategies to reduce guideline discordant prescribing of benzodiazepines. Further work will be necessary to evaluate other sources of center-to-center variability in order to identify other targets for intervention.

Table 1. Patient demographics, comorbidities, and medications by benzodiazepine prescription category.

	No Long-Term BZD		Long Term BZD		
	n=34,020		n=10,926		
Demographics	Mean/n	SD/%	Mean/n	SD/%	p-value
Age (years)	62.5	8.6	62	7.7	<0.001
Female (%)	1191	3.5	539	4.9	<0.001
BMI (kg/m2)	29.7	6.8	29.9	6.7	0.009
Race (%)					<0.001
Caucasian (%)	27486	80.8	9839	90.1	
Black (%)	4670	13.7	565	5.2	
Asian (%)	93	0.3	16	0.2	
Native American (%)	250	0.7	65	0.6	
Other/Unkown (%)	1521	4.4	441	4	
Hispanic (%)	992	2.7	290	2.7	0.753
Current smoking (%)	22714	66.8	7563	69.3	<0.001
Rural (%)	4732	13.9	1571	14.4	0.059
Comorbidities					
Generalized anxiety (%)	5603	16.5	3390	31	<0.001
Major depression (%)	17176	50.5	5768	52.8	<0.001
Substance use disorder (%)	10580	31.1	2553	23.4	<0.001
Bipolar disorder (%)	2424	7.1	1038	9.5	<0.001
Psychotic disorder (%)	2127	6.3	877	8	<0.001
Insomnia (%)	2738	8.1	1024	9.4	<0.001
Obstructive sleep apnea (%)	6486	19.1	2241	20.5	0.001
Traumatic brain injury (%)	731	2.2	293	2.7	0.001
Charlson category (%)					0.06
Score 0-1	15448	45.4	4846	44.4	
Score 2	9157	26.9	2936	26.9	
Score 3+	9415	27.7	3114	28.8	
Greater than 50% SC (%)	30586	89.9	10199	93.4	<0.001
Medications in the last year					
Prazosin (%)	3365	10	1267	11.6	<0.001
MAO inhibitors (%)	19	0.1	8	0.1	0.519
TCA (%)	673	2	324	3	<0.001
Typical antipsychotic (%)	795	2.3	421	3.9	<0.001
Atypical antipsychotic (%)	7996	23.5	3769	34.5	<0.001
SSRI or SNRI (%)	20630	60.6	7653	70	<0.001
Any Z-Drug (%)	4146	12.2	1658	15.2	<0.001
Trazodone (%)	9852	29	3132	28.7	0.555
Doxepin (%)	533	1.6	283	2.6	<0.001
LABA (%)	7894	23.2	2967	27.2	<0.001
LAMA (%)	2603	7.7	962	8.8	<0.001
ICS (%)	10415	30.6	3789	34.7	<0.001
Short acting bronchodilator use					<0.001
None (%)	10532	31	2659	24.3	
1-9 canisters/year (%)	15528	45.6	4539	41.5	
>= 10 canisters/year (%)	7960	23.4	3728	34.1	
>30 days of an opiate	11183	32.9	5913	54.1	<0.001
>30 days of a glucocorticoid	1357	4	597	5.5	<0.001
Healthcare Utilization in the Last Year					
1 or more COPD Exacerbations (%)	5035	14.8	1901	17.4	<0.001
Any ED visit in last year (%)	12867	37.8	4159	38.1	0.648
Any medical admission (%)	7187	21.1	2405	22	0.049
Any psychiatric admission (%)	2336	6.9	647	5.9	0.001

Primary care visits					<0.001
No primary care visits (%)	447	1.3	80	0.7	
1-5 Primary care visits/year (%)	22786	67	6642	60.8	
>= 6 Primary care visits/year (%)	10787	31.7	4204	38.5	
Mental health					<0.001
No mental health visits (%)	6061	17.8	861	7.9	
1-9 Mental health visits/year (%)	19323	56.8	7125	65.2	
>= 10 Mental health visits/year (%)	8636	25.4	2940	26.9	
Any pulmonary visits (%)	6304	18.5	2148	19.7	0.009
Any sleep visits (%)	1587	4.7	519	4.8	0.714

BZD-Benzodiazepine, COPD-chronic obstructive pulmonary disease, OSA-Obstructive Sleep Apnea, SABA- short acting bronchodilator, SAMA-short acting methacholine antagonist, LABA-long acting beta agonist, LAMA-long acting methacholine antagonist, ICS-inhaled corticosteroid,SSRI-selective serotonin reuptake inhibitor, SNRI-serotonin norepinephrine reuptake inhibitor. p-value from chi2 and t-test from categorical and continuous variables, respectively.

Table 2. Center level factors by benzodiazepine prescription category.

	No Long-Term BZD		Long Term BZD		
	n=34,020		n=10,926		
Center level factors (n=130 centers)					
Complexity level					<0.001
Level 1a	11680	34.3	3611	33.1	
Level 1b	4147	12.2	1212	11.1	
Level 1c	7548	22.2	2689	24.6	
Level 2	6172	18.1	1973	18.1	
Level 3	4210	12.4	1371	12.6	
Excluded	263	0.8	70	0.6	
Rurality					0.059
Highly Rural	120	0.4	55	0.5	
Rural	4732	13.9	1571	14.4	
Urban	29288	86.1	9355	85.6	
Quartile of Center PTSD Patient Volume					<0.001
First quartile	4178	12.3	1491	13.7	
Second quartile	6323	18.6	1893	17.4	
Third quartile	8724	25.7	2532	23.2	
Fourth quartile	8724	43.5	4992	45.8	
Veterans perceived overall access to care (/4 points)	3.3	0.1	3.3	0.1	0.394
Veterans perceived access to mental health (/ 5 points)	4.1	0.1	4.1	0.1	0.136
% of Veterans with PTSD receiving subspecialty care	18.0	8.2	18.1	8.4	0.424
% of Veterans with PTSD receiving psychotherapy	67.0	8.9	67.1	9.5	0.658
% of Veterans with PTSD long-term psychotherapy	35.1	6.1	34.6	6.2	<0.001

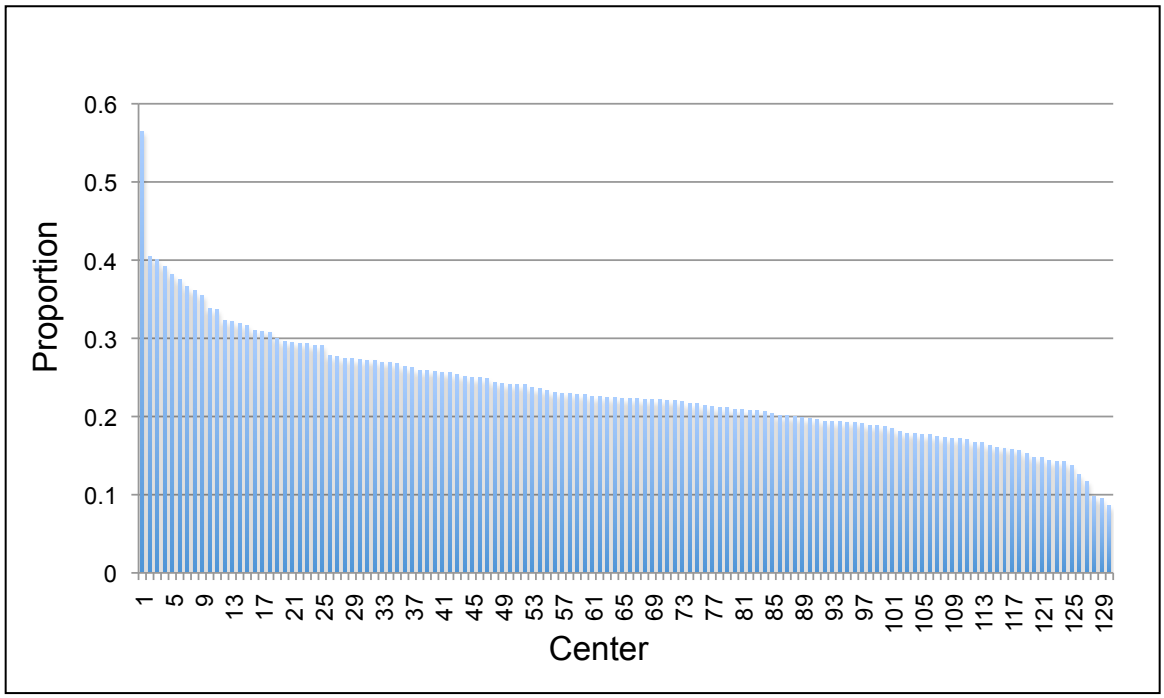
BZD-Benzodiazepine, COPD-chronic obstructive pulmonary disease, PTSD-posttraumatic stress disorder, ED-Emergency Department, SSRI-selective serotonin reuptake inhibitor. p-value from chi2 and t-test from categorical and continuous variables, respectively.

Table 3. Center level associations with long-term benzodiazepine prescriptions.

	Univariate		Fully Adjusted	
Structural factors	OR	95% CI	OR	95% CI
Complexity level				
Level 1a	1.00	ref	1.00	ref
Level 1b	0.95	0.88-1.02	0.97	0.79-1.18
Level 1c	1.15	1.09-1.22	1.07	0.89-1.38
Level 2	1.03	0.97-1.10	1.01	0.83-1.23
Level 3	1.05	0.98-1.13	0.9	0.72-1.12
Excluded	0.86	0.66-1.12	0.78	0.39-1.56
Region				
Northeast	1.00	ref	1.00	ref
Midwest	**1.22**	**1.15-1.31**	1.13	0.94-1.34
South	**1.19**	**1.13-1.27**	**1.22**	1.02-1.47
West	0.94	0.88-1.01	0.85	0.70-1.04
Rurality				
Highly rural	1.00	ref	1.00	ref
Rural	**0.72**	**0.52-0.99**	0.72	0.36-1.43
Urban	**0.70**	**0.51-0.96**	0.67	0.34-1.56
Quartile of PTSD patient volume				
First quartile (766-2223 pts)	1.00	ref	1.00	ref
Second quartile (2280-3470 pts)	**0.84**	**0.78-0.91**	0.86	0.72-1.04
Third quartile (3485-6163 pts)	**0.81**	**0.76-0.88**	0.89	0.73-1.09
Fourth quartile (6202-12987 pts)	0.95	0.89-1.01	0.94	0.75-1.18
Process factors				
Veterans perceived overall access to care (/point)	0.93	0.78-1.10	1.38	0.71-2.71
Veterans perceived access to mental health (/point)	0.89	0.77-1.04	**0.51**	0.32-0.81
% of Veterans with PTSD with subspecialty care	1.00	1.00-1.00	**1.01**	1.00-1.02
% of Veterans with PTSD with receipt of psychotherapy	1.00	1.00-1.00	1.00	0.99-1.00
% of Veterans with PTSD long-term psychotherapy	**0.98**	**0.98-0.99**	0.99	0.98-1.01
Random Effects Parameter	**0.36**	**0.31-0.41**	**0.28**	**0.24-0.33**

All unadjusted odds ratios (OR) obtained from univariate logistic regression except for random effects parameter, which was obtained from a mixed effects model using only center as a random effect. Fully adjusted OR obtained from mixed effects model incorporating all patient and center variables from tables 1 and 2 as fixed effects and center as random effect. CI-Confidence Interval. Ref-referent category. Significant OR in **bold**.

Figure 1. Proportion of Veterans prescribed benzodiazepines long-term by center.



Appendix:

Patient reported access questions:

Overall Access to Care:
Source: Survey of Healthcare Experiences
Description:
Question Stem: "In the past 12 months, not counting the times you needed care right away, how often did you get an appointment as soon as you thought you needed?
Response: 1-Never, 2-Sometimes, 3-Usually, 4-Always
The survey of Healthcare Experiences is mailed to a randomly selected sample of Veterans with an outpatient visit within the last 30 days.

Access to Mental Health Care:
Source: Office of Mental Health Veteran Survey
Description:
Average of 5 items each rated on a 1-5 scale. Responses to survey item stems include 1-strongly disagree, 2-disagree, 3-neither disagree or agree, 4-strongly agree, 5-strongly agree.
Survey item stems are:
1. "I get appointments with my mental health provider on the day that I want or within two weeks of the day that I want."
2. "I can see my mental health provider who prescribes my medications as frequently as needed."
3. "If I have a question about my psychiatric medication I can get in touch with a mental health provider or pharmacist by phone to get my question answered."
4. "I known that I will get a call back if I leave a message for my mental health provider."
5. "I can't see my mental health provider as much as I should because the provider does not have time to see me." (reverse scored)
The Office of Mental Health Veteran Survey is distributed by mail to a random sample of facility patients who had an outpatient appointment in the prior week.

Correlation of Site Level Mental Health Measures over time:

	Correlation 2014 to 2015, r-value
Quartile of PTSD Patient Volume	0.98
Veterans Perceived Access to MH Care	0.62
% of Veterans with PTSD with subspecialty care	0.92
% of Veterans with PTSD with receipt of psychotherapy	0.87
% of Veterans with PTSD receiving psychotherapy who have at least 3 sessions	0.91

PTSD-posttraumatic stress disorder, MH-mental heath. r-value obtained from pearson's correlation of values from 2014 and 2015.

References:

1. Park SY, Bae S, Shin JY. Real-world prescribing patterns of long-acting benzodiazepines for elderly Koreans in 2013. International journal of clinical pharmacology and therapeutics. 2017;55(6):472-9.
2. Lund BC, Bernardy NC, Vaughan-Sarrazin M, Alexander B, Friedman MJ. Patient and facility characteristics associated with benzodiazepine prescribing for veterans with PTSD. Psychiatric services. 2013;64(2):149-55.
3. The Management of Post-Traumatic Stress Working Group. VA/DOD Clinical Practice Guideline for Management of Post-Traumatic Stress. (Version 2.0). Department of Veterans Affairs and the Department of Defense. 2010.
4. Guina J, Rossetter SR, De RB, Nahhas RW, Welton RS. Benzodiazepines for PTSD: A Systematic Review and Meta-Analysis. Journal of psychiatric practice. 2015;21(4):281-303.
5. Celli BR, MacNee W, Force AET. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. The European respiratory journal. 2004;23(6):932-46.
6. Chen SJ, Yeh CM, Chao TF, Liu CJ, Wang KL, Chen TJ, et al. The Use of Benzodiazepine Receptor Agonists and Risk of Respiratory Failure in Patients with Chronic Obstructive Pulmonary Disease: A Nationwide Population-Based Case-Control Study. Sleep. 2015;38(7):1045-50.
7. Ekstrom MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. Bmj. 2014;348:g445.
8. Vozoris NT, Fischer HD, Wang X, Stephenson AL, Gershon AS, Gruneir A, et al. Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD. The European respiratory journal. 2014;44(2):332-40.
9. Chung MC, Jones RC, Harding SA, Campbell J. Posttraumatic Stress Disorder Among Older Patients with Chronic Obstructive Pulmonary Disease. The Psychiatric quarterly. 2016;87(4):605-18.
10. Abrams TE, Blevins A, Weg MW. Chronic obstructive lung disease and posttraumatic stress disorder: current perspectives. International journal of chronic obstructive pulmonary disease. 2015;10:2219-33.
11. Chang CH, Chuang LP, Lin SW, Lee CS, Tsai YH, Wei YF, et al. Factors responsible for poor sleep quality in patients with chronic obstructive pulmonary disease. BMC pulmonary medicine. 2016;16(1):118.
12. Hsieh MH, Lee CT, Tsai PJ, Tsai CJ, Liao YT, Chen VC, et al. Chronic obstructive pulmonary disease and anxiety disorders: a nationwide population-based study in Taiwan. General hospital psychiatry. 2016;42:1-6.
13. Short NA, Allan NP, Stentz L, Portero AK, Schmidt NB. Predictors of insomnia symptoms and nightmares among individuals with post-traumatic stress disorder: an ecological momentary assessment study. Journal of sleep research. 2018;27(1):64-72.
14. Wagner J, Wagner ML. Non-benzodiazepines for the treatment of insomnia. Sleep medicine reviews. 2000;4(6):551-81.

15. Roth T. Hypnotic use for insomnia management in chronic obstructive pulmonary disease. Sleep medicine. 2009;10(1):19-25.
16. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. The Journal of clinical psychiatry. 2005;66(4):469-76.
17. Lazowski LK, Townsend B, Hawken ER, Jokic R, du Toit R, Milev R. Sleep architecture and cognitive changes in olanzapine-treated patients with depression: a double blind randomized placebo controlled trial. BMC psychiatry. 2014;14:202.
18. Lipinska G, Baldwin DS, Thomas KG. Pharmacology for sleep disturbance in PTSD. Human psychopharmacology. 2016;31(2):156-63.
19. Aarts N, Zuurbier LA, Noordam R, Hofman A, Tiemeier H, Stricker BH, et al. Use of Selective Serotonin Reuptake Inhibitors and Sleep Quality: A Population-Based Study. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2016;12(7):989-95.
20. Kluge M, Schussler P, Steiger A. Duloxetine increases stage 3 sleep and suppresses rapid eye movement (REM) sleep in patients with major depression. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2007;17(8):527-31.
21. Monti JM, Torterolo P, Pandi Perumal SR. The effects of second generation antipsychotic drugs on sleep variables in healthy subjects and patients with schizophrenia. Sleep medicine reviews. 2016.
22. Monti JM, Monti D. Sleep in schizophrenia patients and the effects of antipsychotic drugs. Sleep medicine reviews. 2004;8(2):133-48.
23. Singh B, Hughes AJ, Mehta G, Erwin PJ, Parsaik AK. Efficacy of Prazosin in Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis. The primary care companion for CNS disorders. 2016;18(4).
24. Lund BC, Abrams TE, Bernardy NC, Alexander B, Friedman MJ. Benzodiazepine prescribing variation and clinical uncertainty in treating posttraumatic stress disorder. Psychiatric services. 2013;64(1):21-7.
25. Lader M. Benzodiazepines revisited--will we ever learn? Addiction. 2011;106(12):2086-109.
26. Valenstein M, Taylor KK, Austin K, Kales HC, McCarthy JF, Blow FC. Benzodiazepine use among depressed patients treated in mental health settings. The American journal of psychiatry. 2004;161(4):654-61.
27. Selected Veteran Health Statistics. National Center for Veterans Analysis and Statistics. Department of Veterans Affairs, Veteran Health Administration. July 17, 2017.
28. Wong ES, Liu CF, Hernandez SE, Augustine MR, Nelson K, Fihn SD, et al. Longer wait times affect future use of VHA primary care. Healthcare. 2017.
29. Lemke S, Boden MT, Kearney LK, Krahn DD, Neuman MJ, Schmidt EM, et al. Measurement-based management of mental health quality and access in VHA: SAIL mental health domain. Psychological services. 2017;14(1):1-12.
30. Cooke CR, Joo MJ, Anderson SM, Lee TA, Udris EM, Johnson E, et al. The validity of using ICD-9 codes and pharmacy records to identify patients with chronic obstructive pulmonary disease. BMC health services research. 2011;11:37.

31. Steel A, Goldring J. End-of-life care in patients with chronic obstructive pulmonary disease. British journal of hospital medicine. 2015;76(1):C10-3.
32. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2011. WHO. 2010.
33. Beckham JC, Crawford AL, Feldman ME, Kirby AC, Hertzberg MA, Davidson JR, et al. Chronic posttraumatic stress disorder and chronic pain in Vietnam combat veterans. Journal of psychosomatic research. 1997;43(4):379-89.
34. Roberts MH, Mapel DW, Hartry A, Von Worley A, Thomson H. Chronic pain and pain medication use in chronic obstructive pulmonary disease. A cross-sectional study. Annals of the American Thoracic Society. 2013;10(4):290-8.
35. Sharafkhaneh A, Giray N, Richardson P, Young T, Hirshkowitz M. Association of psychiatric disorders and sleep apnea in a large cohort. Sleep. 2005;28(11):1405-11.
36. Forman-Hoffman VL, Bose J, Batts KR, Glasheen C, Hirsch E, Karg RS, et al. Correlates of Lifetime Exposure to One or More Potentially Traumatic Events and Subsequent Posttraumatic Stress among Adults in the United States: Results from the Mental Health Surveillance Study, 2008-2012. CBHSQ Data Review. Rockville (MD)2012.
37. Ajmera M, Sambamoorthi U, Metzger A, Dwibedi N, Rust G, Tworek C. Multimorbidity and COPD Medication Receipt Among Medicaid Beneficiaries With Newly Diagnosed COPD. Respiratory care. 2015;60(11):1592-602.
38. Pugh MJ, Jaramillo CA, Leung KW, Faverio P, Fleming N, Mortensen E, et al. Increasing Prevalence of Chronic Lung Disease in Veterans of the Wars in Iraq and Afghanistan. Military medicine. 2016;181(5):476-81.
39. Hawkins EJ, Malte CA, Grossbard JR, Saxon AJ. Prevalence and Trends of Concurrent Opioid Analgesic and Benzodiazepine Use Among Veterans Affairs Patients with Post-traumatic Stress Disorder, 2003-2011. Pain medicine. 2015;16(10):1943-54.
40. Kroll DS, Nieva HR, Barsky AJ, Linder JA. Benzodiazepines are Prescribed More Frequently to Patients Already at Risk for Benzodiazepine-Related Adverse Events in Primary Care. Journal of general internal medicine. 2016;31(9):1027-34.
41. Bobo WV, Reilly-Harrington NA, Ketter TA, Brody BD, Kinrys G, Kemp DE, et al. Complexity of illness and adjunctive benzodiazepine use in outpatients with bipolar I or II disorder: results from the Bipolar CHOICE study. Journal of clinical psychopharmacology. 2015;35(1):68-74.
42. Haw C, Stubbs J. Benzodiazepines--a necessary evil? A survey of prescribing at a specialist UK psychiatric hospital. Journal of psychopharmacology. 2007;21(6):645-9.
43. Larson EB, Zollman FS. The effect of sleep medications on cognitive recovery from traumatic brain injury. The Journal of head trauma rehabilitation. 2010;25(1):61-7.
44. Hynninen MJ, Pallesen S, Hardie J, Eagan TM, Bjorvatn B, Bakke P, et al. Insomnia symptoms, objectively measured sleep, and disease severity in chronic

obstructive pulmonary disease outpatients. Sleep medicine. 2013;14(12):1328-33.
45. Donabedian A. Evaluating the quality of medical care. The Milbank Memorial Fund quarterly. 1966;44(3):Suppl:166-206.
46. Seal KH, Shi Y, Cohen G, Cohen BE, Maguen S, Krebs EE, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. Jama. 2012;307(9):940-7.
47. Hawkins EJ, Malte CA, Hagedorn HJ, Berger D, Frank A, Lott A, et al. Survey of Primary Care and Mental Health Prescribers' Perspectives on Reducing Opioid and Benzodiazepine Co-Prescribing Among Veterans. Pain medicine. 2016.
48. Korom-Djakovic D, Canamucio A, Lempa M, Yano EM, Long JA. Organization Complexity and Primary Care Providers' Perceptions of Quality Improvement Culture Within the Veterans Health Administration. American journal of medical quality : the official journal of the American College of Medical Quality. 2016;31(2):139-46.
49. Wang V, Maciejewski ML, Helfrich CD, Weiner BJ. Working smarter not harder: Coupling implementation to de-implementation. Healthcare. 2017.
50. Bagshaw SM, Wang X, Zygun DA, Zuege D, Dodek P, Garland A, et al. Association between strained capacity and mortality among patients admitted to intensive care: A path-analysis modeling strategy. Journal of critical care. 2018;43:81-7.
51. Weissman GE, Gabler NB, Brown SE, Halpern SD. Intensive care unit capacity strain and adherence to prophylaxis guidelines. Journal of critical care. 2015;30(6):1303-9.
52. Paulozzi LJ, Mack KA, Hockenberry JM. Variation among states in prescribing of opioid pain relievers and benzodiazepines--United States, 2012. Journal of safety research. 2014;51:125-9.
53. Kim HS, McCarthy DM, Hoppe JA, Mark Courtney D, Lambert BL. Emergency Department Provider Perspectives on Benzodiazepine-Opioid Coprescribing: A Qualitative Study. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2018;25(1):15-24.
54. Kennedy LC, Binswanger IA, Mueller SR, Levy C, Matlock DD, Calcaterra SL, et al. "Those Conversations in My Experience Don't Go Well": A Qualitative Study of Primary Care Provider Experiences Tapering Long-term Opioid Medications. Pain medicine. 2017.
55. St Louis EK, Boeve AR, Boeve BF. REM Sleep Behavior Disorder in Parkinson's Disease and Other Synucleinopathies. Movement disorders : official journal of the Movement Disorder Society. 2017;32(5):645-58.
56. Noyes R, Jr., Garvey MJ, Cook B, Suelzer M. Controlled discontinuation of benzodiazepine treatment for patients with panic disorder. The American journal of psychiatry. 1991;148(4):517-23.