What's Gender Got to Do With It:

Accounting for Differences in Incident Guideline Discordant Prescribing for PTSD Among Women and Men Veterans

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Abstract

Objectives: Women veterans are more likely than men veterans to receive medications that Department of Veterans Affairs clinical practice guidelines recommend against to treat posttraumatic stress disorder (PTSD). To understand this difference, we examined potential confounders in incident prescribing of guideline discordant medications (GDMs) in veterans with PTSD.

Methods: Veterans receiving care for PTSD during 2020 were identified using Veterans Health Administration administrative data. PTSD diagnosis was established by the presence of at least 1 *ICD-10* coded outpatient encounter or inpatient hospitalization during the calendar year 2020. Incident GDM prescribing was assessed during 2021, including benzodiazepines, antipsychotics, select anticonvulsants, and select antidepressants. Log-binomial regression was used to estimate the difference in risk for GDM initiation between men and women, adjusted for patient, prescriber, and facility-level covariates, and to identify key confounding variables.

Results: Of 704,699 veterans with PTSD, 16.9% of women and 10.1% of men initiated a GDM, an increased risk of 67% for women [relative risk (RR) = 1.67; 95% CI, 1.65–1.70]. After adjustment, the gender difference decreased to 1.22 (95% CI, 1.20–1.24) in a fully specified model. Three key confounding variables were identified: bipolar disorder (RR = 1.60; 95% CI, 1.57–1.63), age (<40 years: RR = 1.20 [1.18–1.22]; 40–54 years: RR = 1.13 [1.11–1.16]; ≥65 years: RR = 0.64 [0.62–0.65]), and count of distinct psychiatric medications prescribed in the prior year (RR = 1.14; 1.13–1.14).

Conclusions: Women veterans with PTSD were 67% more likely to initiate a GDM, where more than half of this effect was explained by bipolar disorder, age, and prior psychiatric medication. After adjustment, women veterans remained at 22% greater risk for an incident GDM, suggesting that other factors remain unidentified and warrant further investigation.

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US veterans are at increased risk for posttraumatic stress disorder (PTSD) due to combat exposure and sexual assault in the military,[1] with a greater lifetime prevalence of PTSD among women relative to men.[2,3] Gender- and sex-based differences in trauma exposure, etiology, treatment response, and risk of developing PTSD have been widely studied.[3–7] For instance, many studies have found that men are at increased risk of trauma exposure, but women are more likely to develop PTSD.[3,7,8] However, this difference in risk equalizes or reverses depending on type or history of trauma (eg, combat exposure, sexual assault and child abuse, and multiple traumatic events).[3] This suggests that observed gender differences in individuals with PTSD are complicated by a variety of factors.

Gender differences in medication prescribing have been observed among veterans with PTSD.[9] Women veterans were more likely to receive medications that Department of Veterans Affairs (VA) and Department of Defense (DoD) guidelines recommend against using to treat PTSD (ie, guideline discordant medications [GDMs]).[9] These medications include benzodiazepines, antipsychotics, select anticonvulsants (lamotrigine, tiagabine, topiramate, and valproate), and select antidepressants (amitriptyline and citalopram). Benzodiazepines, for instance, are recommended against use due to both lack of evidence of effectiveness in treating PTSD and the risks outweighing the potential benefits.[9] In 2019, 15.8% of women veterans with PTSD were prescribed benzodiazepines compared to only 10.9% of men veterans with PTSD.[9] Gender differences in GDM prescribing observed among veterans with PTSD were persistent over the decade from 2010 through 2019.[9,10]

Editor's Note

We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

Clinical Points

- Women veterans are more likely than men veterans to receive medications recommended against use for the treatment of posttraumatic stress disorder (PTSD) according to Veterans Affairs/Department of Defense Clinical Practice Guidelines, yet explanations for this disparity were unknown.
- Our findings suggest that 2 of 3 identified mediators—bipolar diagnosis and number of unique psychiatric medications—may point to greater complexities of treating women veterans with PTSD.
- If gender differences in PTSD guideline discordant medication prescribing are indeed driven by clinical complexity, we must investigate why women veterans with PTSD are more complex to treat than men veterans.

Although much research has been dedicated to identifying and addressing sex- and gender-based differences in PTSD, it does not explain why women are more likely to be prescribed PTSD GDM. It has been well documented that gender is a socially constructed phenomenon that takes on configurations that vary by race, class, culture, and environment.[11] In the military, traits such as strength, toughness, aggression, and confidence have been idealized and attributed to "masculinity," thus "men."[3,6] Traits in opposition to "masculinity" (ie, nurturing and empathy) are less valued and attributed to "femininity," thus contributing to gender inequality.[3] Individuals are socialized to believe that "normal" men behave in a "masculine" way and vice versa. For veterans who have experienced trauma, gender norms can be maladaptive, leading men to downplay symptoms or delay help-seeking.[3,12] Women veterans may be more likely to self-report emotional distress, and clinicians may be more likely to screen women for sexual trauma.[3] Thus, we assessed a broad set of variables to explore the possibility that societal gender roles and norms may influence not only how men and women veterans experience PTSD symptoms, but also how their clinical presentation of symptoms is interpreted and differentially treated.[3,6]

METHODS

Data Sources

National administrative data from the Veterans Health Administration (VHA) Corporate Data Warehouse were obtained through the VHA Informatics and Computing Infrastructure. Inpatient and outpatient encounter data were used to identify veterans with PTSD and establish the presence of other psychiatric and medical comorbidities. Outpatient pharmacy data were used to identify prescribing of psychiatric medication, including GDMs for PTSD. Characteristics of prescribing providers, including age, sex, and clinical specialty, were determined from the staff information domain. This study was approved by the University of Iowa Institutional Review Board and the Iowa City Veterans Administration Research and Development Committee.

Patients

The target population was veterans receiving care for PTSD in VHA during 2020. Veterans with PTSD were identified by having at least 1 inpatient hospitalization coded for PTSD (*ICD-10*: F43.1X) during 2020, or at least 1 coded outpatient encounter during 2020 and a second coded outpatient encounter within the prior 730 days.[13,14] Veterans were further required to receive at least 1 dispensed outpatient prescription for a psychiatric medication during 2020 to establish a history of receiving psychiatric pharmacotherapy from VHA.[15]

Guideline Discordant Medications

Medications were identified as guideline discordant based on a classification of "recommended against" or "suggested against," according to the 2017 VA/DoD clinical practice guideline for PTSD.[16] The primary outcome of interest was incident prescribing of at least one of these medications during 2021. This year was selected because it was the most recent year of complete data available at the time the study was conducted. Incident prescribing was defined as an observed prescription during 2021 with no prior prescriptions for the medication dispensed in the prior 365 days. GDM incidence was assessed during 2021, the year after PTSD ascertainment, to ensure prescribing occurred after the PTSD diagnosis.

Analysis

The analysis goals were first to contrast the incidence of GDM prescribing between women and men veterans and second to determine the extent to which an observed difference was explained by confounding variables. Because we hypothesize that culturally driven assumptions about gender may drive observed differences in prescribing GDM to men and women veterans, we refer to a "gender effect" even though we only had access to veterans' self-reported "sex" in the administrative data. The bivariate contrast between gender and risk for incident GDM prescribing was conducted with a χ^2 test, and a log-binomial model was used to determine the unadjusted relative risk (RR). Multivariable log-binomial regression was used to examine the impact of 4 clusters of confounding variables on this relationship: veteran demographics, veteran clinical characteristics, prescribing provider characteristics, and facility characteristics, and to estimate an adjusted RR for incident GDM prescribing between genders.

Veteran demographics in addition to gender included age, race, ethnicity, urban versus rural residence, marital

status, branch of military service, and years of service. Clinical characteristics included psychiatric comorbidities of depressive disorder, anxiety disorder, substance use disorder, psychotic disorder, and bipolar disorder.[9] Assessment of medical comorbidity included the presence of chronic pain,[17–19] sleep disorder,[20] and the Charlson Comorbidity Index.[21] The Charlson Comorbidity Index is a weighted index score based on selected medical diagnoses (eg, diabetes and cancer), which is associated with long-term mortality and among the most widely used measures of comorbidity used in clinical research.[22] Psychiatric and medical diagnoses were established by the presence of at least 1 *ICD-10* coded outpatient encounter or inpatient hospitalization during the calendar year 2020. Provider characteristics of a primary medication prescriber, including age, sex, and clinical specialty, were established for each veteran based on which provider prescribed the greatest total supply days of psychiatric medication dispensed during 2020. The count of unique psychiatric medication prescribers for a given patient was also included in the model, as well as a count of unique psychiatric medications prescribed during 2020. A primary site of care was established based on the VHA facility where the most PTSD-coded encounters were observed during 2020, including the facility type (VA hospital, urban clinic, or rural clinic) and geographic region.

A 2-stage approach was used to determine which of these confounding variables had the most influence as confounders.[23] In the first stage, separate log-binomial regression models were created for each variable cluster. If the RR for the gender effect in the cluster model changed by more than 0.10 from the unadjusted risk estimate, individual variables within the cluster were examined for confounding effects. In this second stage, separate log-binomial regression models were created for each variable within the cluster, along with gender, to determine the change in the RR estimate with its addition, relative to the unadjusted estimate. Individual variables that shifted the RR for the gender effect by more than 0.10 from the unadjusted estimate were identified and compiled into a restricted variable model, whereas variables that failed to demonstrate an independent relationship with GDM risk were removed. Bivariate comparisons of clinical characteristics between men and women were conducted using χ^2 tests for categorical variables and *t* tests for discrete variables. All analyses used a 2-tailed significance level of $\alpha = 0.05$ and were conducted using SAS version 9.4.

RESULTS

Of 870,815 veterans who received care for PTSD in VHA during 2020, 704,699 (81%) were dispensed at least 1 psychiatric medication during this year and comprised the study population. This population included 106,924 (15.2%) women, and contrasts between women and men are presented in Table 1. Women were younger than men, with a greater proportion below age 40 years (32.9% vs 21.3%) and a lower proportion above age 65 years (8.7% vs 39.8%). Men were more likely to be white (68.2% vs 54.4%) and live in rural areas (19.3% vs 13.6%). Women were more likely to be diagnosed with psychiatric comorbidities including depressive disorders and anxiety disorders, whereas men were more likely to be diagnosed with substance use disorder and sleep disorders. Women veterans, relative to men veterans, were more likely to have a primary psychiatric medication prescriber that was female (48.5% vs 38.7%), and the prescriber was somewhat more likely to be a mental health specialist (71.2% vs 67.4%) versus a primary care provider (18.4% vs 22.8%). Women veterans were also more likely to receive PTSD care at a VA medical center (48.2% vs 44.3%) and less likely to receive care from a rurally located VA clinic (5.8% vs 8.4%).

GDMs for PTSD were initiated in 78,552 (11.1%) veterans in the study population during 2021. This frequency was significantly higher ($\chi^2 = 4255$, $P \leq .001$) among women (16.9%, n = 18,101) than among men (10.1%, n = 60,451). Expressed as a RR, women were at 67% greater risk (RR = 1.67; 95% CI, 1.65–1.70) to receive an incident GDM (Table 2). After adjustment for demographics, clinical characteristics, prescriber characteristics, and PTSD service location variables, women were 22% more likely (aRR = 1.22; 95% CI, 1.20–1.24) to initiate a GDM (Table 2). The majority of examined variables reached the screening threshold of significance ($P < .01$) for inclusion in the regression analysis, with provider age and provider gender being excluded.

In the first stage of modeling, 4 clusters of independent variables were evaluated as potential confounders of the relationship between gender and incident GDM risk: clinical characteristics, demographics, prescriber characteristics, and facility characteristics (Table 3). The unadjusted RR for the gender effect (RR = 1.67) served as the base model reference estimate to identify and examine confounding variables. Variable clusters were selected to progress to the second stage of modeling if the absolute value of the RR estimate for the gender effect changed by >0.10. Only 2 clusters produced meaningful changes in the gender effect: clinical characteristics (aRR = 1.23; 95% CI, 1.21–1.25; Δ, −0.44) and demographics (aRR = 1.37; 95% CI, 1.35–1.39; Δ, −0.30). While many prescriber and facility characteristics were significantly associated with GDM risk (Table 2), none of these variables were confounders in the relationship between gender and GDM risk.

In the second stage of modeling, individual variables within the clusters selected from stage 1 were assessed

Table 1.

Candidate Variables Explaining Increased Prescribing of GDMs in Veterans Receiving Care for PTSD in VHA in 2021

Characteristics	Women N = 106,924	Men N = 597,775	*P* value
Demographics			
Age in years, n (%)			<.001
<40	35,198 (32.9)	127,051 (21.3)	
40–54	38,538 (36.0)	149,101 (24.9)	
55–64	23,921 (22.4)	83,936 (14.0)	
≥65	9,267 (8.7)	23,7687 (39.8)	
Race, n (%)			<.001
White	58,112 (54.4)	407,890 (68.2)	
Black or African American	36,611 (34.2)	128,045 (21.4)	
Other identified race	4,942 (4.6)	23,881 (4.0)	
Unknown	7,259 (6.8)	37,959 (6.4)	
Hispanic/Latino ethnicity, n (%)	9,708 (9.1)	54,184 (9.1)	.87
Rural residence, n (%)	14,537 (13.6)	115,146 (19.3)	<.001
Marital status, n (%)			<.001
Married	43,789 (41.0)	378,987 (63.4)	
Divorced	35,009 (32.7)	122,789 (20.5)	
Never married	24,528 (22.9)	77,734 (13.0)	
Other/unknown	3,598 (3.4)	18,265 (3.1)	
Branch of service, n (%)			<.001
Army	59,321 (55.5)	358,059 (59.9)	
Navy	20,403 (19.1)	80,951 (13.5)	
Air Force	18,760 (17.5)	49,812 (8.3)	
Marines	6,827 (6.4)	104,624 (17.5)	
Other/unknown	1,613 (1.5)	4,329 (0.7)	
Length of service, n (%)			<.001
<3, y	32,164 (30.1)	192,025 (32.1)	
3–6, y	39,286 (36.7)	224,168 (37.5)	
≥ 6, y	35,474 (33.1)	181,582 (30.4)	
Clinical characteristics			
Depressive disorder, n (%)	77,927 (72.9)	343,557 (57.5)	<.001
Anxiety disorder, n (%)	21,653 (20.3)	71,335 (11.9)	<.001
Substance use disorder, n (%)	20,077 (18.8)	149,981 (25.1)	<.001
Psychotic disorder, n (%)	4,213 (3.9)	21,741 (3.6)	<.001
Bipolar disorder, n (%)	13,573 (12.7)	37,143 (6.2)	<.001
Sleep disorder, n (%)	41,784 (39.1)	284,791 (47.6)	<.001
Chronic pain, n (%)	60,561 (56.6)	301,286 (50.4)	<.001
Charlson Comorbidity Index, mean (SD)	1.2 (1.7)	2.7 (2.8)	<.001
Prior psychiatric medications, mean (SD)	3.2 (1.8)	2.8 (1.6)	<.001
Psychiatric prescribers, n (%)			<.001
1	45,641 (42.7)	282,486 (47.3)	
2	32,588 (30.5)	181,784 (30.4)	
3 or more	28,695 (26.8)	133,505 (22.3)	
Primary prescriber characteristics			
Age in years, n (%)			<.001
<45	30,303 (28.3)	147,419 (24.7)	
45–59	35,232 (33.0)	198,003 (33.1)	
≥60	23,626 (22.1)	154,053 (25.8)	
Unknown	17,763 (16.6)	98,300 (16.4)	
Gender, n (%)			<.001
Male	24,910 (23.3)	207,427 (34.7)	
Female	51,880 (48.5)	231,549 (38.7)	
Unknown	30,134 (28.2)	158,799 (26.6)	
Specialty, n (%)			<.001
Mental health	76,181 (71.2)	402,963 (67.4)	
Primary care	19,619 (18.4)	136,052 (22.8)	
Resident physician	3,683 (3.4)	21,724 (3.6)	
Other, unknown specialty	7,441 (7.0)	37,036 (6.2)	

(continued)

Table 1 (continued).

Characteristics	Women N = 106,924	Men N = 597,775	*P* value
PTSD caseload, n (%)			<.001
<50	27,864 (26.1)	171,067 (28.6)	
50–124	23,932 (22.4)	125,408 (21.0)	
125–249	33,848 (31.7)	178,460 (29.9)	
≥250	21,280 (19.9)	122,840 (20.5)	
Primary PTSD service location			
Facility type, n (%)			<.001
VA hospital	51,489 (48.2)	265,064 (44.3)	
Urban clinic	29,246 (46.1)	282,810 (47.3)	
Rural clinic	6,189 (5.8)	49,901 (8.4)	
Geographic region, n (%)			<.001
Northeast	10,255 (9.6)	70,584 (11.8)	
Midwest	15,998 (15.0)	101,245 (16.9)	
West	22,401 (21.0)	127,439 (21.3)	
South	58,270 (54.5)	298,507 (49.9)	

Abbreviations: GDM = guideline discordant medication, PTSD = posttraumatic stress disorder, VA = Veterans Affairs, VHA = Veterans Health Administration.

individually as potential confounders in the relationship between gender and GMD risk (Table 4). Variables that emerged as potential confounders were prior psychiatric medication prescriptions (aRR = 1.44; 95% CI, 1.42–1.46; Δ, −0.23), bipolar disorder diagnosis (aRR = 1.55; 95% CI, 1.53–1.58, Δ, −0.12), Charlson Comorbidity Index (aRR = 1.51; 95% CI, 1.49–1.53; Δ, −0.16), and age (aRR = 1.41; 95% CI, 1.39–1.43; Δ, −0.26). In a multivariable model containing these 4 variables, in addition to gender, the Charlson Comorbidity Index no longer met the >0.10 threshold and was excluded. The resulting final restricted variable model found a 23% greater risk for GDM among women (aRR = 1.23; 95% CI, 1.21–1.24), relative to men, after adjustment for age, prior psychiatric medication exposure, and bipolar disorder (Table 4). Effect estimates for these 3 variables in the final restricted variable model were bipolar disorder (RR = 1.60; 95% CI, 1.57–1.63), age (<40 years: RR = 1.20 [1.18–1.22]; 40–54 years: RR = 1.13 [1.11–1.16]; ≥65 years: RR = 0.64 [0.62–0.65]), and count of distinct psychiatric medications prescribed in the prior year (RR = 1.14; 1.13–1.14).

DISCUSSION

This study found that women veterans with PTSD were 67% more likely than men veterans with PTSD to be prescribed an incident GDM in 2021. We also found that, while some provider and facility characteristics were significantly associated with GDM prescribing, they did not explain the observed gender difference. Interestingly, the sex of the provider was not associated with gender differences in incident PTSD GDM prescribing. Together, this suggests that patients' clinical characteristics likely account for women's relatively greater risk of receiving a PTSD GDM prescription. Notably, RR estimates of the gender effect were nearly equivalent between the full model adjusted for all covariates (RR = 1.22; 95% CI, 1.20–1.24) and the reduced model containing just the 3 variables meeting our definition as clinically meaningful (RR = 1.23; 95% CI, 1.21–1.24). These 3 variables—age, prior psychiatric medication exposure, and bipolar disorder diagnosis—accounted for approximately two-thirds of the gender difference in risk of being prescribed a PTSD GDM.

Although we found that age partially accounts for the gender difference in PTSD GDM prescriptions, we expect it is most likely a confounding variable and not a mediator of this relationship. Women veterans with PTSD were significantly younger than men in our study population, which likely reflects the recent increase in US veterans who are women and enrolled in VHA.[24] Given that younger veterans were more likely to be prescribed a GDM, women veterans were then more likely to receive these medications partly by account of their younger age.[25] Finally, 32.9% of women who received treatment for PTSD were under 40 years old, which means they were also of reproductive age and possibly receiving medications that might have negative consequences with reproduction.

Bipolar disorder also emerged as a confounding variable and potential explanatory mediator of the gender effect in PTSD GDM prescribing. Interestingly, we found that women veterans with PTSD were twice as likely to be diagnosed with bipolar disorder as compared to men. Because some of the PTSD GDMs (eg, some anticonvulsants and antipsychotics) are indicated for bipolar disorder, this could partially account for the increased occurrence of PTSD GDM prescriptions among women veterans. Although a GDM, anticonvulsants have been shown to be

Table 2.

Candidate Variables Demonstrating a Statistically Significant Relationship[a] With GDM Prescribing in a Multivariable Log-Binomial Regression Model

		Log-binomial regression	
		Unadjusted	Adjusted
Characteristic	Incident GDM, n (%)	RR (95% CI)	aRR (95% CI)
Demographics			
Gender			
Female	18,101 (16.9)	1.67 (1.65–1.70)	1.22 (1.20–1.24)
Male	60,451 (10.1)	Reference	Reference
Age, y			
<40	23,819 (14.7)	1.22 (1.19–1.24)	1.22 (1.20–1.25)
40–54	25,458 (13.6)	1.12 (1.10–1.15)	1.16 (1.13–1.18)
55–64	13,011 (12.1)	Reference	Reference
≥65	16,264 (6.6)	0.55 (0.53–0.56)	0.69 (0.67–0.71)
Race			
White	52,193 (11.2)	Reference	Reference
Black or African American	17,982 (10.9)	0.98 (0.96–0.99)	0.88 (0.87–0.90)
Other identified race	3,380 (11.7)	1.05 (1.01–1.08)	0.99 (0.96–1.02)
Unknown	4,997 (11.1)	0.99 (0.96–1.01)	0.98 (0.95–1.01)
Hispanic/Latino ethnicity			
Yes	7,392 (11.6)	1.04 (1.02–1.07)	0.97 (0.95–0.99)
No	71,160 (11.1)	Reference	Reference
Residence			
Urban	65,337 (11.4)	Reference	Reference
Rural	13,215 (10.2)	0.90 (0.88–0.91)	0.96 (0.94–0.98)
Marital status			
Married	43,074 (10.2)	Reference	Reference
Divorced	19,627 (12.4)	1.22 (1.20–1.24)	1.06 (1.04–1.07)
Never married	13,821 (13.5)	1.33 (1.30–1.35)	1.03 (1.01–1.04)
Other/unknown	2,030 (9.3)	0.91 (0.87–0.95)	1.00 (0.96–1.04)
Branch of service			
Army	44,923 (10.8)	Reference	Reference
Navy	12,681 (12.5)	1.16 (1.13–1.18)	1.08 (1.06–1.09)
Air Force	8,573 (12.5)	1.16 (1.14–1.19)	1.00 (0.99–1.02)
Marines	11,593 (10.4)	0.97 (0.95–0.99)	0.96 (0.95–0.98)
Other/unknown	782 (13.2)	1.22 (1.14–1.31)	1.05 (0.98–1.11)
Length of service, y			
<3	23,196 (10.3)	Reference	Reference
3–6	30,819 (11.7)	1.13 (1.11–1.15)	1.01 (0.99–1.02)
≥6	34,547 (11.3)	1.09 (1.08–1.11)	0.97 (0.95–0.99)
Clinical characteristics			
Depressive disorder			
Yes	52,742 (12.5)	1.37 (1.35–1.39)	1.10 (1.09–1.12)
No	25,810 (9.1)	Reference	Reference
Anxiety disorder			
Yes	14,416 (15.5)	1.48 (1.45–1.50)	1.10 (1.08–1.12)
No	64,136 (10.5)	Reference	Reference
Substance use disorder			
Yes	25,347 (14.9)	1.50 (1.48–1.52)	1.13 (1.11–1.15)
No	53,205 (10.0)	Reference	Reference
Psychotic disorder			
Yes	5,982 (23.1)	2.16 (2.11–2.21)	1.26 (1.24–1.29)
No	72,570 (10.7)	Reference	Reference
Bipolar disorder			
Yes	11,999 (23.7)	2.32 (2.29–2.37)	1.50 (1.47–1.53)
No	66,553 (10.2)	Reference	Reference
Sleep disorder			
Yes	39,473 (12.1)	1.17 (1.15–1.19)	1.04 (1.02–1.05)
No	39,079 (10.3)	Reference	Reference

(continued)

Table 2 (continued).

Characteristic	Incident GDM, n (%)	Log-binomial regression	
		Unadjusted	Adjusted
		RR (95% CI)	aRR (95% CI)
Chronic pain			
Yes	46,128 (12.8)	1.35 (1.33–1.37)	1.21 (1.19–1.22)
No	32,424 (9.5)	Reference	Reference
Charlson Comorbidity Index (per unit)	—	0.91 (0.91–0.91)	0.99 (0.99–0.99)
Prior psychiatric medications (per unit)	—	1.19 (1.19–1.19)	1.10 (1.10–1.10)
Psychiatric prescribers			
1	29,285 (8.9)	Reference	Reference
2	23,528 (11.0)	1.23 (1.21–1.25)	1.08 (1.06–1.10)
3 or more	25,739 (15.9)	1.78 (1.75–1.81)	1.17 (1.15–1.20)
Primary prescriber characteristics			
Provider specialty			
Mental health	57,866 (12.1)	Reference	Reference
Primary care	12,786 (8.2)	0.68 (0.67–0.69)	0.84 (0.82–0.86)
Resident physician	3,090 (12.2)	1.01 (0.97–1.04)	0.96 (0.92–0.99)
Other, unknown specialty	4,810 (10.8)	0.90 (0.87–0.92)	0.94 (0.92–0.97)
Provider PTSD caseload			
<50	20,235 (10.2)	0.89 (0.87–0.91)	1.08 (1.06–1.11)
50–124	16,984 (11.4)	1.00 (0.98–1.02)	1.04 (1.02–1.06)
125–249	24,920 (11.7)	1.03 (1.01–1.05)	1.04 (1.02–1.05)
≥250	16,413 (11.4)	Reference	Reference
Primary PTSD service location			
Facility type			
VA hospital	38,841 (12.3)	Reference	Reference
Urban clinic	34,192 (10.3)	0.84 (0.83–0.85)	0.94 (0.93–0.95)
Rural clinic	5,519 (9.8)	0.80 (0.78–0.82)	0.97 (0.94–0.99)
Geographic region			
Northeast	9,280 (11.5)	1.05 (1.02–1.07)	0.99 (0.99–1.02)
Midwest	13,308 (11.4)	1.03 (1.02–1.05)	0.99 (0.98–1.01)
West	16,806 (11.2)	1.02 (1.00–1.04)	0.97 (0.96–0.99)
South	39,158 (11.0)	Reference	Reference

[a]Candidate variables that did not meet criteria for retention in the model ($P < .01$) were provider age and provider sex.

Abbreviations: aRR = adjusted relative risk, GDM = guideline discordant medication, PTSD = posttraumatic stress disorder, RR = relative risk, VA = Veterans Affairs.

prescribed appropriately to veterans with PTSD, usually for a comorbid condition.[26] However, this does not explain why more women veterans than men veterans with PTSD had comorbid bipolar diagnoses. Historically, men and women were thought to have a comparable lifetime prevalence of bipolar disorder.[27] After reviewing large-sample clinical studies conducted between 2011 and 2020, Dell'Osso et al[28] found an increase in the diagnosis of bipolar disorder among females, although they note that further epidemiologic studies are needed to investigate this trend. Other studies have found that women with bipolar disorder had significantly higher odds of having comorbid PTSD among veterans and among the general population.[29,30] However, Walter et al [31] found no significant gender differences in the likelihood of receiving a comorbid bipolar diagnosis among military service personnel with PTSD. It could be that women veterans with PTSD may express distress or emotional dysregulation in a way that mimics or overlaps with bipolar disorder symptoms, potentially leading to a bipolar diagnosis and medications to manage those symptoms. Several studies have investigated possible gender differences in the expression and severity of PTSD symptoms; however, evidence is mixed.[3,7,32] Future research is necessary to understand why and how more women than men veterans with PTSD are diagnosed with bipolar disorder.

Number of unique psychiatric medications prescribed in the prior year also partially accounted for the observed gender difference in incident PTSD GDMs. A larger number of unique prior psychiatric medication prescriptions could indicate greater treatment complexity for women veterans with PTSD. There is some evidence to indicate gender differences in the expression of PTSD, with some studies suggesting that women with PTSD are more likely than men to internalize expressions of distress and develop internalizing psychopathologies, such as depression and anxiety.[3,32,33] As with previous studies, we found

Table 3.

Stage 1 of Log-Binomial Regression Modeling: Examining Candidate Variable Clusters in Confounding the Relationship Between Gender and Risk for Incident GDM for PTSD

Statistical model	Risk estimate for female (reference = male) aRR (95%CI)	Difference in RR from unadjusted model
Gender, unadjusted	RR = 1.67 (1.65–1.70)	
Variable clusters		
Clinical characteristics	1.23 (1.21–1.25)	−0.44[a]
Demographics	1.37 (1.35–1.39)	−0.30[a]
Prescriber characteristics	1.65 (1.62–1.67)	−0.02
Facility characteristics	1.66 (1.64–1.69)	−0.01

[a]Variable clusters were selected to continue to the second stage of modeling if adjustment produced a change in the risk estimate of the gender effect by more than >0.10 relative to the unadjusted risk estimate.
Abbreviations: aRR = adjusted relative risk, GDM = guideline discordant medication, PTSD = posttraumatic stress disorder, RR = relative risk.

that women veterans with PTSD were more likely than men veterans to be diagnosed with psychiatric comorbidities, whereas men were more likely to be diagnosed with substance use and sleep disorders.[34,35] Thus, women veterans with PTSD may be more likely than men veterans to be prescribed psychiatric medications to manage their comorbid conditions, and these medications may be recommended against use for PTSD (eg, antipsychotics).[31] However, the number of unique prior psychiatric medications accounted for a significant portion of the gender difference in PTSD GDMs even after controlling for diagnosed psychiatric comorbidities. It is also possible that greater incidence of prior psychiatric medication prescribing for women veterans with PTSD could indicate a pattern of more medication change, suggesting challenges in treating complex mental health symptoms. Finally, gender socialization may impact health-seeking for PTSD. Studies have found that men are less likely to seek help for mental health concerns, as well as associations between masculine gender role norms and negative attitudes toward psychiatric care.[3,12,36]

While potential mediating factors, such as bipolar disorder and prior prescribing, may point to management challenges due to psychiatric comorbidities or greater symptom severity, women veterans with PTSD were still 22% more likely than men veterans to be prescribed a GDM after controlling for these factors. This residual gender difference suggests that other important factors remain unidentified. One possible explanation is type of trauma exposure. Women veterans report a higher prevalence of military sexual trauma than men veterans,[37,38] and studies have pointed to greater mental health symptom severity, including PTSD, among men and women seeking care for sexual trauma.[39,40] Although a meta-analysis found women's increased risk of sexual violence did not fully account for gender differences in PTSD,[33] Pulcino et al[41] found that a history of sexual trauma increased the risk of developing PTSD following later, unrelated traumatic experiences. Future research could analyze combat and sexual trauma flags in VA administrative data to investigate potential associations between sex and GDM prescribing. Ho et al[42] found that women reported greater levels of complex PTSD (CPTSD) than men but found no gender difference in CPTSD diagnosis. They hypothesize that women may experience more severe CPTSD symptoms than men, but possibly not to a level that increases their risk of meeting diagnostic criteria for CPTSD relative to men.[42] Prior work has used a dimensional and symptom cluster–based approach and found that severity of PTSD symptom clusters was associated with prescribed medications, such as antipsychotics, to target those symptoms independently of a comorbid bipolar or psychotic disorder.[43] Further analyses of our study's data could use a similar approach, stratifying by sex to identify possible drivers of observed differences in prescribing GDM among women and men veterans with PTSD.

Military and VHA care experiences may also contribute to women's 22% increased risk in receiving PTSD GDM. Women veterans with PTSD lived and worked, and some now receive care, in male-dominated environments. In interviews with rural women veterans with chronic pain, some women reported feeling dismissed, not believed, or stereotyped because of their gender when communicating with providers and health care staff at VHA.[44] Johnson et al[44] referred to examples of this type of communication as disenfranchising talk. It is possible that women veterans with PTSD may also experience disenfranchising talk or gender stereotyping when utilizing health care, whether through providers' interpretation of women's symptom presentation or their need for certain medications. Further research should investigate gender disparities in PTSD GDM and heed the imperative to understand how women veterans with PTSD experience care.

LIMITATIONS

This study was limited by the lack of robust administrative data for gender-expansive veterans with PTSD. Although VHA has implemented self-identified gender identity questionnaires and clinical reminders in the electronic medical record, this information is not yet sufficiently populated to be useful for large population-based studies. Thus, our study assumes that individuals labeled as male and female in VHA administrative data self-identify or are identified by their providers concordantly. Because

Table 4.

Stage 2 of Log-Binomial Regression Modeling: Examining Individual Variables in Confounding the Relationship Between Gender and Risk for Incident GDM for PTSD, Using Candidate Variable Clusters From Stage 1

Statistical model	Risk estimate for female (reference = male) aRR (95%CI)	Difference in RR from unadjusted model
Gender, unadjusted	RR = 1.67 (1.65–1.70)	
Individual clinical characteristics		
Prior psychiatric medications	1.44 (1.42–1.46)	−0.23[a]
Charlson Comorbidity Index	1.51 (1.49–1.53)	−0.16[a]
Bipolar disorder	1.55 (1.53–1.58)	−0.12[a]
Depressive disorder	1.61 (1.58–1.63)	−0.06
Anxiety disorder	1.62 (1.59–1.64)	−0.05
Substance use disorder	1.72 (1.69–1.75)	−0.05
Psychiatric prescribers	1.63 (1.60–1.65)	−0.04
Sleep disorder	1.70 (1.68–1.73)	0.03
Chronic pain	1.65 (1.62–1.67)	−0.02
Psychotic disorder	1.66 (1.64–1.69)	−0.01
Individual demographics		
Age	1.41 (1.39–1.43)	−0.26[a]
Marital status	1.61 (1.59–1.64)	−0.06
Branch of service	1.65 (1.63–1.68)	−0.02
Race	1.69 (1.67–1.72)	0.02
Hispanic/Latino ethnicity	1.67 (1.65–1.70)	0.00
Rural residence	1.67 (1.64–1.69)	0.00
Length of service	1.67 (1.65–1.70)	0.00
Final restricted variable model[b]	1.23 (1.21–1.24)	
Fully specified model[c]	1.22 (1.20–1.24)	

[a]Variables were selected for the final restricted variable model if adjustment produced a change in the risk estimate of the gender effect by more than >0.10 relative to the unadjusted risk estimate.
[b]Variables initially selected for the final restricted variable model included prior psychiatric medications, Charlson Comorbidity Index, bipolar disorder, and age. When integrating these variables, the Charlson Comorbidity Index was adjusted out of the model. Thus, the final restricted variable model included age, bipolar disorder, and prior psychiatric medications.
[c]Relative risk estimate for the gender effect in a fully specified model including all covariates, as shown in Table 2.
Abbreviations: aRR = adjusted relative risk, GDM = guideline discordant medication, PTSD = posttraumatic stress disorder, RR = relative risk.

our analysis relies on administrative data, it is difficult to determine its clinical accuracy and validity. In addition, we were only able to identify medications dispensed through the VHA, which may underestimate GDM exposure from non-VHA sources, or misclassify some prevalent recipients as incident recipients. However, it is unclear that these sources of error would be systematically different between gender groups. Our interpretation of the reasons for GDM prescribing is also limited by not knowing precisely which indication or indications a medication was prescribed for each patient, as this is not recorded in VHA administrative data. Finally, veterans with PTSD may have been underidentified in our cohort selection because ascertainment was conducted during the calendar year 2020, and some veterans may not have received VHA services because of the COVID-19 pandemic.

CONCLUSION

Our findings suggest that 2 of 3 identified confounding factors—bipolar diagnosis and number of unique psychiatric medications—may point to greater complexities of treating women veterans with PTSD. This study contributes to literature exploring possible explanations for observed gender differences in the treatment of PTSD. Further mixed-methods research is needed to determine additional unexplained factors for the gender difference in GDM prescribing. If gender differences in PTSD GDM prescribing are indeed driven by clinical complexity, we must investigate why women veterans with PTSD are more complex to treat than men veterans. To inform clinical practice guidelines, future research is also needed to identify the distinct needs of women veterans and the impact of psychiatric comorbidities on their PTSD treatment.

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