ORIGINAL RESEARCH

Antipsychotic Prescriptions in Iraq and Afghanistan Veterans With Posttraumatic Stress Disorder in Department of Veterans Affairs Healthcare, 2007–2012

Beth E. Cohen, MD, MAS; Ying Shi, PhD; Thomas C. Neylan, MD; Shira Maguen, PhD; and Karen H. Seal, MD, MPH

ABSTRACT

Objective: Antipsychotic medications have been increasingly prescribed for off-label uses, including treatment of posttraumatic stress disorder (PTSD). Given limited knowledge about their use in returning Iraq and Afghanistan veterans with PTSD, we explored rates of antipsychotic use in this population and correlations with sociodemographic, military service, and psychiatric factors.

Method: Iraq and Afghanistan veterans with a PTSD diagnosis based on *ICD-9-CM* codes enrolled in Veterans Administration care between January 1, 2007, and September 30, 2011, were followed through September 30, 2012. Patients with a comorbid diagnosis of schizophrenia or bipolar disorder were excluded. Poisson regression models evaluated factors associated with prescriptions for antipsychotic versus other psychiatric medications (primary outcome).

Results: The mean age of our study population was 29.3 years, and 9.4% were women. Of 186,460 veterans with PTSD diagnoses examined, 19.9% received no psychiatric medications, and the remainder received psychiatric medications that excluded (61.2%) or included (18.9%) antipsychotics. In adjusted models, several factors were independently associated with antipsychotic use, including male sex (adjusted relative risk = 1.25; 95% CI, 1.20–1.30) and enlisted rank (1.44; 95% CI, 1.35–1.53). Increased likelihood of antipsychotic prescribing was associated with suicidal ideation (4.77; 95% CI, 4.59–4.95) and comorbid psychiatric diagnoses including personality disorder (4.27; 95% CI, 4.09–4.46), drug use disorder (3.56; 95% CI, 3.43–3.69), and alcohol use disorder (2.75; 95% CI, 2.65–2.84).

Conclusions: A substantial minority of Iraq and Afghanistan veterans diagnosed with PTSD received antipsychotics. Male veterans, those of enlisted rank, and those with suicidal ideation and psychiatric comorbidities were more likely to receive antipsychotics than other types of psychiatric medications. Providers should be cautious about antipsychotic use, given their known metabolic risks and questionable benefits for PTSD.

J Clin Psychiatry 2015;76(4):406–412

Submitted: *October 28, 2013; accepted April 25, 2014.*
Online ahead of print: *March 3, 2015 (doi:10.4088/JCP.13m08857).*
Corresponding author: *Beth E. Cohen, MD, MAS, San Francisco VA Medical Center, Box 111A1, 4150 Clement St, San Francisco, CA 94120 (Beth.Cohen@va.gov).*

To date, over 2.5 million American men and women have served in support of military operations in Iraq and Afghanistan.[1] Among those eligible for care, over half have enrolled in Department of Veterans Affairs (VA) health care.[2] Many of these veterans in VA care have received diagnoses of posttraumatic stress disorder (PTSD),[3] which has been associated with comorbid psychiatric disorders, such as depression and alcohol use disorders,[4,5] as well as physical health problems, including metabolic and cardiovascular disease.[6,7] Although the prevalence of PTSD diagnoses in veterans seeking VA health care has steadily increased, the majority of patients have not received a minimally adequate course of mental health therapy.[8]

Antipsychotic medications have been increasingly prescribed for a variety of non–psychosis-related mental health problems, including PTSD.[9,10] This trend has accelerated over the past decade despite a lack of solid evidence to support use of antipsychotics for these conditions.[11] In fiscal year 2007, approximately 19% of VA patients from multiple eras diagnosed with PTSD were prescribed antipsychotics without a US Food and Drug Administration (FDA)–approved indication. Among veterans prescribed off-label antipsychotics, 42% had received a diagnosis of PTSD.[12] Following mixed results from several small trials evaluating the efficacy of atypical antipsychotic use for PTSD,[13,14] a VA multisite randomized placebo-controlled trial demonstrated no advantage from the adjunctive use of the atypical antipsychotic risperidone over placebo for antidepressant-resistant PTSD.[15] It is unclear whether results of these more recent trials have affected the use of antipsychotics among veterans with PTSD enrolled in VA health care.

In addition to the lack of evidence of benefit of antipsychotics for PTSD, metabolic risks, such as obesity and insulin resistance, have also emerged as significant problems associated with their use.[16–18] This may be particularly concerning for younger returning veterans given that these medications could, over time, escalate the already elevated risk for obesity and cardiovascular disease that is associated with PTSD.[19,20] In light of these potential risks and the recent data about the lack of efficacy of antipsychotics in the treatment of PTSD, the objective of this study was to examine the prescribing patterns of VA practitioners from 2007 to 2012 and identify patient characteristics associated with antipsychotic medication use in Iraq and Afghanistan veterans diagnosed with PTSD. Identifying subgroups of veterans who are most likely to receive these medications may help to improve prescribing practices and reduce risk of metabolic complications in this young group of veterans.

Clinical Points

- Antipsychotics are prescribed to a substantial minority of returning Iraq and Afghanistan veterans diagnosed with posttraumatic stress disorder (PTSD) who do not have a diagnosis of bipolar disorder or schizophrenia.
- Male sex and comorbid psychiatric conditions, particularly substance use and personality disorders, were associated with greater use of antipsychotics compared to other types of psychiatric medications.
- Clinicians should carefully weigh the risks and benefits of antipsychotic use in veterans with PTSD.

METHOD

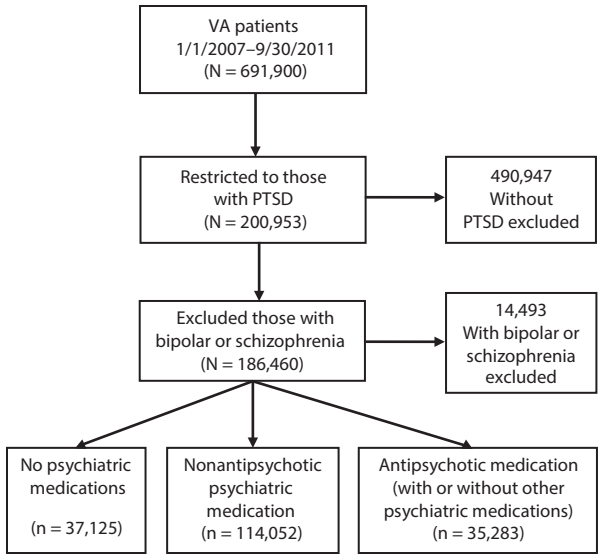
Study Population

The study population was identified using the VA Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) Roster, a national database of veterans who have separated from service in Iraq and Afghanistan and have had at least 1 clinical encounter in the VA health care system. Figure 1 illustrates the selection of our study population. Starting with all Iraq and Afghanistan veterans who had an initial visit to any VA health care facility after separating from service between January 1, 2007, and September 30, 2011 (N = 691,900), we restricted our study to the 200,953 who had received a diagnosis of PTSD. We then excluded 14,493 veterans with a diagnosis of bipolar affective disorder or schizophrenia, as these are widely accepted FDA-approved indications for use of antipsychotic medications, leaving a total of 186,460 patients for the final study population. As several antipsychotics have been approved for use in treatment-resistant depression, we conducted sensitivity analyses additionally excluding patients with a diagnosis of depression who were taking 1 of these antipsychotics along with an antidepressant medication. The date of the initial PTSD diagnosis was between January 1, 2007, and September 30, 2011, in order to allow for at least 1 year of follow-up time to observe prescriptions before the study end date of September 30, 2012.

Data Sources

The national VA OEF/OIF/OND Roster contains demographic and military service information, but does not contain information about education, socioeconomic status, employment, level of combat exposure, and race/ethnicity data.[21] The OEF/OIF/OND Roster was linked to 2 other national VA databases: (1) the VA National Patient Care Database, which contains information on VA clinic visits and associated clinical diagnoses, and (2) the VA Decision Support System, which contains detailed pharmacy records. The study was approved by the Committee on Human Research, University of California, San Francisco and the Human Research Protection Program at the San Francisco VA Medical Center. A waiver of informed consent was approved by the institutional review board of record.

Figure 1. Flow Diagram of Cohort Derivation



Abbreviations: PTSD = posttraumatic stress disorder, VA = Department of Veterans Affairs.

Psychiatric Medication Status

The primary outcome was medication prescription status, classified as (1) no psychiatric prescriptions, (2) prescription for psychiatric medications other than antipsychotics, or (3) prescription for antipsychotic medication, including atypical antipsychotics, such as aripiprazole and clozapine, as well as typical antipsychotics, such as haloperidol (see list in Supplementary eTable 1 at PSYCHIATRIST.COM). Nonantipsychotic psychiatric medications included antidepressants, mood stabilizers, and sedative-hypnotics (see list in Supplementary eTable 1). Prescriptions for psychiatric medications were included in analyses if they were for at least a 30-day supply and if they occurred after the index PTSD diagnosis.

Additional Variables

Sociodemographic characteristics included age, sex, race/ethnicity, and marital status. Military characteristics included component type (National Guard or Reserve vs active duty), branch of service (Army, Navy, Air Force, Marines), rank (enlisted vs officer), number of deployments (1 or ≥2), and service separation date. *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) diagnoses and V codes were used to classify mental health conditions (for example V62.84 was used to classify suicidal ideation). We included comorbid mental health diagnoses that were coded anytime before or up to 6 months after the antipsychotic or other psychiatric medication prescription.

Statistical Analyses

Patients were divided into 3 groups: (1) no psychiatric prescriptions, (2) prescription for psychiatric medications other than antipsychotics, or (3) prescription for antipsychotic medication (with or without other psychiatric medications).

Table 1. Sociodemographic and Military Service Characteristics Among 186,460 Iraq and Afghanistan Veterans With a Diagnosis of Posttraumatic Stress Disorder

Characteristic	Total (N = 186,460)	
Age, y		
Mean (SD)	29.3 (8.8)	
Median (IQR)	26 (22–35)	
	n	%
Gender		
Female	17,526	9.4
Male	168,934	90.6
Race		
White	95,320	51.1
Black	21,391	11.5
Hispanic	20,982	11.3
Other	48,767	26.1
Marital status		
Never married	95,727	51.3
Married	81,687	43.8
Divorced/widowed/other	9,046	4.9
Component		
National Guard/reserve	79,841	42.8
Active duty	106,619	57.2
Rank		
Officer	7,765	4.2
Enlisted	178,695	95.8
Branch		
Army	134,638	72.2
Marines	31,864	17.1
Navy	11,068	5.9
Air Force	8,890	4.8
Multiple deployments[a]		
No	105,995	56.9
Yes	80,291	43.1
Geographic location[a]		
Urban	100,320	59.5
Rural	68,247	40.5

[a]The following variables have data missing: multiple deployments, 0.09% missing; geographical location, 9.6% missing.
Abbreviation: IQR = interquartile range.

Characteristics of participants in the 3 medication groups were compared with χ^2 tests for categorical variables, analysis of variance for normally distributed continuous variables, and Kruskal-Wallis tests for nonnormal continuous variables. Poisson regression with robust error variance was used to calculate adjusted relative risks (RRs) of prescription for antipsychotic versus nonantipsychotic psychiatric medication among various sociodemographic subgroups. Similar analyses were conducted to examine the association of specific mental health conditions and the number of mental health diagnoses with prescription for antipsychotic versus other psychiatric medications. We also examined time from PTSD diagnosis to first prescription of antipsychotics and of other psychiatric medications. In addition, given that several antipsychotics are FDA approved for use in treatment-resistant depression, we conducted sensitivity analyses in which we also excluded participants with a depression diagnosis receiving prescriptions for antidepressant medication and any of the following antipsychotics within 30 days of each other: aripiprazole after November 20, 2007; quetiapine after December 4, 2009; and olanzapine after March 23, 2009. Finally, to evaluate trends in prescribing following the publication of an important negative randomized controlled trial[15] of the antipsychotic risperidone, we examined the proportion of patients diagnosed with PTSD prescribed antipsychotics in several years prior to the study publication date (August 3, 2007–August 2, 2008; August 3, 2009–August 2, 2010; and August 3, 2010–August 2, 2011) and the year following the study publication date (August 3, 2011–August 3, 2012). All tests of significance were 2-tailed, with an α of .05. SAS version 9.3 (SAS Institute Inc.) was used for all analyses.

RESULTS

Among the population of 186,640 Iraq and Afghanistan veterans diagnosed with PTSD but without diagnoses of bipolar disorder or schizophrenia, 37,125 (19.9%) received no psychiatric medications, 114,052 (61.2%) received psychiatric medications other than antipsychotics, and 35,283 (18.9%) received antipsychotics (Figure 1). Of those receiving antipsychotics, 1.4% received typical and 96.4% received atypical medications, and 2.2% received both. Table 1 shows the sociodemographic and military service characteristics of the population. Of note, the study population had a mean age of 29 years (SD = 9), and 9.4% were women.

Factors Associated With Antipsychotic Use

The distribution of sociodemographic and military service factors among those not prescribed medications, those prescribed psychiatric medications other than antipsychotics, and those prescribed antipsychotics is shown in Table 2. In fully adjusted models including all of these covariates, male sex, active duty versus National Guard/Reserve status, enlisted versus officer rank, Army versus other branches, and rural versus urban location were all positively associated with receipt of antipsychotic versus other types of psychiatric medication (Table 3). Having multiple deployments was negatively associated with antipsychotic medication prescription. The mean time from PTSD diagnosis to prescription for antipsychotic medications was 158 days (interquartile range [IQR], 20–538) versus 14 days (IQR, 1–91) for other types of psychiatric medications.

Table 4 shows the association of antipsychotic use with suicidal ideation and psychiatric comorbidities. Those with suicidal ideation or with comorbid mental health diagnoses, particularly personality disorder and substance use disorders, were significantly more likely to be prescribed antipsychotics than those with PTSD alone. Antipsychotics also were more likely to be prescribed in patients with a greater total number of psychiatric diagnoses. Examining temporal trends in prescription of antipsychotics surrounding the negative randomized controlled trial of risperidone as an adjunctive therapy for PTSD, we found 16.7% of patients diagnosed with PTSD were prescribed antipsychotics for the dates examined from August 2, 2007, to August 3, 2008, versus 17.4% for similar dates in 2008–2009, 17.4% for 2009–2010, 16.4% in the year immediately preceding publication of the article, and 15.2% in the year following publication.

Table 2. Prescription of Psychiatric Medications by Sociodemographic and Military Service Characteristics Among 186,460 Iraq and Afghanistan Veterans With a Diagnosis of Posttraumatic Stress Disorder[a]

Characteristic	Veterans Without Psychiatric Medication Prescriptions (n = 37,125)		Veterans Prescribed Nonantipsychotic Psychiatric Medications (n = 114,052)		Veterans Prescribed Antipsychotic Medication (n = 35,283)	
Age, y						
Mean (SD)	28.8 (8.8)		29.4 (8.8)		29.4 (8.7)	
Median (IQR)	25 (22–34)		26 (22–35)		26 (22–35)	
	n	%	n	%	n	%
Gender						
Female	3,201	18.3	11,551	65.9	2,774	15.8
Male	33,924	20.1	102,501	60.7	32,509	19.2
Race						
White	18,669	19.6	58,704	61.6	17,947	18.8
Black	4,018	18.8	13,382	62.6	3,991	18.7
Hispanic	4,381	20.9	12,591	60.0	4,010	19.1
Other	10,057	20.6	29,375	60.2	9,335	19.1
Marital status						
Never married	21,112	22.0	57,902	60.5	16,713	17.5
Married	14,553	17.8	50,451	61.8	16,683	20.4
Divorced/ widowed/other	1,460	16.1	5,699	63.0	1,887	20.9
Component						
National Guard/ reserve	15,457	19.4	49,664	62.2	14,720	18.4
Active duty	21,668	20.3	64,388	60.4	20,563	19.3
Rank						
Officer	2,275	29.3	4,575	58.9	915	11.8
Enlisted	34,850	19.5	109,477	61.3	34,368	19.2
Branch						
Army	24,672	18.3	82,954	61.6	27,012	20.1
Marines	7,986	25.1	18,889	59.3	4,989	15.7
Navy	2,498	22.6	6,695	60.5	1,875	16.9
Air Force	1,969	22.2	5,514	62.0	1,407	15.8
Multiple deployments						
No	19,898	18.8	64,711	61.0	21,386	20.2
Yes	17,189	21.4	49,244	61.3	13,858	17.3
Geographic location						
Urban	20,759	20.7	61,141	60.9	18,420	18.4
Rural	11,654	17.1	42,207	61.8	14,386	21.1

[a]All *P* values are < .0001.
Abbreviation: IQR = interquartile range.

Table 3. Adjusted Relative Risk of Antipsychotic Medication Prescription by Sociodemographic and Military Service Characteristics Among Iraq and Afghanistan Veterans With a Diagnosis of Posttraumatic Stress Disorder (PTSD)

Characteristic	Veterans Prescribed Antipsychotic Medication Versus Those Prescribed Nonantipsychotic Psychiatric Medications: Adjusted Relative Risk (95% CI)[a]	*P* Value
Age increase by 10-y intervals	0.99 (0.97–1.00)	.12
Gender		
Female	1 (reference)	
Male	1.25 (1.20–1.30)	< .0001
Race		
White	1 (reference)	
Black	0.99 (0.96–1.02)	.46
Hispanic	1.03 (0.99–1.06)	.11
Other	0.97 (0.95–0.99)	.01
Marital status		
Never married	1 (reference)	
Married	1.09 (1.06–1.11)	< .0001
Divorced/widowed/other	1.14 (1.09–1.19)	< .0001
Component		
National Guard/reserve	1 (reference)	
Active duty	1.16 (1.13–1.19)	< .0001
Rank		
Officer	1 (reference)	
Enlisted	1.44 (1.35–1.53)	< .0001
Branch		
Army	1 (reference)	
Marines	0.83 (0.80–0.85)	< .0001
Navy	0.94 (0.90–0.98)	.005
Air Force	0.89 (0.85–0.94)	< .0001
Multiple deployments		
No	1 (reference)	
Yes	0.91 (0.90–0.93)	< .0001
Geographic location		
Urban	1 (reference)	
Rural	1.08 (1.06–1.10)	< .0001
No. of follow-up mo in 6-mo intervals since initial PTSD diagnosis date	1.10 (1.10–1.11)	< .0001

[a]The relative risk for each variable is adjusted for all other covariates listed in the table.

Sensitivity Analyses

Our sensitivity analyses excluded an additional 17,631 patients with diagnoses of PTSD and depression prescribed an antipsychotic approved for use in treatment-resistant depression (Supplementary eFigure 1). In general, conclusions were similar to our primary analyses. In fully adjusted models, male sex, active duty versus National Guard/Reserve status, enlisted versus officer rank, Army versus other branches, and rural versus urban location were all associated with increased likelihood of prescription of antipsychotic versus other types of psychiatric medication (Supplementary eTable 2). Associations of antipsychotic use and psychiatric comorbidities were also similar to our primary analyses, with associations being particularly strong for substance abuse and personality disorders, though the magnitudes were somewhat reduced (Supplementary eTable 3).

DISCUSSION

In this study of Iraq and Afghanistan veterans who used VA health care and were diagnosed with PTSD, we found that a substantial minority of patients (18.9%) received prescriptions for antipsychotic medications between 2007 and 2012 after excluding patients with bipolar disorder and schizophrenia. Male veterans and those in the Army, of lower rank and active duty status, were more likely to be prescribed antipsychotics. In addition, when personality disorder, substance use disorders, and suicidal ideation were comorbid with PTSD, there was substantially increased use of antipsychotics versus other types of psychiatric medications. Findings were similar after also excluding patients who may have been prescribed FDA-approved antipsychotics for use in treatment-resistant depression.

This study is the first to focus on antipsychotic prescription in Iraq and Afghanistan veterans with newly diagnosed PTSD, and it expands upon prior studies in other

Table 4. Prevalence of Comorbid Diagnoses and Adjusted Relative Risk of Antipsychotic Prescription Among Iraq and Afghanistan Veterans With a Diagnosis of Posttraumatic Stress Disorder (PTSD)

Variable	Total (N = 186,460)	Veterans Prescribed Antipsychotic Medication, n (%)	Veterans Prescribed Antipsychotics Versus Those Prescribed Nonantipsychotic Psychiatric Medications: Adjusted Relative Risk (95% CI)[a]	*P* Value
Psychiatric diagnoses				
PTSD only	41,162	3,655 (8.9)	1.00 (reference)	
Comorbid depression	103,393	26,334 (25.5)	2.30 (2.22–2.37)	< .0001
Comorbid anxiety disorder	55,001	13,514 (24.6)	2.39 (2.31–2.47)	< .0001
Comorbid panic disorder	8,473	2,970 (35.1)	3.06 (2.93–3.19)	< .0001
Comorbid adjustment reaction/ disorder	44,810	9,016 (20.1)	2.06 (1.98–2.13)	< .0001
Comorbid attention-deficit/ hyperactivity disorder	6,014	1,480 (24.6)	2.60 (2.45–2.75)	< .0001
Comorbid alcohol use disorder	41,684	12,149 (29.2)	2.75 (2.65–2.84)	< .0001
Comorbid drug use disorder	17,987	7,171 (39.9)	3.56 (3.43–3.69)	< .0001
Comorbid personality disorder	4,361	2,181 (50.0)	4.27 (4.09–4.46)	< .0001
No. of psychiatric diagnoses				
1	41,162	3,655 (8.9)	1.00 (reference)	
2	62,223	9,416 (15.1)	1.47 (1.41–1.52)	< .0001
≥ 3	83,075	22,212 (26.7)	2.53 (2.44–2.61)	< .0001
Other diagnoses[b]				
Comorbid suicidal ideation	5,988	3,287 (54.9)	4.77 (4.59–4.95)	< .0001
Comorbid sleep disorder	19,257	4,829 (25.1)	2.50 (2.40–2.60)	< .0001
Comorbid pain	147,785	30,080 (20.4)	2.30 (2.15–2.46)	< .0001

[a]Adjusted for sociodemographic, military service characteristics, and number of follow-up months since initial PTSD diagnosis date.
[b]Reference group for adjusted relative risk is the group with PTSD only.

populations. A survey[22] of 482 veterans from Vietnam and later eras with PTSD found 15% of patients were prescribed atypical antipsychotics in the absence of an FDA indication. In a study of all VA patients in fiscal year 2007, Leslie and colleagues[12] found that 279,778 individuals received antipsychotic medications and that 60% of these patients had no FDA-approved indication (psychotic or bipolar disorder) at that time. Although the study was not focused on patients with PTSD, the authors did report that 19% of those with a diagnosis of PTSD received antipsychotics, equal to the proportion of patients in our sample who were prescribed antipsychotics. Examining demographic factors associated with antipsychotic use, Bernardy and colleagues[23] found that women were more likely than men to receive atypical antipsychotics in a study of all VA patients from 1999 to 2009. However, gender differences were reduced after adjusting for age and other demographic factors. Similar to our study, they also found that veterans living in rural areas were more likely to receive antipsychotics, though the effect was modest.

Understanding the rationale behind the use of antipsychotics for off-label conditions such as PTSD is complex and will most likely require detailed qualitative studies. Still, our study and prior analyses of administrative data offer some insights. In our sample, patients with PTSD and greater mental health comorbidity and disorders that are challenging to treat, such as personality disorders, substance use disorders, and suicidality, were significantly more likely to receive antipsychotic prescriptions, indicating that these medications may be reserved for complex and higher-risk patients. The study by Bernardy and colleagues[23] described above also found that psychiatric comorbidities were associated with increased use of antipsychotics. Prior studies have demonstrated that patients with psychiatric hospitalizations were significantly more likely to have been prescribed an antipsychotic (OR = 8.01, $P < .001$), further indicating antipsychotics may have been prescribed for patients with more complex or acute mental health disturbances and/or those with high risk behaviors such as suicidality.[22] Antipsychotics may also be reserved for patients who do not respond to first-line therapies for PTSD as suggested by the longer time to prescription for antipsychotics versus other psychiatric medications in our study. The study by Jain and colleagues[22] also supports this theory, as nearly half of the patients prescribed off-label antipsychotics received them after a prescription for a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI).

Regardless of the rationale behind use, data supporting the efficacy of antipsychotics for treatment of PTSD are limited. A 2011 review[24] of antipsychotic clinical trials by the Agency for Healthcare Research and Quality found that only risperidone had "moderate" evidence of benefit for PTSD as an adjunctive treatment, with other antipsychotics having little or no evidence. However, following that review, a multicenter VA-based trial by Krystal and colleagues[15] found patients with military-related PTSD with serotonin reuptake inhibitor–resistant symptoms treated with risperidone for 6 months had no

improvement in overall PTSD symptoms or quality of life compared to those taking placebo. Of note, in post hoc analyses, the study by Krystal and colleagues[15] did find small, though statistically significant, improvements in reexperiencing and hyperarousal PTSD symptoms, and it is possible antipsychotics are being targeted to patients with resistant symptoms in these clusters. Our study is the first to examine antipsychotic use in the VA after the publication of this trial.[15] Indeed, we found the proportion of Iraq and Afghanistan veterans diagnosed with PTSD who were prescribed antipsychotics decreased modestly in the year following this study. In a recent publication by Bernardy and colleagues,[25] among VA patients, the use of antipsychotic medication for PTSD declined from 20% to 13.9% between 1999 and 2009. In contrast, use of SSRIs and SNRIs increased from 49.7% to 58.9% during this time frame, suggesting that these guideline-recommended therapies[26] may be replacing use of medications with less evidence of benefit.

The strengths of the current study include access to a large population through use of national VA data and detailed information from pharmacy records. However, our findings should be interpreted in light of several limitations. First, as this study used administrative data, our assessment of PTSD and comorbid conditions was based on diagnostic coding from clinical records and not clinical interviews. Second, we cannot determine whether the antipsychotic or psychiatric medication was specifically prescribed for PTSD or identify which specific PTSD symptoms were being targeted. Third, because this was an observational design, we could not infer causality, nor can we understand the rationale of the prescribing clinicians for selecting a particular class of medications. Finally, we focused our study on veterans from Iraq and Afghanistan given the growing number seeking care for PTSD, but our findings may not be generalizable to other populations of veterans or to veterans receiving care outside of the VA.

In summary, we found that a substantial minority of returning Iraq and Afghanistan veterans diagnosed with PTSD were receiving prescriptions for antipsychotic medications in the absence of a diagnosis of bipolar disorder or schizophrenia. Patients receiving antipsychotic medications may be those who are more difficult to treat given comorbid conditions such as personality disorders, substance use disorders, and suicidality. With the limited evidence supporting a benefit of antipsychotic medications for PTSD and their potential adverse metabolic side effects, clinicians should take particular caution in prescribing these medications. It is encouraging that results from our study and others demonstrate that the use of antipsychotics in patients with PTSD is declining over time, perhaps in response to findings from clinical trials and recommendations from expert guidelines. Further research is needed to clarify the risks and benefits of antipsychotic use in this population and to identify alternative safe adjunctive treatments for the group of patients with PTSD for whom current treatment or therapy is not effective.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others).

Author affiliations: Departments of Medicine (Drs Cohen and Seal) and Psychiatry (Drs Neylan, Maguen, and Seal), University of California, San Francisco; and San Francisco Veterans Affairs Medical Center (all authors).

Potential conflicts of interest: **Dr Neylan** reports receiving study medication from Actelion for a study funded by the US Department of Defense and receiving study medication from GlaxoSmithKline for a study funded by the US Department of Veterans Affairs (VA). **Drs Cohen, Shi, Maguen**, and **Seal** report no financial or other relationship relevant to the subject of this article.

Funding/support: Dr Cohen was supported by National Heart, Lung, and Blood Institute grant K23 HL 094765-01 and a grant from the American Heart Association Clinical Research Program. This work was also supported by the VA Health Services Research and Development Research Enhancement Award Program at the San Francisco VA Medical Center.

Role of the sponsor: The funding organizations were not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Disclaimer: The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of any of these funding agencies.

Acknowledgment: The authors would like to thank Gregory Cohen, MSW, of the Department of Epidemiology, Mailman School of Public Health, Columbia University for work on the conceptualization and initial drafting of the first sections of this article. Mr Cohen has no financial disclosures.

Additional information: The OEF/OIF/OND roster is created by linking the Department of Defense Manpower Data Center roster of Military personnel who served in OEF/OIF/OND who were separated from active duty and eligible for VA benefits with the VA's electronic administrative data. Information about access to these data can be obtained by contacting the VA Informatics and Computing Infrastructure (VINCI) at VINCI@va.gov. For additional information, see Health Services Research and Development Web site: http://www.hsrd.research.va.gov/for_researchers/vinci/default.cfm.

Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. Bilmes LJ. The Financial Legacy of Iraq and Afghanistan: How Wartime Spending Decisions Will Constrain Future National Security Budgets. HKS Faculty Research Working Paper Series RWP13-006 March 2013. https://research.hks.harvard.edu/publications/workingpapers/citation.aspx?PubId=8956. Accessed October 30, 2014.
2. Analysis of VA Health Care Utilization among Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND) Veterans. Quarter 1, 2012. Department of Veterans Affairs Epidemiology Program PDHSHG, Office of Public Health. http://www.publichealth.va.gov/docs/epidemiology/healthcare-utilization-report-fy2012-qtr1.pdf. Updated March 2012. Accessed October 30, 2014.
3. Seal KH, Metzler TJ, Gima KS, et al. Trends and risk factors for mental health diagnoses among Iraq and Afghanistan veterans using Department of Veterans Affairs health care, 2002–2008. *Am J Public Health*. 2009;99(9):1651–1658.
4. Seal KH, Bertenthal D, Miner CR, et al. Bringing the war back home: mental health disorders among 103,788 US veterans returning from Iraq and Afghanistan seen at Department of Veterans Affairs facilities. *Arch Intern Med*. 2007;167(5):476–482.
5. Seal KH, Cohen G, Waldrop A, et al. Substance use disorders in Iraq and Afghanistan veterans in VA healthcare, 2001–2010: implications for screening, diagnosis and treatment. *Drug Alcohol Depend*. 2011;116(1–3):93–101.
6. Frayne SM, Chiu VY, Iqbal S, et al. Medical care needs of returning veterans with PTSD: their other burden. *J Gen Intern Med*. 2011;26(1):33–39.
7. Stecker T, Fortney J, Owen R, et al. Co-occurring medical, psychiatric, and alcohol-related disorders among veterans returning from Iraq and Afghanistan. *Psychosomatics*. 2010;51(6):503–507.
8. Seal KH, Maguen S, Cohen B, et al. VA mental health services utilization in Iraq and Afghanistan veterans in the first year of receiving new mental health diagnoses. *J Trauma Stress*. 2010;23(1):5–16.
9. Alexander GC, Gallagher SA, Mascola A, et al. Increasing off-label use of antipsychotic medications in the United States, 1995–2008.

Pharmacoepidemiol Drug Saf. 2011;20(2):177–184.
10. Comer JS, Mojtabai R, Olfson M. National trends in the antipsychotic treatment of psychiatric outpatients with anxiety disorders. *Am J Psychiatry*. 2011;168(10):1057–1065.
11. Shekelle P, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of off-label use of atypical antipsychotics. Agency for Healthcare Research and Quality. Rockville, MD; 2007. http://www.effectivehealthcare.ahrq.gov/repFiles/Atypical_Antipsychotics_Final_Report.pdf. Updated January 2007. Accessed October 30, 2014.
12. Leslie DL, Mohamed S, Rosenheck RA. Off-label use of antipsychotic medications in the department of Veterans Affairs health care system. *Psychiatr Serv*. 2009;60(9):1175–1181.
13. Pae CU, Lim HK, Peindl K, et al. The atypical antipsychotics olanzapine and risperidone in the treatment of posttraumatic stress disorder: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials. *Int Clin Psychopharmacol*. 2008;23(1):1–8.
14. Berger W, Mendlowicz MV, Marques-Portella C, et al. Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: a systematic review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(2):169–180.
15. Krystal JH, Rosenheck RA, Cramer JA, et al; Veterans Affairs Cooperative Study No. 504 Group. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. *JAMA*. 2011;306(5):493–502.
16. Smith M, Hopkins D, Peveler RC, et al. First- v second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry*. 2008;192(6):406–411.
17. Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. *J Clin Psychiatry*. 2007;68(suppl 4):8–13.
18. Foley DL, Morley KI. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. *Arch Gen Psychiatry*. 2011;68(6):609–616.
19. Cohen BE, Marmar C, Ren L, et al. Association of cardiovascular risk factors with mental health diagnoses in Iraq and Afghanistan war veterans using VA health care. *JAMA*. 2009;302(5):489–492.
20. Maguen S, Madden E, Cohen B, et al. The relationship between body mass index and mental health among Iraq and Afghanistan veterans. *J Gen Intern Med*. 2013;28(suppl 2):S563–S570.
21. Maguen S, Ren L, Bosch JO, et al. Gender differences in mental health diagnoses among Iraq and Afghanistan veterans enrolled in veterans affairs health care. *Am J Public Health*. 2010;100(12):2450–2456.
22. Jain S, Greenbaum MA, Rosen C. Concordance between psychotropic prescribing for veterans with PTSD and clinical practice guidelines. *Psychiatr Serv*. 2012;63(2):154–160.
23. Bernardy NC, Lund BC, Alexander B, et al. Gender differences in prescribing among veterans diagnosed with posttraumatic stress disorder. *J Gen Intern Med*. 2013;28(suppl 2):S542–S548.
24. Maglione M, Maher AR, Hu J, et al. Off-label use of atypical antipsychotics: an update. Comparative Effectiveness Review Number 43. Prepared by the Southern California Evidence-based Practice Center under Contract No. HHSA290-2007-10062-10061. Rockville, MD: Agency for Healthcare Research and Quality. 2011. http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=778. Updated September 27, 2011. Accessed October 30, 2014.
25. Bernardy NC, Lund BC, Alexander B, et al. Prescribing trends in veterans with posttraumatic stress disorder. *J Clin Psychiatry*. 2012;73(3):297–303.
26. Department of Veterans Affairs DoD. Clinical practice guideline for management of post-traumatic stress, version 2.0. http://www.healthquality.va.gov/PTSD-FULL-2010c.pdf Updated October 2010. Accessed October 30, 2014.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Antipsychotic Prescriptions in Iraq and Afghanistan Veterans With Posttraumatic Stress Disorder in Department of Veterans Affairs Healthcare, 2007–2012

Author(s): Beth E. Cohen, MD, MAS; Ying Shi, PhD; Thomas C. Neylan, MD; Shira Maguen, PhD; and Karen H. Seal, MD, MPH

DOI Number: 10.4088/JCP.13m08857

List of Supplementary Material for the article

1. eTable 1 — Psychiatric medication classification
2. eTable 2 — Adjusted Relative Risk of Antipsychotic Medication Prescription by Sociodemographic and Military Service Characteristics Among 168,829 Iraq and Afghanistan Veterans With a Diagnosis of Posttraumatic Stress Disorder (PTSD)
3. eTable 3 — Prevalence of comorbid diagnoses and adjusted relative risk of antipsychotic prescription among Iraq and Afghanistan veterans with a diagnosis of PTSD
4. eFigure 1 — Flow diagram of cohort derivation

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1: Psychiatric medication classification[a]

Typical Antipsychotics[b]	Atypical Antipsychotics
CHLORPROMAZINE	ARIPIPRAZOLE
CHLORPROTHIXENE	CLOZAPINE
FLUPHENAZINE	LURASIDONE
HALOPERIDOL	OLANZAPINE
LOXAPINE	PALIPERIDONE
MESORIDAZINE BESYLATE	QUETIAPINE
MOLINDONE	RISPERIDONE
PERPHENAZINE	ZIPRASIDONE
PIMOZIDE	
THIORIDAZINE	
THIOTHIXENE	
TRIFLUOPERAZINE	
Other Psychiatric Medications	
ALPRAZOLAM	ISOCARBOXAZID
AMITRIPTYLINE	LAMOTRIGINE
AMOXAPINE	LITHIUM
BUPROPION	LORAZEPAM
CARBAMAZEPINE	MAPROTILINE
CHLORAL HYDRATE	MEPROBAMATE
CHLORDIAZEPOXIDE	MIRTAZAPINE
CITALOPRAM	NEFAZODONE
CLOMIPRAMINE	NORTRIPTYLINE
CLONAZEPAM	OXAZEPAM
CLORAZEPATE	PAROXETINE
DESIPRAMINE	PHENELZINE SULFATE
DESVENLAFAXINE	PRAZOSIN
DIAZEPAM	PROTRIPTYLINE
DIVALPROEX	SELEGILINE
DOXEPIN	SERTRALINE
DULOXETINE	TEMAZEPAM
ESCITALOPRAM	TRANYLCYPROMINE
ESTAZOLAM	TRAZODONE
ESZOPICLONE	TRIAZOLAM
FLUOXETINE	VALPROATE SODIUM
FLURAZEPAM	VENLAFAXINE
FLUVOXAMINE	ZALEPLON
IMIPRAMINE	ZOLPIDEM

[a] Medications were restricted to those available for prescription through the Veterans Administration

[b] The typical antipsychotics prochlorperazine and promethazine were excluded because they are commonly prescribed for non-psychiatric indications, such as nausea and emesis.

Supplementary eTable 2. Adjusted Relative Risk of Antipsychotic Medication Prescription by Sociodemographic and Military Service Characteristics Among 168,829 Iraq and Afghanistan Veterans With a Diagnosis of Posttraumatic Stress Disorder (PTSD)

Characteristics	Veterans Prescribed Antipsychotic Medication Versus Those Prescribed Nonantipsychotic Psychiatric Medications	
	Adjusted RR (95% CI)[a]	**p-value**
Age increase by 10-year intervals	0.93 (0.91, 0.95)	< .0001
Gender		
Female	1 (Reference)	
Male	1.50 (1.42, 1.59)	< .0001
Race		
White	1 (Reference)	
Black	0.94 (0.90, 0.99)	0.01
Hispanic	0.96 (0.92, 1.01)	0.14
Other	0.95 (0.91, 0.98)	0.003
Marital status		
Never Married	1 (Reference)	
Married	1.07 (1.03, 1.10)	0.0002
Divorced/ Widowed/Other	1.12 (1.05, 1.20)	0.0015
Component		
National Guard/Reserve	1 (Reference)	
Active Duty	1.23 (1.19, 1.27)	< .0001
Rank		
Officer	1 (Reference)	
Enlisted	1.52 (1.38, 1.68)	< .0001
Branch		
Army	1 (Reference)	
Marines	0.86 (0.83, 0.90)	< .0001
Navy	0.90 (0.84, 0.97)	0.0032
Air Force	0.83 (0.77, 0.90)	< .0001
Multiple deployment(s)		
No	1 (Reference)	
Yes	0.93 (0.90, 0.96)	< .0001
Geographical Location		
Urban	1 (Reference)	
Rural	1.05 (1.02, 1.08)	0.0011
Number of follow-up months in 6-month intervals since initial PTSD diagnosis date	1.16 (1.16,1.17)	< .0001

[a] Each variable is adjusted for all other variables.

Supplementary eTable 3. Prevalence of comorbid diagnoses and adjusted relative risk of antipsychotic prescription among Iraq and Afghanistan veterans with a diagnosis of PTSD

	Total (N=168,829)	Veterans receiving antipsychotics w/ and w/o other psychiatric medications n (%)	Veterans receiving antipsychotic medication prescriptions vs. other psychiatric medications	
			Adjusted RR (95% CI) [a]	p-value
Psychiatric Diagnoses				
PTSD only	40,425	2,918 (7.2)	1.00 (Ref.)	
Comorbid Depression	87,574	10,515 (12.0)	1.46 (1.41, 1.52)	< .0001
Comorbid Anxiety Disorder	47,461	5,974 (12.6)	1.64 (1.57, 1.71)	< .0001
Comorbid Panic Disorder	6,784	1,281 (18.9)	2.13 (2.01, 2.27)	< .0001
Comorbid Adjustment Reaction/Disorder	40,060	4,266 (10.7)	1.44 (1.38, 1.51)	< .0001
Comorbid ADHD	5,198	664 (12.8)	1.73 (1.59, 1.88)	< .0001
Comorbid AUD	35,123	5,588 (15.9)	1.97 (1.88, 2.05)	< .0001
Comorbid DUD	13,998	3,182 (22.7)	2.65 (2.52, 2.78)	< .0001
Comorbid Personality Disorder	3,060	880 (28.8)	3.25 (3.05, 3.47)	< .0001
Number of Psychiatric Diagnoses	**n (%)**	**n (%)**		
1	40,425	2,918 (7.2)	1.00 (Ref.)	
2	57,968	5,161 (8.9)	1.12 (1.07, 1.17)	< .0001
≥ 3	70,436	9,573 (13.6)	1.72 (1.65, 1.79)	< .0001
Other Diagnoses[b]				
Comorbid Suicidal ideation	3,823	1,122 (29.4)	3.47 (3.26, 3.68)	< .0001
Comorbid Sleep disorder	16,539	2,111 (12.8)	1.69 (1.60, 1.79)	< .0001
Comorbid Pain	132,263	14,558 (11.0)	1.68 (1.56, 1.82)	< .0001

[a] Adjusted for sociodemographic, military service characteristics, and number of follow-up months since initial PTSD diagnosis date.

[b] Reference group for adjusted relative risk is also PTSD only.

Supplementary eFigure 1. Flow diagram of cohort derivation