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ORIGINAL REPORT

Off-label use of second generation antipsychotics for post-traumatic stress disorder in the Department of Veterans Affairs: time trends and sociodemographic, comorbidity, and regional correlates

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ABSTRACT

Purpose Second generation antipsychotics (SGAs) are widely used for post-traumatic stress disorder (PTSD), although without strong evidence base. With substantial numbers of veterans returning from Iraq/Afghanistan conflicts with PTSD, it is important to characterize the extent of SGA use and identify associated factors.

Methods We determined time trends and patient characteristics associated with the use of SGAs in veterans with PTSD, without comorbid schizophrenia or bipolar disorders, using the Department of Veterans Affairs national administrative data 2003–2010.

Results Among 732 085 veterans with PTSD, 27.6% received an intentional trial of an SGA in 2003–2010. The annual number treated with SGAs almost doubled (45 268 to 84 197, $p < 0.001$), while prescribing rates decreased (28.6% to 21.5%, $p < 0.001$). In multivariate analyses, African Americans (odds ratio (OR) = 1.07, 95%confidence interval (CI) = 1.06–1.09) and Hispanics (OR = 1.13, 95%CI = 1.10–1.17) were more likely to receive SGAs than Whites. Strongest clinical associations were with prior diagnosis of depression (OR = 1.96; 95%CI = 1.94–1.99), substance use disorders (OR = 1.86; 95%CI = 1.84–1.88), and other anxiety disorders (OR = 1.27; 95%CI = 1.26–1.29) (all $p - < 0.0001$) as well as cardiovascular risk factors. Veterans previously deployed to Iraq/Afghanistan had lower likelihood of SGA receipt. Substantial regional differences were demonstrated (South > Northeast; Midwest and West < Northeast; $p < 0.0001$); regional administrative units (veterans integrated service networks) contributed minimally to regional differences.

Conclusions Post-traumatic stress disorder population growth is driving substantial increases in SGA use. Decreasing rates of the Department of Veterans Affairs prescribing may be due to integrated system-wide mechanisms (e.g., national practice guidelines), although regional variations remain prominent. These analyses provide foundational steps for identifying modifiable provider-level and organization-level determinants of SGA prescription in this growing population. Published 2013. This article is a U.S. Government work and is in the public domain in the USA.

KEY WORDS—antipsychotics; post-traumatic stress disorder; diffusion of innovations; pharmacoepidemiology

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INTRODUCTION

Second generation antipsychotics (SGAs) are among the most widely used drug class, with sales over $14.6b in 2008, exceeding sales even for lipid-lowering drugs and proton-pump inhibitors.[1] SGAs comprise three of the top four most costly medications for Medicaid[2] and four of the 10 most costly medications for the Department of Veterans Affairs (VA) at over $335m in fiscal year 2009 (VA National Pharmacy Benefits Management Services, written communication

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12/14/2012). Increasing use has also prompted concern well beyond the US (e.g., Refs. [3–5]).

Available evidence indicates that SGAs, including aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone, are widely used for post-traumatic stress disorder (Pharmacy Benefits Management Services) without Food and Drug Administration (FDA) indication, a fact that has received ample attention both in the scientific literature (e.g., Ref. [6]) and popular media (e.g., Refs. [7–9]). However, the evidence base supporting SGA monotherapy or adjuvant use in PTSD is limited to retrospective data, open trials, and small randomized controlled trials (e.g., Refs. [10–14]). Early clinical practice guidelines determined that the data were inconclusive for the use of SGAs in PTSD,[15–17] and in 2008, the Institute of Medicine concurred.[18] Some recent guidelines have been open to SGA use, but only in individuals who do not respond to front-line serotonin reuptake inhibitors.[19–21] However, a recent large, multi-site controlled trial reported no clinical benefit of adjunctive use of risperidone in veterans who failed to respond to serotonin reuptake inhibitors.[22]

Second generation antipsychotics are also not without risk. Several have been associated with sudden death[23] as well as diabetes, obesity, and increased cardiovascular risk (e.g., Ref. [24]), which themselves represent added generators of healthcare costs and morbidity.[25] These risks have prompted regulatory concern.[26]

Thus, the principles of evidence-based practice suggest that the use of these medications should be very limited in PTSD. However, clinicians may also base treatment decisions on their own practice-based evidence.[27–29] For example, PTSD shares symptoms with bipolar disorder, such as irritability, poor sleep, and high rates of impulsivity; because all SGAs have FDA indications for bipolar disorder, it is credible that SGAs could have beneficial effects in PTSD as well (e.g., Ref. [30]).

We hypothesized that SGA use in PTSD is widespread in VA, especially because up to 60% of SGA prescriptions in the VA are for off-label purposes.[31] It is critical to characterize their use over time and identify factors that increase likelihood of their administration, particularly at this time of great growth of the PTSD population.[32]

Therefore, we analyzed nationwide administrative data from the VA to address the following study aims:

(1) Describe the overall and annual numbers and rates of SGA prescription for PTSD 2003–2010.
(2) Identify patient demographic and comorbidity characteristics associated with increased likelihood of prescription of any SGA and SGAs individually.
(3) Describe regional variation of SGA prescription within VA.

METHODS

This study was approved by the VA Central Institutional Review Board.

Population

Administrative records were gathered from the Austin Information Technology Center from 2003 to 2010. All VA service users during this time period who received a diagnosis of PTSD (International Classification of Diseases-9 code 309.81) at one inpatient or two outpatient service contacts[33] in a given year were included in the study population. Those with any diagnosis of psychotic (295.0–295.9) or bipolar disorder (296.0, 296.1, and 296.4–296.89) in that year were excluded.

Definition of second generation antipsychotics exposure

We focused our analyses on *intentional trials* of oral SGAs, which we defined as receipt of at least one 30-day outpatient prescription for any dose of an SGA or three consecutive days of inpatient administration during a given year. We reasoned that shorter-term administrations of SGAs could reflect as-needed or short-term symptomatic needs rather than concerted treatment of the disorder. We determined that 30 days was the modal outpatient prescription length, with little variation in usage rate resulting from sensitivity analysis around this duration (e.g., only 6–8% of SGA prescriptions were for <30 days). Additionally, those subjects with hospitalizations <3 days who received SGAs were adequately identified utilizing the 30-day outpatient prescription that followed discharge. We included any daily dose because there is no established SGA dosage for PTSD. The non-SGA group included veterans diagnosed with PTSD who did not meet criteria for SGA exposure but had at least one prescription for any other type of medication from VA in 2003–2010.

Demographic and clinical correlates

Demographic characteristics included age, gender, race/ethnicity (White, African American, Hispanic, other; those endorsing both White and Hispanic or African American and Hispanic were classified as Hispanic), marital status (married, other), and disability status (>50% VA service-connected pension, which relieves copays for prescriptions and clinical services for that disability). Geographic regions were categorized as Northeast, Midwest, South, or West.[34,35] Missing values for potential correlates were <0.1% for most

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variables, with 11.3% missing for race/ethnicity, and 1.5% for marital status disability.

Comorbidities were identified that may affect the likelihood of prescription of any, or specific, SGAs. Comorbid conditions (Table S1 of the Supporting Information Section) were identified by the occurrence of any inpatient or outpatient International Classification of Diseases-9 diagnosis up to 2 years prior to the time first treatment encounter for PTSD during study years. Among medical disorders, we included hyperlipidemia, diabetes mellitus, obesity, cardiovascular risk (any of these three diagnoses), and cardiac dysrhythmia. Among mental health diagnoses, we included depressive disorders, substance use disorders (except tobacco), other anxiety disorders (panic, generalized anxiety, phobic, obsessive-compulsive, and other anxiety disorders) sleep disorders, and traumatic brain injury. We identified subjects with prior deployment to the Iraq/Afghanistan conflicts among those receiving services during or after 2008 when this identifier was first introduced into the dataset (veterans were queried regarding whether they had ever served in these conflicts, 2003–present)[36]; secondary analyses were carried out on this subpopulation.

Data analyses

We calculated annual and overall SGA exposure rates (relative risk) 2003–2010. The change in number of SGA users was estimated by ordinary regression model treating time as the predictor, whereas change in rate of SGA usage was estimated by simple logistic regression model (any SGA versus none), again treating time as the predictor.

Correlates of SGA use were identified by odds ratios (ORs) using univariate logistic regression followed by multivariate logistic regression. We also calculated the *c*-statistic, a concordance measure for overall predictive value of the model; when used for binary outcomes, it is equivalent to the area under the receiver operating characteristic curve.[37] The statistic ranges from 0 to 1, with a value of 0.50 indicating prediction by chance alone (no association) and a value of 0.70 or above considered to represent substantive association.[38] We secondarily explored whether correlates differed among individual SGAs utilizing the subsample who received at most one type of SGA during 2003–2010, using analysis of variance or chi-squared analysis. For a subsample aged 18–49 years who had information on prior deployment to the Iraq/Afghanistan conflict (ever/never), multivariate logistic regression was performed to investigate whether such a deployment has an effect in the use of SGA. We also ran sensitivity analyses to explore effects of requiring two PTSD diagnoses and the effects of excluding subjects who received only one 30-day intentional trial.

Regional differences were further characterized using estimated probability, the probability that an individual with PTSD being treated in a given region would receive an SGA after controlling for other characteristics. Generalized linear mixed modeling was performed to determine the percent of variance explained by region and administrative unit (Veterans Integrated Service Network, VISN), treating both region and VISN (nested within region) as random effects.

RESULTS

Time trends in second generation antipsychotic use

Demographic characteristics are summarized in Table 1. Table 2 shows the number and rate of SGA prescription by year.

Among 732 085 veterans with PTSD, 202 065 (27.6%) received an intentional trial of an SGA in 2003–2010 (Table 2). The annual number of veterans treated for PTSD increased from 158 297 to 391 377, and those treated with SGAs almost doubled from 2003 to 2010 (45 268 to 84 197; average annual increase 5224; 95%CI = 4422–6026, $p < 0.0001$). The majority utilized a single SGA during 2003–2010 (73.8%; two SGAs: 20.2%, three SGAs: 4.9%, four or more: 1.1%). There was significant heterogeneity in use of individual drugs. By using ordinary regression models with *N* as dependent variable and time as predictor, there were significant average yearly increases for aripiprazole (2619 users, 95%confidence interval (CI) = 1896–3342; $p = 0.0001$), quetiapine (3437, 95%CI = 2098–4776; $p = 0.0008$), and ziprasidone (384; 95%CI = 316–452; $p < 0.0001$), and decreases for olanzapine (−860; 95%CI = −1280–−440; $p = 0.0024$), with no change for risperidone (45; 95%CI = −200–290; $p = 0.67$).

Regarding rates, simple logistic regression, with time as the predictor, indicated that the odds of using any SGA, olanzapine, quetiapine, and risperidone significantly decreased over time, evidenced by the per year OR (any SGA, OR = 0.937 (95%CI = 0.936–0.938; $p < 0.0001$), olanzapine 0.771 (95%CI = 0.768–0.774; $p < 0.0001$), quetiapine 0.955 (95%CI = 0.953–0.957; $p < 0.0001$), and risperidone 0.874 (95%CI = 0.872–0.876; $p < 0.0001$)). In comparison, the odds of using aripiprazole and ziprasidone significantly increased as time increased: for aripiprazole OR = 1.371 (95% CI = 1.365–1.378; $p < 0.0001$) and ziprasidone 1.015 (95%CI = 1.009–1.021; $p < 0.0001$).

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Table 1. Patient characteristics by reference and second generation antipsychotic groups*

Variable	No SGA $N = 530\,020$	Any SGA $N = 202\,065$	Group comparison†
	Mean (SD)	Mean (SD)	*p*-value
Age	52.9 (15.2)	52.6 (12.9)	<0.0001
	N (%)	*N* (%)	*p*-value
Male	491 541 (92.7)	187 597 (92.8)	0.13
Race‡			
White	342 228 (73.9)	134 004 (71.8)	<0.0001
African American	87 410 (18.9)	40 197 (21.5)	
Hispanic	18 524 (4.0)	8129 (4.4)	
Other	14 766 (3.2)	4208 (2.3)	
Married‡	290 713 (55.8)	105 267 (52.7)	<0.0001
Service-connected disability > 50%‡	202 389 (38.2)	106 615 (52.8)	<0.0001
Region			
Northeast	80 871 (15.3)	31 089 (15.4)	<0.0001
Midwest	95 510 (18.0)	33 866 (16.8)	
South	210 073 (39.6)	95 296 (47.2)	
West	143 566 (27.1)	41 814 (20.7)	
Comorbidity			
Diabetes	111 912 (21.1)	46 066 (22.8)	<0.0001
Hyperlipidemia	251 125 (47.4)	106 270 (52.6)	<0.0001
Obesity	106 947 (20.2)	48 765 (24.1)	<0.0001
Cardiovascular risk¶	307 269 (58.0)	128 747 (63.7)	<0.0001
Cardiac dysrhythmia	33 052 (6.2)	12 969 (6.4)	0.0041
Depression	294 443 (55.6)	146 304 (72.4)	<0.0001
Substance use disorders	122 693 (23.1)	72 882 (36.1)	<0.0001
Other anxiety disorder	131 216 (24.8)	63 859 (31.6)	<0.0001
Sleep disorder	56 039 (10.6)	26 676 (13.2)	<0.0001
Traumatic brain injury	24 176 (4.6)	11 037 (5.5)	<0.0001

SGA, secondary generation antipsychotic; SD, standard deviation.
*Fiscal years 2003–2010, total number of unique patients $N = 732\,085$.
†*p*-values were calculated by two-sample *t*-test of means, or chi-squared test of proportions.
‡On the basis of smaller *N*, due to missing values. Missing values: race 11.3%, marital status 1.5%, and copay status 0.09%.
§Veterans with >50% service-connected disability do not have copayments for medications or other clinical services for the condition for which they are disabled.
¶Cardiovascular risk was defined as one or more of: diabetes, hyperlipidemia, and obesity.

Correlates of secondary generation antipsychotic use

Univariate analyses (Table 3) indicated that those receiving an SGA were significantly younger and less likely to be married, without gender differences. African Americans and Hispanics were significantly more likely than Whites to receive an SGA, as were those with a rating of >50% disability (no copay). Among clinical characteristics, prior diagnosis of diabetes, hyperlipidemia, obesity, cardiac dysrhythmia, and overall cardiovascular risk were associated with higher likelihood of SGA use. Depression, substance use disorders, and other anxiety disorders were all substantially over-represented among SGA users as were, to a lesser degree, sleep disorders and traumatic brain injury.

Multivariate analyses (Table 3) largely paralleled univariate results. Among demographic characteristics, African Americans (OR = 1.07, 95%CI = 1.06–1.09; $p < 0.0001$) and Hispanics (OR = 1.13, 95%CI = 1.10–1.17; $p < 0.0001$) were more likely to receive SGAs than Whites.

Among comorbidities, the strongest positive associations were demonstrated for depression (OR = 1.96, 95%CI = 1.94 ~ 1.99; $p < 0.0001$), substance use disorders (OR = 1.86, 95%CI = 1.84–1.88; $p < 0.0001$), and other anxiety disorders (OR = 1.27, 95%CI = 1.26–1.29; $p < 0.0001$). Additional associations were seen with prior diagnosis of hyperlipidemia (OR = 1.19, 95%CI = 1.17–1.20; $p < 0.0001$), obesity (OR = 1.16, 95%CI = 1.14–1.17; $p < 0.0001$), sleep disorders (OR = 1.17, 95%CI = 1.15–1.19; $p < 0.0001$), and traumatic brain injury (OR = 1.12, 95%CI = 1.09–1.15; $p < 0.0001$). The overall model predicted SGA use moderately (*c*-statistic = 0.67).

Out of 664 260 who had data on Iraq/Afghanistan deployment, 541 204 (81.5%) had never been deployed, and 123 056 (18.5%) had been deployed. Those deployed versus never-deployed were less likely to use SGAs (OR = 0.68; 95% CI = 0.67–0.69; $p < 0.0001$). Further logistic modeling indicated a closing of the gap with age, with OR = 0.39 (95% CI = 0.38–0.40; $p < 0.0001$) for those in their 20s,

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Table 2. Number and percentage of post-traumatic stress disorder patients prescribed with secondary generation antipsychotics by year*

Fiscal year	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone	Any SGA	No SGA	Total patients
2003	105 (0.1%)	11 277 (7.1%)	21 798 (13.8%)	16 493 (10.4%)	1350 (0.9%)	45 268 (28.6%)	113 029 (71.4%)	158 297
2004	805 (0.4%)	9819 (5.4%)	30 242 (16.6%)	17 684 (9.7%)	1699 (0.9%)	53 968 (29.7%)	128 025 (70.3%)	181 993
2005	2930 (1.4%)	7710 (3.6%)	37 790 (17.7%)	18 126 (8.5%)	2205 (1.0%)	62 042 (29.1%)	150 930 (70.9%)	212 972
2006	4644 (2.0%)	6256 (2.7%)	40 931 (17.6%)	17 270 (7.4%)	2655 (1.1%)	65 195 (28.0%)	167 359 (72.0%)	232 554
2007	5992 (2.3%)	5410 (2.1%)	42 367 (16.2%)	16 938 (6.5%)	2984 (1.1%)	67 256 (25.8%)	193 635 (74.2%)	260 891
2008	9232 (3.1%)	5220 (1.7%)	45 830 (15.2)	16 751 (5.6%)	3513 (1.2%)	73 320 (24.3%)	228 048 (75.7%)	301 368
2009	15 205 (4.4%)	5319 (1.5%)	47 271 (13.7)	17 075 (4.9%)	3905 (1.1%)	80 051 (23.2%)	265 407 (76.8%)	345 458
2010	18 357 (4.7%)	5355 (1.4%)	47 229 (12.1%)	18 102 (4.6%)	3776 (1.0%)	84 197 (21.5%)	307 180 (78.5%)	391 377
2003–2010 (unique subjects)	35 066 (4.8%)	26 471 (3.6%)	132 834 (18.1%)	63 469 (8.7%)	11 855 (1.6%)	202 065 (27.6%)	530 020 (72.4%)	732 085

SGA, secondary generation antipsychotic; PTSD, post-traumatic stress disorder.
*The No-SGA group denotes those patients diagnosed with PTSD but not treated with an SGA in 2003–2010. Total is the sum of Any-SGA + Reference. Individual subjects may appear in multiple annual counts, if they received an SGA in a given year, but appear only once in the total unique subjects row.

which increased steadily to OR = 0.81 (95% CI = 0.77–0.85; $p < 0.0001$) for those in their 40s.

Sensitivity analyses

Sensitivity analysis restricting the sample to those with >2 PTSD diagnoses reduced the sample from 732 085 to 679 612 (reduced by $n = 52\,473$, 7.17%). Comparing this model with the original, the absolute change in ORs ranged from 0 to 0.043; service-connected disability changed from 2.064 to 2.107 (change = 0.043). All other ORs changed <0.025.

Sensitivity analysis also investigated those who had ongoing versus single-month treatment by reclassifying those who had a single 30-day trial as non-exposed ($n = 56\,841$, 7.76%). Comparing this model with the original, the absolute change in ORs ranged from 0.000 to 0.101; service-connected disability reduced from 2.064 to 1.963 (change = 0.101). All other ORs changed <0.067.

Correlates of use of individual secondary generation antipsychotics

Among those who had exposure to only one type of SGA 2003–2010, we found inter-SGA differences for each demographic and clinical characteristic (data available on request). We conducted two cross-SGA comparisons, selected *a priori*, on the basis of clinical literature, using aripiprazole as the reference drug. Pre-existing cardiovascular risk was associated with less olanzapine use (OR = 0.61, 95%CI = 0.57–0.65, $p < 0.0001$), whereas cardiac dysrhythmia was associated with less ziprasidone use (OR = 0.82, 95%CI = 0.68–0.99; $p = 0.034$).

Regional differences

In multivariate analyses controlling for the aforementioned characteristics and using Northeast as reference (Table 4), SGAs were utilized more in the South (OR = 1.18, 95%CI = 1.16–1.20; $p < 0.0001$), and less in Midwest (OR = 0.89, 95%CI = 0.87–0.91; $p < 0.0001$) and West (OR = 0.75, 95%CI = 0.73–0.76, $p < 0.0001$). Estimated probabilities indicated that a veteran with PTSD treated in the South had a 32.2% chance (95%CI = 31.8–32.7%) of receiving an SGA, whereas a similar individual treated in the West had a 23.8% chance (95% CI = 23.4–24.3%), with Northeast (29.0%; 95%CI = 28.5–29.5%), and Midwest (27.0%; 95%CI = 26.6–27.5%) intermediate. Similar patterns were seen for individual SGAs, except for olanzapine, for which Northeast had the highest estimated probability. Nested random-effects analysis indicated that VA's 21 administrative units (VISNs) contributed minimally to regional effects, with a VISN-to-region variance ratio of 1%; corresponding variance ratios for individual SGAs were 0.02–18%.

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Table 3. Logistic regression model predicting use of any secondary generation antipsychotic

	Univariate model				Multivariate model			
	N total = 732 085; Ref = 530 020; SGA = 202 065				*N* total = 642 026; Ref = 457 317; SGA = 184 709			
Variable	OR	95% CI		*p*-value	OR	95% CI		*p*-value
Age (in 10-year unit)	0.98	0.98	0.99	<0.0001	0.97	0.96	0.97	<0.0001
Male	1.02	0.995	1.04	0.1332	1.09	1.06	1.11	<0.0001
Black (ref white)*	1.17	1.16	1.19	<0.0001	1.07	1.06	1.09	<0.0001
Hispanic (ref white)*	1.12	1.09	1.15	<0.0001	1.13	1.10	1.17	<0.0001
Other race (ref white)*	0.73	0.70	0.75	<0.0001	0.83	0.80	0.86	<0.0001
Married	0.88	0.87	0.89	<0.0001	0.92	0.91	0.93	<0.0001
Service-connected disability >50%[c]	1.81	1.79	1.83	<0.0001	2.06	2.04	2.09	<0.0001
Midwest (ref Northeast)	0.92	0.91	0.94	<0.0001	0.89	0.87	0.91	<0.0001
South (ref Northeast)	1.18	1.16	1.20	<0.0001	1.18	1.16	1.20	<0.0001
West (ref Northeast)	0.76	0.75	0.77	<0.0001	0.75	0.73	0.76	<0.0001
Diabetes	1.10	1.09	1.12	<0.0001	0.98	0.97	0.99	0.0048
Hyperlipidemia	1.23	1.22	1.25	<0.0001	1.19	1.17	1.20	<0.0001
Obesity	1.26	1.24	1.27	<0.0001	1.16	1.14	1.17	<0.0001
Cardiac dysrhythmia	1.03	1.01	1.05	0.0039	0.98	0.95	1.00	0.0307
Depression	2.10	2.08	2.12	<0.0001	1.96	1.94	1.99	<0.0001
Substance use disorders	1.87	1.85	1.89	<0.0001	1.86	1.84	1.88	<0.0001
Other anxiety disorder	1.40	1.39	1.42	<0.0001	1.27	1.26	1.29	<0.0001
Sleep disorder	1.29	1.27	1.31	<0.0001	1.17	1.15	1.19	<0.0001
Traumatic brain injury	1.21	1.18	1.24	<0.0001	1.12	1.09	1.15	<0.0001
c-statistic	—				0.67			

SGA, secondary generation antipsychotic; OR, odds ratio; CI, confidence interval.
*Note: For race/ethnicity, *N* total = 649 466; Ref = 462 928; SGA = 186 538

Table 4. Adjusted odds ratio and estimated probability of being prescribed with single secondary generation antipsychotic for post-traumatic stress disorder patients by region

	Individual SGA exposure					
Region	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone	Any SGA
Adjusted OR (95% CI) Reference = Northeast*						
Midwest	1.04	0.90	0.90	0.87	1.06	0.89
	(0.97, 1.10)	(0.84, 0.96)	(0.87, 0.92)	(0.83, 0.90)	(0.92, 1.23)	(0.87, 0.91)
South	1.33	0.93	1.18	1.05	1.90	1.18
	(1.26, 1.41)	(0.88, 0.98)	(1.16, 1.21)	(1.01, 1.08)	(1.68, 2.14)	(1.16, 1.20)
West	0.85	0.67	0.77	0.69	0.93	0.75
	(0.80, 0.91)	(0.63, 0.72)	(0.75, 0.79)	(0.67, 0.72)	(0.81, 1.08)	(0.73, 0.76)
Estimated probability in % (95% CI)[†]						
Northeast	1.9	2.0	13.6	5.3	0.3	29.0
	(1.8, 2.1)	(1.9, 2.2)	(13.2, 14.0)	(5.0, 5.6)	(0.3, 0.4)	(28.5, 29.5)
Midwest	2.1	1.7	12.8	4.6	0.4	27.0
	(2.0, 2.3)	(1.6, 1.9)	(12.5, 13.2)	(4.3, 4.8)	(0.3, 0.5)	(26.6, 27.5)
South	2.5	1.7	15.3	5.4	0.7	32.2
	(2.3, 2.7)	(1.6, 1.9)	(14.9, 15.7)	(5.2, 5.7)	(0.6, 0.8)	(31.8, 32.7)
West	1.8	1.5	11.3	3.9	0.4	23.8
	(1.6, 1.9)	(1.3, 1.6)	(10.9, 11.6)	(3.7, 4.1)	(0.3, 0.4)	(23.4, 24.3)

SGA, secondary generation antipsychotic; PTSD, post-traumatic stress disorder; OR, odds ratio; CI, confidence interval.
*For individual SGAs, a multiple six-category logistic regression was performed with the comparison category being the non-SGA reference group. For any SGA, a binary logistic regression was performed with the comparison category being the non-SGA reference group. Models were based on multivariate logistic regression adjusted for covariates provided in Table 4. All ORs in the table were significant at the 0.05 level except for aripiprazole (Midwest) and ziprasidone (Midwest and West).
[†]Estimated probability indicates the probability that an individual with PTSD being treated in a given region would receive an SGA. For instance, an individual with PTSD treated in the West would have a 23.8% probability of receiving an SGA, whereas a similar individual treated in the South would have a 32.2% probability of receiving an SGA, an 8.4% difference between regions.

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DISCUSSION

Trends in secondary generation antipsychotic use

The number of veterans with PTSD who received an SGA almost doubled from 2003 to 2010, driven primarily by an increase in the PTSD population. The overall rate of SGA prescribing for PTSD is in good agreement with other VA data,[31,39] and the decrease in receipt of any SGA after 2006 is notable. Reasons for reduced prescribing rate have yet to be established, although the FDA warning in 2003 regarding the risk of metabolic effects with SGAs may have decreased all-diagnosis SGA use.[40] Additionally, the FDA black-box warning in 2005 regarding sudden death in the elderly treated with SGAs may have had impact beyond that age group.[41] Within VA, the decrease also parallels a decrease in the off-label benzodiazepine use for PTSD.[42]

It is not surprising that time trends differ among SGAs, with decreases in the number of veterans utilizing the older medications, olanzapine and risperidone, and increases in the newer medications, aripiprazole, and (until 2010) ziprasidone (Table 2). The high use of quetiapine, which more than doubled during the study period with peak rate in 2006, may be due in part to its common use in low doses as a hypnotic (e.g., Refs. [31,43]).

Correlates of secondary generation antipsychotic use

The strongest correlates with SGA use were the associations with psychiatric comorbidities, with additional associations with racial/ethnic status and cardiac risk. Findings were robust to sensitivity analyses on definition of PTSD and SGA exposure. Minority status was associated with higher rates of SGA use, a finding previously reported in Medicaid populations,[44] and for all-diagnosis use of SGAs in veterans.[31] However, historically, the literature on racial/ethnic disparities in the use of SGAs versus older antipsychotics for psychotic disorders indicated that African Americans typically received SGAs less frequently,[45–54] as may also be true for Hispanics.[45,50,54] It is not clear whether the pattern of SGA use in the present context represents greater tendency for minority subjects to receive more novel (albeit not FDA-approved) treatments, or whether unmeasured clinical factors are responsible.

Secondary generation psychotic use was most strongly associated with depression, substance use, and other anxiety disorders. The evidence base for SGA use in major depression was developing during the years of this study,[55] and this may have contributed to the association of SGA use with comorbid depression. Treatment of refractory anxiety symptoms with SGAs is common in other diagnostic groups (e.g., Ref. [56]), and the presence of substance use disorders typically precludes the use of potentially addictive benzodiazepines. SGA use with comorbid traumatic brain injury may reflect the desire to treat impulsivity that can be characteristic of such disorders,[57,58] although the tendency for SGAs to lower the seizure threshold[59] is a cause for concern.

That pre-existing cardiovascular risk factors were associated with increased likelihood of SGA use does not necessarily indicate lack of quality of care, because SGAs as a group are heterogeneous in side effect profile.[23,24] Consistent with this interpretation, olanzapine, which is associated with increased cardiac risk, was less likely to be used than aripiprazole in veterans with such risk.

Veterans previously deployed to Iraq/Afghanistan had lower likelihood of receiving an SGA compared with those without deployment. It may be that such individuals are less likely to receive any psychopharmacologic treatment or that SGAs are reserved for those later in the course of treatment for PTSD. Further analyses that account for clinical course will be required to further explore these alternatives.

Regional differences in secondary generation antipsychotic use

Regional differences were striking. Higher rates in the South are consistent with retail pharmacy data on SGA use, which demonstrated a relative risk of 1.42, although without control for patient-level factors.[60] Our analyses indicate that such variation is predominantly geographic, rather than administrative, in nature. Other studies indicate that VA service users in the South self-report worse mental and physical quality of life scores than those in other regions by as much as 0.50 standard deviation, suggesting sociodemographic or clinical differences.[34,35] Thus, it is also possible that the South treats veterans with more severe PTSD, who are in turn more likely to receive SGAs. However, such differences may also reflect regional differences in provider practice patterns, as has been demonstrated widely for medical, surgical, and other mental health practices (e.g., Ref. [61]).

Future directions

The potential impact of SGAs in PTSD grows as the population increases both in the US and internationally.[62–64] Stable to decreasing VA prescribing rates is notable in this context. Decreases may be because the VA is an integrated healthcare system with a highly developed electronic health record, a national

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formulary, widely disseminated clinical practice guidelines for PTSD,[10] and a system for integrated medical communication by the Pharmacy Benefits Management Services that spans national to local levels. VA rates can provide background perspective for studies of other less integrated healthcare sectors with high utilization of SGAs in the US and abroad.[1–5]

Study of SGAs within VA provides an important opportunity to identify mechanisms of spread of healthcare innovations. Investigation of regional variation of SGA use in VA can help to determine the degree to which such innovations are subserved by classical diffusion mechanisms[65] versus local organizational factors.[66,67] Study of SGA use in VA is particularly attractive because VA has a uniform national formulary, SGAs prescriptions are high frequency events, and there are relatively low barriers to adoption because prescribing behavior does not require expensive technology or new resources.

Finally, it is not yet clear whether SGAs are used primarily in individuals who have failed evidence-based treatments, or whether SGAs are used as front-line treatment, bypassing evidence-based recommendations. Similarly, overall impact of SGAs in this population in clinical practice is unclear. For example, although SGAs as a group may be associated with increased cardiovascular risk, it is possible that such treatment may improve mental health indices, or even reduce overall mortality.

Limitations

We considered intentional trials of any dose of an SGA, rather than counting any single prescription as an exposure, and rather than adopting therapeutic dose ranges for other disorders. Future investigation of dose ranges can determine whether, for example, small daily doses of quetiapine identify distinct patterns of use for distinct subpopulations (e.g., Refs. [31,43]). We did not investigate clinical course or severity variables in these analyses, a clear next step. We focused on oral SGAs because long-acting injectable medications, which are not reliably recorded in VA national datasets. We could not account for treatments or diagnoses given outside of the VA, as is true for most such administrative database studies. Finally, growth in the number of veterans who used services for PTSD suggests that the population in 2010 may differ in salient characteristics from the population in 2003. Time-trend analyses in correlates of use can provide further information on this issue.

Conclusions

The number of prescriptions for SGAs for veterans with PTSD is increasing substantially because of the growth of that population, although rates of prescribing individual SGAs are mostly stable to decreasing. Further understanding of the determinants of SGA use, their overall impact, and the social and organizational determinants of prescriber behavior are the critical next steps in rational policy development.[68]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- The use of SGAs for PTSD is increasing in the VA despite lack of evidence base; this increase is due to growth in the population, whereas rates of prescribing are decreasing for most SGAs.
- African American and Hispanic veterans are more likely than Whites to receive SGAs, as are veterans with comorbid depression, substance use disorders, other anxiety disorders, or elevated cardiovascular risk; however, veterans deployed to Iraq/Afghanistan are less likely to receive SGAs.
- Regional differences are notable, with the South having the highest rates of use while controlling for patient characteristics.
- Characterizing such patient-level variables is essential for further investigation of organization-level and provider-level determinants of SGA prescribing.

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Drs Lee and Kazis had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix Table 1: ICD-9 Codes for Clinical Comorbidity Covariates.

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