Pharmacotherapy of PTSD in the U.S. Department of Veterans Affairs: Diagnostic- and Symptom-Guided Drug Selection

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Background: Although increasing numbers of war veterans are seeking treatment for posttraumatic stress disorder (PTSD) at the U.S. Department of Veterans Affairs (VA), information on the role of psychotropic pharmacotherapy in their treatment has not been available.

Method: Records of psychotropic prescriptions for all VA patients diagnosed with ICD-9 PTSD (N = 274,297) in fiscal year 2004 (October 1, 2003, to September 30, 2004) were examined. Descriptive statistics and multivariable logistic regression were used to identify veteran characteristics and measures of service use that were associated with receipt of any psychotropic medication and, among users of such medications, with use of each of 3 medication classes: antidepressants, anxiolytics/sedative-hypnotics, and antipsychotics.

Results: Most veterans diagnosed with PTSD received psychotropic medication (80%), and among these, 89% were prescribed antidepressants, 61% anxiolytics/sedative-hypnotics, and 34% antipsychotics. Greater likelihood of medication use was associated with greater mental health service use and comorbid psychiatric disorders. Among comorbidities, medication-appropriate comorbid diagnoses were the most robust predictors of use of each of the 3 medication subclasses, i.e., depressive disorders were associated with antidepressant use, anxiety disorders with anxiolytic/sedative-hypnotic use, and psychotic disorders with antipsychotic use. Use of anxiolytics/sedative-hypnotics and antipsychotics in the absence of a clearly indicated diagnosis was substantial.

Conclusion: Diverse psychotropic medication classes are extensively used in the treatment of PTSD in the VA. While disease-specific use for both PTSD and comorbid disorders is common, substantial use seems to be unrelated to diagnosis and thus is likely to be targeted at specific symptoms (e.g., insomnia, anxiety, nightmares, and flashbacks) rather than diagnosed illnesses. A new type of efficacy research may be needed to determine symptom responses to psychotropic medications as well as disorder responses, perhaps across diagnoses.

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Although increasing numbers of war veterans are seeking treatment for posttraumatic stress disorder (PTSD) at the U.S. Department of Veterans Affairs (VA), information on the role of psychotropic pharmacotherapy in their treatment has not been available. While the research literature on treatment of PTSD has grown in recent years, studies of the delivery of PTSD interventions in real-world service systems is limited, and more specifically, there have been no studies of psychopharmacologic treatment provided for veterans with PTSD in the VA. The present pharmacoepidemiologic study uses national data on all psychotropic prescriptions provided to veterans who received a diagnosis of PTSD in the VA in fiscal year 2004 to identify use of medication treatment strategies in the absence of supporting evidence or when research evidence is conflicting. In contrast to the usual direction of influence in which research is used to guide practice, this study considers the possibility that empirical study of the use of various medications in the treatment of PTSD in usual practice could reveal unrecognized practices that may be valuable or, at least, deserving of further study. We thus follow a novel research strategy in which data on real-world practice are explored as a potential guide for future research.[1]

Data on the effectiveness of psychotropic drugs in the treatment of PTSD are limited and not altogether consistent.[2] While there is evidence that antidepressants can be effective in the treatment of PTSD,[3] this evidence is

weaker in war veterans than in other populations.[4–9] There is also limited evidence that other psychotropic medications may be efficacious in treating war-related PTSD or accompanying symptoms. Among these are anxiolytics[5,10–12] and antipsychotics.[13–16] Both anxiolytics and sedative-hypnotics are often used to facilitate sleep and diminish hyperarousal in PTSD.

In addition to identifying rates of various medications in the treatment of PTSD, we compare use of these medications among patients treated in specialty mental health programs and among veterans treated exclusively in primary care or specialty medical-surgical clinics. We further identify specific sociodemographic characteristics and comorbid diagnoses that are associated with use of various classes of medication to determine whether these treatments are being used specifically to treat PTSD or rather to treat comorbid psychiatric conditions.

METHOD

Sample and Sources of Data

All veterans seen in the VA medical centers who had at least 1 primary or secondary diagnosis of PTSD on at least 1 outpatient encounter or inpatient discharge were included (N = 274,297). Data on service use and sociodemographic and diagnostic characteristics were derived from national administrative databases. Data on patients treated by the Readjustment Counseling Service (the Vet Center program) are not included in VA medical center workload databases. The VA psychotropic prescription drug records for these patients in fiscal year 2004 (October 1, 2003, to September 30, 2004) were obtained from the VA Drug Benefit Management System files. The records of these patients were then merged to create the database examined for this study.

Measures

Data describing patient characteristics such as age, income, gender, ethnicity, receipt of VA disability compensation, comorbid psychiatric diagnoses, and both outpatient and inpatient service utilization were also obtained from VA workload databases. *International Classification of Diseases, Ninth Revision* (ICD-9) codes were used to identify the following non–mutually exclusive comorbid diagnoses: dementia/Alzheimer's disease, alcohol abuse/dependence, drug abuse/dependence, schizophrenia, bipolar disorder, major affective disorder, dysthymic disorder, PTSD, and other anxiety disorders. Clinic and bed section codes were used to distinguish patients who received services from mental health specialty clinics or inpatient programs and those treated exclusively in primary care or general medical programs.

To simplify the analyses, we focused on 3 broad classes of psychotropic drugs most commonly used in the treatment of PTSD: antidepressants (including tricyclic antidepressants [TCAs], monoamine oxidase inhibitors [MAOIs], and selective serotonin reuptake inhibitors [SSRIs]), anxiolytics or sedative-hypnotics (including benzodiazepines and other drugs classified as anxiolytics or sedative-hypnotics), and antipsychotics, including both first-generation antipsychotics and second-generation antipsychotics (SGAs).

Analysis

First, we examined the frequency with which veterans were prescribed each medication class, comparing those treated in specialty mental health clinics with those treated exclusively elsewhere. We next compared the characteristics of veterans who received versus those who did not receive any psychotropic medication, as well as the characteristics of veterans who received versus those who did not receive each of the 3 broad classes identified in the Measures section.

Next, we used multivariable logistic regression to identify veteran characteristics and measures of service use that were independently associated with receipt of any psychotropic medication and, among users of such medications, with each of the 3 medication subclasses. The first set of analyses was conducted on the entire sample of patients diagnosed with PTSD and included a dichotomous variable representing use of any specialty mental health services during the year. These analyses were then repeated on the subgroup that had received specialty mental health services and included a dichotomous variable representing any psychiatric hospitalization during the year, and a continuous variable representing the number of outpatient mental health visits during the year.

Given the very large sample size, trivial effects could be highly significant. With these considerations, we opted for a stringent criterion: a 5% shift in frequency or an odds ratio (OR) of over 2.0 for small base-rate responses. Either of these criteria would be statistically significant at $p < .001$ with this sample size.

RESULTS

Altogether, 274,297 VA patients received a diagnosis of PTSD in fiscal year 2004. The vast majority (89%) received treatment in a specialty mental health program, with only 11% treated exclusively in primary care or medical-surgical specialty clinics. These patients averaged a mean ± SD age of 56.1 ± 11.0 years and had a mean ± SD yearly income of $20,112 ± $28,470; 94% were male, 47% were white, 12% were African American, 4% were Hispanic, and 38% were classified as "unknown race" (Table 1).

Among these patients, medication use was common with 80% (N = 220,612) receiving at least 1 prescription for a psychotropic medication. Among users, 89% received at least 1 prescription for an antidepressant, 61%

received at least 1 anxiolytic or sedative-hypnotic, and 34% received an antipsychotic. Within the antidepressants, SSRIs were the predominant choice (85% of all medication users), as were sedative-hypnotics among the anxiolytics/sedative-hypnotics (41% of all medication users), and SGAs among the antipsychotics (32% of all medication users).

Rates of any psychotropic medication use were generally lower among patients treated exclusively in primary care/medical-surgical specialty settings (51.5%) than in specialty mental health clinics (84.0%) (Table 2). Among users, the greatest difference between those treated in mental health and medical clinics involved use of antipsychotics (35.2% vs. 12.3%) and the smallest differences involved use of antidepressants (89.4% vs. 77.3%).

Among patients who received any medication, those prescribed each of the 3 specified classes were more likely to have been diagnosed with comorbid psychiatric diagnoses, to have been treated in a mental health specialty clinic or a psychiatric inpatient unit, and had a greater number of mental health outpatient visits in comparison to other veterans (Table 1).

More specifically, veterans who received medications in each of the 3 specific medication classes were more likely than other veterans to have been diagnosed with conditions that are specific indications for those medications. For example, depression and dysthymic disorder were more common among those who received antidepressants than among those who did not; anxiety disorders were more common among those who received antianxiety/sedative-hypnotic drugs than among other veterans; and schizophrenia and bipolar disorder were more common among those who received antipsychotics than among other veterans (Table 1). At the same time, in the case of antipsychotics, 77% of patients did not have one of the indicated diagnoses (76% in mental health clinics and 90% of those seen in non–mental health clinics).

Table 1. Sociodemographic and Clinical Characteristics of U.S. Veterans Diagnosed With Posttraumatic Stress Disorder by Treatment Group[a]

Characteristic	Entire Sample (N = 274,297)		Veterans Who Received Any Psychotropic Medication (N = 220,612)					
	Any Prescription		Antidepressant		Anxiolytic/Sedative-Hypnotic		Antipsychotic	
	Yes (N = 220,612)	No (N = 53,685)	Yes (N = 195,371)	No (N = 25,241)	Yes (N = 133,925)	No (N = 86,687)	Yes (N = 74,150)	No (N = 146,462)
Sociodemographics								
Age, mean (SD), y	55.8 (10.5)	57.2 (12.6)	55.6 (10.4)	57.4 (11.5)	55.9 (10.2)	55.6 (10.9)	54.1 (9.6)	56.6 (10.8)
African American	11.6	11.0	11.3	13.9	11.1	12.3	15.4	9.7
Hispanic	4.4	2.4	4.4	4.1	4.8	4.8	4.8	4.2
Unknown race	38.3	49.4	38.7	36.2	36.2	41.6	32.7	41.2
60%–100% Disability rating	54.7	42.3	54.6	55.7	57.3	50.7	56.3	54.0
10%–50% Disability rating	18.1	22.9	18.2	17.0	16.7	20.1	15.8	19.2
Clinical characteristics								
Anxiety disorder	20.0	10.1	20.3	18.2	22.8	15.8	22.9	18.6
Major depressive disorder	23.7	8.7	25.6	8.8	24.7	22.2	28.0	21.5
Dysthymic disorder	40.6	59.5	43.0	21.7	40.3	41.0	41.9	39.9
Bipolar disorder	6.7	2.5	6.1	18.2	6.6	6.7	13.1	3.4
Schizophrenia	4.7	1.7	3.9	10.7	4.5	5.0	12.1	0.9
Alcohol abuse	17.6	11.7	17.6	17.2	18.4	16.2	23.1	14.8
Drug abuse	12.4	7.3	12.3	13.3	13.3	11.1	19.0	9.1
Alzheimer's disease or other dementias	1.2	0.8	1.1	1.6	1.0	1.3	1.8	0.8
Any mental health treatment	84.0	51.5	93.9	86.1	94.0	91.5	97.5	90.8
Any inpatient treatment	8.0	0.7	8.1	7.4	9.7	5.4	16.6	3.7
No. of outpatient visits, mean (SD)	14.6 (31.2)	8.1 (23.7)	14.8 (31.1)	12.8 (32.4)	15.6 (32.1)	12.9 (29.9)	20.3 (39.6)	11.5 (25.6)

[a]Values are expressed as percent except where otherwise noted.

Receipt of Any Psychotropic Medication

Multivariable logistic regression showed the strongest predictors of receipt of any psychotropic prescription were receipt of services in a specialty mental health clinic and comorbid psychiatric diagnoses, especially affective disorders and schizophrenia, which doubled the likelihood of receiving medication (Table 3). Veterans who received VA disability compensation at a 60% to 100% disability rating were also about twice as likely to have received a prescription. Among the subgroup of patients who received treatment within a specialty mental health clinic, the most powerful predictor of

Table 2. Use of Specific Group of Medications for Entire Sample, Patients Seen in Mental Health Clinics, and Patients Seen in Primary Care, %

Medication Class	Total (N = 274,297, 100%)	MH Clinic (N = 244,332, 89.1%)	Non–MH Clinic (N = 29,965, 10.9%)
Any prescription	80.4	84.0	51.5
Of those with any prescription (N = 220,612)			
Antidepressant	88.6	89.4	77.3
SSRI	85.0	86.4	68.9
TCA	2.3	12.2	14.7
MAOI	0.1	0.1	0.0
Anxiolytic/sedative-hypnotic	60.7	61.4	52.2
Benzodiazepine	24.2	30.9	30.3
Sedative/hypnotic	24.2	30.9	30.3
Antipsychotic	33.6	35.2	12.3
FGA	3.2	3.3	2.2
SGA	32.1	33.8	10.7

Abbreviations: FGA = first-generation antipsychotic, MAOI = monoamine oxidase inhibitor, MH = mental health, SGA = second-generation antipsychotic, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 3. Logistic Regression Analysis of Sociodemographic, Diagnostic, and Mental Health Service Use Predictors of Psychotropic Medication Prescription Among Veterans Diagnosed With PTSD (N = 274,297)

Predictor	Any Prescription, OR	Antidepressant, OR	Anxiolytic/Sedative-Hypnotic, OR	Antipsychotic, OR
Sociodemographic predictor				
Age (per 10 year interval)	–0.91	–0.85	1.19	–0.82
African American	–0.81	–0.87	–0.79	1.24
Hispanic	1.50	1.09	1.12	1.03
Unknown race	–0.73*	1.03	0.81	–0.79*
60%–100% Disability rating	2.18*	1.24	1.32*	1.26
10%–50% Disability rating	1.18	1.14	–0.97	–0.93
Diagnostic predictor				
Anxiety disorder	1.71*	–0.90*	1.60*	1.17
Major depressive disorder	2.47*	3.16*	1.09	1.32*
Dysthymic disorder	2.32*	2.57*	–0.94	1.04
Bipolar disorder	2.10*	–0.52*	–0.94	3.40*
Schizophrenia	2.16*	–0.36*	–0.83	12.21*
Alcohol abuse	1.15*	–0.95*	1.14	1.16*
Drug abuse	1.16*	–0.83*	1.22	1.50*
Alzheimer's disease or other dementias	1.57	0.87*	–0.73	3.49*
Any mental health treatment	3.69*	2.19*	1.38*	2.93*
Mental health service use predictor				
Mental health inpatient	5.88*	0.99	1.82	3.05*
Mental health outpatient (per 10 visits)	1.02*	1.02*	1.02*	1.03*

*p < .0001.
Abbreviation: PTSD = posttraumatic stress disorder.

receiving psychotropic medication was receipt of inpatient mental health treatment (OR = 5.88), although the number of outpatient visits also had a significant but small effect (OR = 1.02 for each 10 visits) (Table 3).

Antidepressants

Among patients who received psychotropic medications, the most powerful predictors of receiving antidepressants were a codiagnosis of major depressive disorder (OR = 3.16) or dysthymic disorder (OR = 2.57) (Table 3). Comorbid diagnoses of bipolar disorder or schizophrenia reduced the likelihood of receiving antidepressant medication by 48% and 64%, respectively. Among the subgroup of patients who received mental health services, antidepressant use was not significantly associated with inpatient hospitalization but was associated with greater outpatient service use (OR = 1.02 for each 10 visits) (Table 3).

Anxiolytics/Sedative-Hypnotics

The strongest diagnostic predictor of receiving a prescription for an anxiolytic or sedative-hypnotic was codiagnosis of anxiety disorder (OR = 1.60). Veterans who received 60% to l00% VA disability compensation were also slightly more likely (OR = 1.32) to receive anxiolytics/sedative-hypnotics than others. Among

mental health users, psychiatric hospitalization almost doubled the likelihood of anxiolytics/sedative-hypnotic use, and the number of outpatient visits, again, had a weak association (OR = 1.02 for each 10 visits) (Table 3).

Antipsychotics

The strongest diagnostic predictor of receipt of antipsychotic medication was a codiagnosis of schizophrenia, which increased the odds 12 fold. Other codiagnoses that strongly predicted receipt of antipsychotics were bipolar disorder (OR = 3.40) and Alzheimer's disease or other dementias (OR = 3.49). Veterans diagnosed with alcohol abuse were modestly more likely to receive antipsychotic medication (OR = 1.16). African Americans were also modestly more likely to receive antipsychotics (OR = 1.24), but other sociodemographic characteristics have only small effects. Among patients who received treatment in specialty mental health clinics, those who received inpatient mental health treatment were 3 times more likely than others to receive antipsychotic medications, and, again, the number of outpatient visits had a significant but small effect (OR = 1.03 for each 10 visits) (Table 3).

DISCUSSION

This study examined national data on psychotropic prescriptions written for all veterans who received a diagnosis of PTSD in the VA in fiscal year 2004. Medication use was common, with over 80% of patients prescribed at least 1 psychotropic medication. Among those who received such medications, the most commonly used class was antidepressants (89% of users), the only class within which several agents have received formal U.S. Food and Drug Administration (FDA) approval for treatment of PTSD. Two other psychotropic classes were frequently prescribed for PTSD patients: anxiolytics/sedative-hypnotics (61%) and antipsychotics (34%), both of which represent off-label use (i.e., use without FDA disease-specific approval). Only 11% of patients diagnosed with PTSD were treated exclusively in primary care or medical-surgical specialty clinics, but, consistent with the increasing emphasis on treatment of mental illness in primary care settings, they received similar medications, albeit at somewhat lower rates.

The strongest predictors of all medication use were general indicators of severity such as comorbid psychiatric diagnoses; more frequent use of specialty mental health services, especially inpatient use; and receipt of VA disability compensation. However, it was especially notable that, within the 3 medication subclasses, clinically relevant comorbid diagnoses were the most robust predictors, both as indications and contraindications, for each of the medication classes. For example, major depressive disorder and dysthymic disorder were most strongly associated with antidepressant use, while schizophrenia or bipolar disorder significantly decreased the likelihood of receiving antidepressants, perhaps being contraindicated for fear of precipitating manic or psychotic symptoms. Similarly, codiagnosis of anxiety disorder was associated with greater likelihood of use of anxiolytics/sedative-hypnotics while bipolar disorder, schizophrenia, and dementia were associated with less use (perhaps to avoid potential risk for addiction in a population with a high predilection for addictive behavior[17,18] or for compromising cognition in dementia[19]).

As one would expect, schizophrenia and bipolar disorder were the strongest predictors of receiving antipsychotic medication. African Americans were more likely than others to receive antipsychotics. Others have reported over-diagnosis of schizophrenia and increased likelihood of receiving maintenance antipsychotic treatment for bipolar disorder among African Americans.[20,21] Less expected were modest positive associations of antipsychotic prescription and alcohol and drug abuse/dependence. Second-generation antipsychotics may reduce substance use,[22] and perhaps that strategy is being used by some in the treatment of PTSD.

While medications not officially approved for treatment of PTSD often appear to have been used to treat appropriate comorbidities, we also examined the rates of use of classes of medication studied for which there was no diagnostic justification in the administrative records. The most striking pattern of such use involved extensive use of antipsychotics among patients without comorbid psychotic conditions. Altogether 33.6% of those who received medications received a prescription for an antipsychotic, 30% of the entire sample of veterans diagnosed with PTSD, while the rates of comorbid diagnosis of schizophrenia and bipolar disorder among medication users were only 12.1% and 13.1%, respectively. Among those who received antipsychotics, 77.0% had a diagnosis of neither schizophrenia nor bipolar disorder. Among patients prescribed anxiolytics/sedative-hypnotics, only 22.8% were diagnosed with another anxiety disorder, although others are likely to have received these drugs for symptomatic treatment of insomnia, anxiety, or hyperarousal in the absence of a full disorder.

While it is impossible to determine the clinical rationale for the prescription of antipsychotic medications from administrative data, the most likely explanation is that off-label use of these drugs was used to target symptoms associated either with PTSD itself (for example, sleep disturbances or "reliving" symptoms of PTSD that did not warrant a diagnosis of psychotic disorder) or with comorbid psychiatric illnesses. It is also possible that in some cases physicians were directly trying to treat PTSD or other psychiatric illnesses with off-label medications, on the basis of their clinical judgment, intuition, or scattered research reports.[23] Objective diagnostic tests are

not available for any psychiatric disorders, and many symptoms emerge across a wide range of disorders. Without more detailed review of the medical record than is possible here, the rationale for these prescriptions cannot be determined, but there seems to be substantial, "off-label" symptom-focused use.

The most important limitation of this study is the reliance on administrative data, and especially on unvalidated and possibly unrecorded diagnoses. Some off-label prescribing may reflect failure to enter all relevant diagnostic codes. In addition, since only 1 diagnostic entry for PTSD was needed to be included in this study as a PTSD patient, some misdiagnoses are likely. Some prescription drug data may also have failed to be added to the national files, but the high rates of prescription drug use in this sample suggest that such data loss is likely to have been modest. This study is also limited in that the vast majority of patients served prior to the recent conflict in the Middle East. A separate pharmacoepidemiologic study is needed of those newest of veterans.

While focused on the treatment of PTSD in the VA, this study also draws attention to the larger issue of prescription of psychotropic medications off-label or without a clear diagnostic indication. One of the objectives of the development of the DSM-III was that psychiatric diagnoses would be based on more explicit and operational diagnostic criteria than had previously been available. It was hoped that clearer definitions of psychiatric disorders would lead to more rational, disease-specific pharmacotherapy. However, as this study suggests, choices of medication, while significantly associated with some indicated diagnoses, are not entirely determined by such diagnoses. Although we lack data on the clinical thinking behind the observed patterns of prescription drug use, it seems likely that some prescribing is driven by symptoms, such as insomnia, anxiety, nightmares, or intrusive memories, rather than by full diagnoses.

These observations suggest a possible direction for future research that would examine the efficacy of drugs for specific symptoms, either within or even across a range of diagnoses. Studies of off-label use of drugs like risperidone[14] and prazosin[24] in the treatment of PTSD, in fact, represent important steps in this direction. Following this line of thinking, it would be useful to know when anxiety emerges in schizophrenia whether an antianxiety agent, an antidepressant, or either an additional antipsychotic medication or increased antipsychotic dosing would be most effective. Posttraumatic stress disorder is often accompanied by anxiety, depression, and quasi-hallucinations in the form of flashbacks. The differential effectiveness of treatment of these symptoms with various drug classes has begun to be studied in clinical trials but remains a potentially ripe area for research.

Psychotropic medication is extensively used in the treatment of PTSD in the VA. While disease-specific use for both PTSD and comorbid disorders is clear in these data, substantial use is likely to be targeted at specific symptoms rather than diagnoses. A new type of efficacy research may be needed to determine symptom as well as disorder responses to psychotropic medications.

Drug names: prazosin (Minipress and others), risperidone (Risperdal).

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