Anticonvulsant Medication use in Veterans with Posttraumatic Stress Disorder

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Abstract

Objective: Anticonvulsants have been studied for many indications, including posttraumatic stress disorder (PTSD). The limited efficacy research on anticonvulsants for PTSD is mixed. However, anticonvulsants are prescribed widely to Veterans with PTSD. Our objective was to measure trends and factors associated with anticonvulsant prescription among Veterans with PTSD.

Method: We obtained administrative and pharmacy data for Veterans who initiated PTSD treatment in the Department of Veterans Affairs (VA) between 2004 and 2013 (n=731,520). We identified those who received anticonvulsants during the year following their initial clinical PTSD diagnosis and examined common indications for anticonvulsant use, patient characteristics, and

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service use characteristics. Using logistic regression, we determined the predictors of anticonvulsant initiation among those without an indication.

Results: Although 24.9% of patients in the cohort received an anticonvulsant during their initial year of PTSD treatment, 94.6% had an indication unrelated to PTSD and 51.2% initiated anticonvulsant use before their PTSD diagnosis. While there was growth in anticonvulsant initiation over the 10-year period, this was explained both by growth in indications unrelated to PTSD and increased use of anticonvulsants for these indications. The rate of anticonvulsant initiation without an indication was stable at approximately 5% throughout the period, with patient and service use characteristics driving the selection of individual agents.

Conclusion: A large and increasing proportion of Veterans with PTSD receive anticonvulsant prescriptions. However, this may be appropriate use driven by increased prevalence of comorbid conditions that may be an indication for anticonvulsant use, including pain and headache disorders.

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a mental health condition that sometimes follows exposure to a traumatic event.[1] Symptoms include reexperiencing the trauma, avoidance of reminders of the trauma, hyperarousal, and negative cognitions. PTSD affects approximately 6% of the United States (US) population during their lifetime.[2] Rates are higher in combat or military-exposed populations such as Veterans who use health services provided by the US Department of Veterans Affairs (VA).[3, 4]

Convergent findings from recent meta-analyses indicate that four antidepressant medications are effective treatments for PTSD, including the selective serotonin reuptake inhibitors (SSRI) fluoxetine, sertraline, and paroxetine, as well as the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine.[5, 6] Despite the availability of a large number of antidepressants to treat PTSD, many patients do not respond to these agents.[7–10] Therefore, there has been research into other drug classes such as atypical antipsychotics, adrenergic antagonists, and anticonvulsants as potential treatments for PTSD.[5, 6]

Anticonvulsants are medications developed to inhibit propagation of seizures in the brain by suppressing the rapid and excessive firing of neurons.[11] Typically, anticonvulsants enhance the function of inhibitory ϒ-aminobutyric acid (GABA) or reduce the release of excitatory glutamate through action at sodium or potassium channels.[12] The theoretical model relating PTSD to seizure disorder is derived from the similarities between two neurobiological phenomena: kindling and behavioral sensitization.[13] In kindling, an electrical or chemical stimulus that was previously subconvulsant elicits a seizure after repeated intermittent administration to the same animal's brain. In behavioral sensitization, repeated exposure to a noxious environmental stimulus that initially produced little or no response eventually produces a profound response. Therefore, both processes have in common the ability to increase physiological or behavioral responsivity to repeated presentation of the same inducing stimulus.[14] As a result of the similarities in proposed mechanisms of hypersensitivity in seizure disorder and in PTSD, anticonvulsants have been suggested as potential treatments for PTSD.[15]

There have been randomized placebo-controlled trials (RCTs) of at least five different anticonvulsants for the treatment of PTSD. This includes one of the GABA reuptake inhibitor tiagabine,[16] one RCT of the sodium channel antagonist lamotrigine,[17] one of the calcium channel modulator pregabalin,[18] two of the sodium channel antagonist divalproex, [19, 20] and four of topiramate,[21–24] which has multiple mechanisms of action at sodium channels, calcium channels, and GABA receptors. In summary, a small pilot study indicates that lamotrigine may be a promising medication for PTSD, a single study of pregabalin indicates a significant advantage that may not be clinically meaningful, and topiramate appears to confer a statistically significant and clinically meaningful advantage versus placebo. Current evidence does not support the efficacy of tiagabine or divalproex in the treatment of PTSD. Current practice guidelines do not recommend anticonvulsants as first or second-line treatments for PTSD.[25–28]

Despite mixed results in clinical trials, one existing study indicates that VA patients with PTSD commonly received anticonvulsants in clinical practice. In a national survey of 482 VA users with new PTSD diagnoses between 2006 and 2007, 81% received treatment with any psychotropic medication.[29] Of those who received a medication, 22% were treated with a mood stabilizer (a larger category of medications generally including both lithium and anticonvulsants) in the year following their diagnosis. Even after excluding patients with seizure disorder and bipolar disorder, it appeared that 18% of patients received a mood stabilizer as PTSD treatment during their first year of care. However, many questions remain. Given that anticonvulsants are commonly prescribed for indications other than seizure disorder and bipolar disorder, including pain syndromes, headaches, alcohol use disorder, impulse control disorders, and restless legs syndrome, it is important to account for these additional conditions.

As the evidence is stronger for some agents than others, it is critical to understand which specific anticonvulsants patients with PTSD receive. The publication of RCT results may have affected clinical practice and because some agents have only recently become available, understanding longitudinal use is important. Finally, survey may not be the most appropriate way to understand overall prescription practices in the VA. While survey methods allow researchers to add important explanatory variables not easily abstracted from the electronic medical record such as PTSD severity and interest in various treatments, low response rates may introduce biases.

In this study, we use pharmacy and electronic medical records to understand anticonvulsant receipt for all patients with new episodes of PTSD care from 2004 to 2013. Our objective was to measure trends in anticonvulsant prescriptions among VA users with PTSD and to determine factors associated with initiation of these agents in Veterans without a clear non-PTSD anticonvulsant indication.

Method

Data Source

We used the VA corporate data warehouse (CDW) to identify patients with new PTSD treatment episodes from fiscal year 2004 through fiscal year 2013. We obtained patient

demographic information as well as encounter, diagnostic, and pharmacy data from the CDW. The Dartmouth College Committee for the Protection of Human Subjects, the White River Junction VA Medical Center Research and Development Committee, and VA National Data Systems approved this study.

Patients

We included VA users who received a primary diagnosis of PTSD at two or more outpatient encounters, at least one of which occurred in a mental health setting, over the course of 90 days between October 1, 2003 and September 30, 2013, and had not met this criterion during the prior two years. We examined one year of treatment receipt following the first diagnosis of the two qualifying diagnoses. When patients met the cohort inclusion criteria multiple times over the 10-year period, only their first episode was included.

Anticonvulsant Use

We examined all medications dispensed by VA pharmacies during the year following the index PTSD diagnosis. Anticonvulsant drug names were classified into categories for individual agents and an overall category. The anticonvulsant drug class label was used to confirm our coding. We determined both whether patients received each anticonvulsant and whether they received any anticonvulsant during the year.

Potential Moderators: We developed three groups of potential moderators. First, we examined clinical uses for which anticonvulsants are indicated or widely recommended by assessing comorbid diagnoses for the year before and year following the index PTSD diagnosis. These included impulse control disorders, alcohol use disorders, bipolar disorder, schizoaffective disorder, restless legs syndrome, headache disorders, pain disorders, and seizure disorders. We also identified patients who received the plurality of their anticonvulsant prescriptions from neurology or rehabilitation as a marker that the medication might be primarily intended for a non-psychiatric indication. Second, we examined patient factors including age, gender, military service-connected disability for PTSD, psychiatric comorbidity, and history of traumatic brain injury during the year following the index PTSD diagnosis. For history of traumatic brain injury, we also examined the two years before the index PTSD diagnosis. Third, we examined treatment receipt factors during the year following the index PTSD diagnosis. This included number of outpatient mental health visits, whether patients had any inpatient mental health admissions, whether patients received any psychotropic medication, total number of psychotropic medications, and whether patients received the plurality of their anticonvulsant prescriptions from mental health or primary care. To determine whether clinicians attempted to follow relevant treatment recommendations, we also determined whether patients also received a medication recommended for PTSD in clinical practice guidelines from the US Department of Veterans Affairs and Defense (VA/DoD CPGs).[27]

Analysis

There were five steps to our analysis. First, we summarized cohort characteristics and compared patients who received anticonvulsants with those who did not using t-test or χ^2 analysis, as appropriate. Second, we mapped patients' anticonvulsant prescriptions to

diagnostic data indicating possible indications for prescription unrelated to PTSD. We indicated when the anticonvulsant-diagnosis match aligned with a US Food and Drug Administration (FDA) indication. We also indicated when the anticonvulsant-diagnosis match aligned with common off-label prescription recommendations. Because no agency had uniform clinical practice guidelines across all possible indications, we used recommendations from UpToDate®, the clinical decision support tool most commonly used by physicians at the point of care.[30.] For the last three steps, we focused on anticonvulsant initiation by excluding patients who received anticonvulsants prior to their index PTSD diagnosis. In the third step, we calculated initiation rates for any anticonvulsant and for each individual agent for the overall 10-year period and for each individual fiscal year. We then calculated the absolute and relative change in prescription frequency from 2004 to 2013. In the fourth step, we calculated anticonvulsant initiation rates for patients without any anticonvulsant indication and among those with the most common indications. We then calculated the absolute and relative change in prescription frequency for these groups from 2004 to 2013. In the fifth step, we developed a logistic regression model to predict initiation of any anticonvulsant and the most commonly prescribed anticonvulsants among patients without an indication for anticonvulsant use using multivariate models controlling for patient and service use characteristics. All analyses were completed in SAS (Version 9.4, Carey NC).

Results

Over the 10-year period, 731,520 Veterans met our inclusion criteria, and a quarter received an anticonvulsant during the year following their index PTSD diagnosis. Those who received anticonvulsants differed from those who did not on all patient and service use characteristics (Table 1). Patients who received an anticonvulsant were more likely to be diagnosed with each of the indications for anticonvulsant use. The most common indications were pain disorders, headache disorders, alcohol use disorders, and bipolar and schizoaffective disorders. Patients who received an anticonvulsant were slightly younger, more likely to be women, and had lower rates of military service-connected disability for PTSD. In addition, they had higher rates of psychiatric comorbidities and more commonly had a history of traumatic brain injury. They had more mental health visits, were more likely to be admitted to inpatient psychiatric units, and received a greater number of psychotropic medications, including those recommended for PTSD.

Gabapentin was by far the most commonly prescribed agent. Most patients who received it were also diagnosed with a pain disorder (Table 2). Gabapentin was also the most-commonly prescribed agent in all other indication groups except impulse control disorders and bipolar and schizoaffective disorders, where valproic acid was most commonly used. An anticonvulsant-diagnosis match aligned with an indication in 79.9% of cases and that percentage rose to 90.0% when including additional recommendations. The most common agents prescribed to the 9,517 Veterans who received an anticonvulsant with no identifiable indication (and thus may have been used as a primary PTSD treatment) were gabapentin, valproic acid, lamotrigine, topiramate, and carbamazepine.

Among the 607,776 Veterans who did not receive an anticonvulsant prior to their index PTSD diagnosis, 14.6% initiated any anticonvulsant in the subsequent year. This proportion grew over the 10-year period from 11.6% to 17.5%, a 50.9% relative increase (Figure 1). Most of the increase in anticonvulsant initiation was due to gabapentin, which almost doubled from 5.4% to 10.2%. Whereas initiation of valproic acid was nearly as common as initiation of gabapentin in the early years of the cohort, initiation of both valproic acid (4.3% to 4.1%) and carbamazepine (0.6% to 0.5%) decreased slightly over time. There were large relative increases in initiation of topiramate (1.2% to 2.8%; a 141.7% relative increase) and lamotrigine (0.6% to 1.9%; a 185.9% relative increase) over time, but use of these medications accounted for relatively few anticonvulsant starts.

The proportion of patients without an indication for anticonvulsants decreased over time (22.0% to 15.8%; a 28.2% relative decrease) and initiation of anticonvulsants in this group was stable, ranging between 4.8% and 5.2% during the 10-year period (Table 3). However, growing populations of patients with comorbid pain and headache disorders were over 50% more likely to receive an anticonvulsant in 2013 than in 2003. While there was little growth in alcohol use disorders and a decrease in bipolar and schizoaffective disorders, initiation of anticonvulsants also became more common in these groups.

Among the group of 87,626 patients without an identifiable indication for an anticonvulsant who were treated with any psychotropic medication, 6.3% initiated an anticonvulsant. Multivariate logistic regression models to predict the initiation of anticonvulsants in general and of specific agents had good discriminative ability, with c-statistics of approximately 0.7 (Table 4). Compared to those who received any psychotropic medication, patients who initiated an anticonvulsant were likely to be younger men with personality disorders and a history of traumatic brain injury who did not receive one of the recommended medications for PTSD despite being prescribed a high number of psychotropic medications.

Different patterns emerged in predicting the choice of specific agents among the subgroup of 5,532 patients who initiated any anticonvulsant in the absence of an identifiable indication. Patients who received gabapentin were older non-psychotic Veterans with substance use disorders. They tended to receive their gabapentin from their primary care doctors. These patients also were more often prescribed recommended medications for PTSD. While they took fewer psychotropic medications and were less likely to be admitted to inpatient psychiatry, a high number of mental health visits was also associated with increased odds of receiving gabapentin. Patients who received valproic acid tended to be younger men with psychotic and personality disorders as well as traumatic brain injuries that were seen by psychiatrists. Patients who received lamotrigine tended to be women with unipolar depressive disorders who were seen by psychiatrists and did not receive a recommended medication for PTSD. Patients who received topiramate tended to be younger women with traumatic brain injury who were seen by a psychiatrist. The small and declining number of patients who received carbamazepine tended to receive their anticonvulsants from their primary care physicians, although they had higher odds of inpatient psychiatric admission and receiving a high number of psychiatric medications.

Discussion

Using administrative and pharmacy data, we confirmed prior survey results suggesting that a large proportion of patients with PTSD receive an anticonvulsant. Furthermore, we showed that this practice is increasing over time. However, we differ from prior research in finding that almost all patients receiving these agents have an indication for anticonvulsant use unrelated to PTSD. Thus, it appears most anticonvulsant prescriptions in patients with PTSD are given appropriately for other disorders or health problems. By examining the many reasons for anticonvulsant initiation over our 10-year window, we have found an increase in prevalence of conditions that may be an indication for anticonvulsant use. However, it is important to note that using administrative data, we cannot tell whether anticonvulsants were prescribed specifically for these indications. At the same time, neuropsychiatric comorbidity appears to drive anticonvulsant initiation in the small number of Veterans without an identifiable indication. While it is possible that PTSD contributes to a physician's choice to prescribe an anticonvulsant, there is every indication that VA physicians are choosing these agents parsimoniously based on complex constellations of medical and psychiatric problems.

It is important to highlight the complexity of Veterans initiating treatment for PTSD in the VA and to note that many of these Veterans may be refractory to the first-line recommended medications for PTSD. Regardless of whether they receive an anticonvulsant, 84.2% had a diagnosis for which anticonvulsants are indicated or recommended. This includes 73.3% with a pain disorder, 29.4% with a headache disorder and 27.1% with an alcohol use disorder. For most patients in our cohort, PTSD is one of many concerns. It is possible that in these cases, physicians chose medications they hope will have a positive effect on as many problems as possible. For example, recent evidence indicates that in addition to helping decrease alcohol consumption,[31] topiramate decreases PTSD symptoms in patients with comorbid alcohol use disorders and PTSD.[32] Future anticonvulsant trials should address other major comorbidity groups such as patients with PTSD and pain or headaches.

Even in the case of patients without an identifiable indication for anticonvulsant use, comorbidity appears to drive the selection of individual agents. For example, lamotrigine is indicated for the treatment and prevention of depressive episodes among patients with bipolar disorder.[33] While there is some indication that this medication is helpful for PTSD symptoms,[17] it was prescribed preferentially to patients with a comorbid unipolar depressive disorder in our cohort. This perhaps represents clinicians' application of the evidence in bipolar depression to unipolar depression, though two recently published negative RCTs of lamotrigine for unipolar depression indicate this is an incorrect extension of the literature.[34,35] It is unclear why gabapentin was the most frequently initiated agent among patients without an identifiable indication for an anticonvulsant. A case series of 30 patients treated in a PTSD specialty clinic at one VA medical center between 1997 and 2000 indicated that gabapentin was most commonly initiated for PTSD-related sleep difficulties, with clinicians reporting positive results.[36] Given our finding that gabapentin is the most popularly prescribed anticonvulsant among Veterans with PTSD and that there have been no RCTs of gabapentin for PTSD,[37] the authors' call for prospective, controlled studies continues to be well-justified.

There are several limitations to this study. Firstly, it is a retrospective cohort study. We were not able to ask patients and clinicians why they chose to use anticonvulsants as part of their treatment plans. While we believe our work to be the most detailed analysis in this area, it is possible that both our choices around cohort construction and clinical coding errors could have unduly influenced our findings. Secondly, we included only patients with PTSD in our cohort. Therefore, it is not possible to tell how a PTSD diagnosis influences the decision to prescribe an anticonvulsant. Finally, while FDA indications for several anticonvulsants are in place for a relatively narrow spectrum of pain disorders (trigeminal, glossopharyngeal, post-herpetic, and diabetic neuralgia as well as fibromyalgia), it appears that these agents are being prescribed to patients with a wider range of pain disorders. There has not been extensive study of anticonvulsants for those other pain conditions.

In summary, our findings indicate that most anticonvulsant prescribing among VA PTSD patients appears to be reasonable and justified by high levels of comorbidity. In the small group of patients with PTSD who have no identifiable indication for an anticonvulsant, comorbidity appears to drive the selection of individual agents. Overall, it appears that when treating highly complex patients with PTSD, VA physicians try to use medications likely to have a positive effect on as many conditions as possible. Additional prospective research on the use of anticonvulsants in major comorbidity groups, such as patients with pain and PTSD is indicated.

acknowledgements:

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Clinical Points:

- Despite mixed results in clinical trials, existing data indicate that VA patients with PTSD commonly receive anticonvulsants in clinical practice.

- However, given that anticonvulsants are commonly prescribed for other indications, is important to account for comorbidity.

- While it is possible that PTSD contributes to a physician's choice to prescribe an anticonvulsant, there is every indication that VA physicians are choosing these agents parsimoniously based on complex constellations of medical and psychiatric problems.
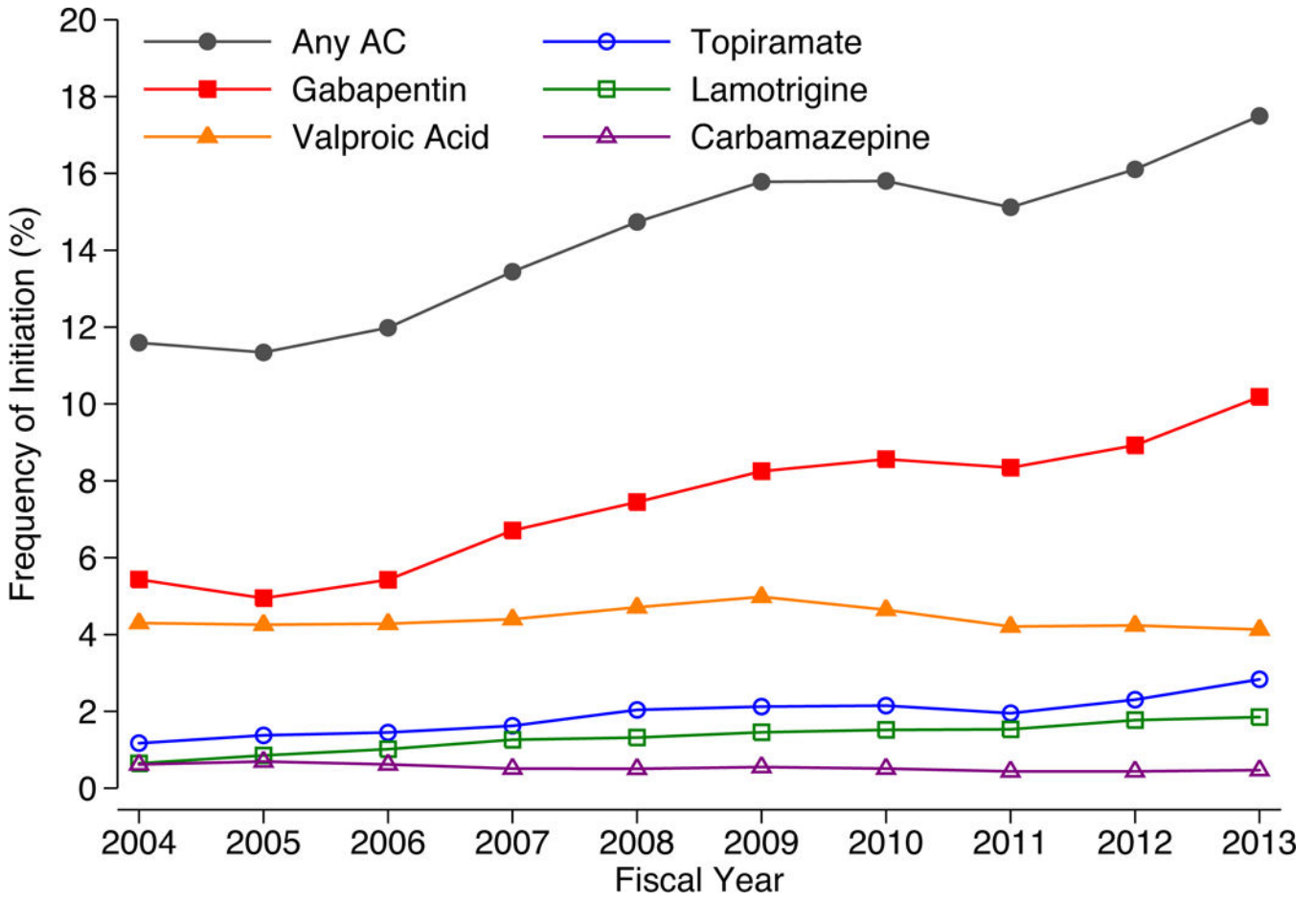
Figure 1.
Frequency of Anticonvulsant Initiation Among Veterans with New Episodes of PTSD Care[a]

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[a]Note. Excludes patients who received an anticonvulsant before their index PTSD diagnosis. AC=Anticonvulsant

Table 1.

VA Users with New Episodes of PTSD Care from 2004–2013 by Anticonvulsant Use

Group, % (n)	All Patients (731,520)	Received AC 24.9 (182,077)	No AC 75.1 (549,443)
Common Indications for Anticonvulsants			
Any Indication, % (n)	84.2 (615,587)	94.6 (172,385)	80.7 (443,202)
Any Indication or Plurality from Neurology/Rehabilitation, % (n)	84.2 (615,762)	94.8 (172,560)	80.7 (443,202)
Impulse Control Disorders, % (n)	1.4 (10,516)	2.7 (4,982)	1.0 (5,534)
Alcohol Use Disorders, % (n)	27.1 (198,116)	32.2 (58,586)	25.4 (139,530)
Bipolar & Schizoaffective Disorders, % (n)	8.0 (58,836)	19.4 (35,233)	4.3 (23,603)
Restless Legs Syndrome, % (n)	1.1 (8,284)	2.0 (3,708)	0.8 (4,576)
Headache Disorders, % (n)	29.4 (214,780)	45.4 (82,661)	24.1 (132,119)
Pain Disorders, % (n)	73.3 (536,172)	84.9 (154,491)	69.5 (381,681)
Seizure Disorders, % (n)	3.2 (23,014)	7.7 (14,049)	1.6 (8,965)
Plurality of AC Prescriptions from Neurology, % (n)	-	4.0 (7,211)	-
Plurality of AC Prescriptions from Rehabilitation, % (n)	-	1.7 (3,159)	-
Indication established before first AC Prescription, % (n)	-	94.6 (171,872)	-
Indication established before Index PTSD Diagnosis, % (n)	67.5 (493,889)	79.5 (144,721)	63.6 (349,168)
No non-PTSD Indication, % (n)	15.8 (115,718)	5.2 (9,517)	19.3 (106,241)
Patient Characteristics			
Age, M (SD)	49.9 (15.4)	49.3 (14.4)	50.1 (15.7)
Men, % (n)	91.5 (669,663)	89.4 (162,757)	92.3 (506,906)
Military Service-Connected Disability for PTSD, % (n)	65.9 (482,048)	60.7 (110,592)	67.6 (371,456)
Psychotic Disorders (Non-Schizoaffective), % (n)	4.0 (29,350)	6.5 (11,792)	3.2 (17,558)
Unipolar Depressive Disorders, % (n)	58.9 (430,467)	66.4 (120,843)	56.4 (309,624)
Anxiety Disorders (Non-PTSD), % (n)	26.1 (191,098)	31.4 (57,202)	24.4 (133,896)
Personality Disorders, % (n)	4.0 (29,272)	7.7 (14,060)	2.8 (15,212)
Substance Use Disorders (Non-Alcohol), % (n)	33.7 (246,180)	42.7 (77,710)	30.7 (168,470)
History of Traumatic Brain Injury, % (n)	9.3 (67,756)	14.0 (25,554)	7.7 (42,202)
Service Use Characteristics			

Group, % (n)	All Patients (731,520)	Received AC 24.9 (182,077)	No AC 75.1 (549,443)
Mental Health Visits, M (SD)	17.6 (22.4)	24.1 (27.7)	15.4 (19.8)
Inpatient Mental Health Admissions, % (n)	8.9 (65,040)	17.0 (31,024)	6.2 (34,016)
Received Any Psychiatric Medication, % (n)	90.5 (661,904)	100 (182,077)	87.3 (479,827)
Number of Psychotropic Medications, M (SD)	3.9 (2.5)	5.7 (2.9)	3.2 (2.0)
Received AC before Index PTSD Diagnosis, % (n)	16.9 (123,744)	51.2 (93,291)	5.5 (30,453)
Any Recommended Medication for PTSD, % (n)	76.9 (562,773)	85.2 (155,170)	74.2 (407,603)
Plurality of AC Prescriptions from Mental Health, % (n)	-	42.5 (77,441)	-
Plurality of AC Prescriptions from Primary Care, % (n)	-	20.0 (36,471)	-

Note. AC=Anticonvulsant, M=mean, SD=standard deviation; All differences significant at p<0.0001

Table 2.

Individual Patients with PTSD Receiving Prescriptions for Each Anticonvulsant by Non-PTSD Indication[a]

Anticonvulsant Rank	Overall	No Indication Identified	By Individual Indication						
			Impulse Control Disorders	Alcohol Use Disorders	Bipolar & Schizoaffective Disorders	Restless Legs Syndrome	Headache Disorders	Pain Disorders	Seizure Disorders
1	Gabapentin 102,791	Gabapentin 4,605	Valproic Acid 2,464	Gabapentin 32,192	Valproic Acid 17,567	Gabapentin 2,650	Gabapentin 47,076	Gabapentin 92,459	Gabapentin 5,976
2	Valproic Acid 49,197	Valproic Acid 2,761	Gabapentin 2,127	Valproic Acid 19,128	Gabapentin 12,205	Valproic Acid 640	Valproic Acid 21,146	Valproic Acid 39,312	Valproic Acid 3,737
3	Topiramate 22,803	Lamotrigine 915	Lamotrigine 543	Topiramate 6,516	Lamotrigine 8,198	Topiramate 426	Topiramate 16,414	Topiramate 19,471	Levetiracetam 2,048
4	Lamotrigine 17,009	Topiramate 670	Topiramate 486	Lamotrigine 5,902	Topiramate 3,794	Lamotrigine 319	Lamotrigine 7,196	Lamotrigine 13,552	Topiramate 1,936
5	Carbamazepine 8,627	Carbamazepine 482	Carbamazepine 418	Carbamazepine 3,007	Carbamazepine 2,841	Carbamazepine 134	Carbamazepine 3,794	Carbamazepine 6,973	Phenytoin 1,930
6	Pregabalin 4,748	Phenytoin 340	Phenytoin 108	Phenytoin 1,717	Oxcarbazepine 651	Pregabalin 207	Pregabalin 3,056	Pregabalin 4,528	Lamotrigine 1,684
7	Phenytoin 4,631	Levetiracetam 143	Oxcarbazepine 102	Levetiracetam 1,253	Phenytoin 597	Levetiracetam 95	Levetiracetam 1,798	Phenytoin 3,574	Primidone 1,488
8	Levetiracetam 3,746	Primidone 116	Pregabalin 86	Pregabalin 1,129	Pregabalin 594	Primidone 94	Phenytoin 1,696	Levetiracetam 3,033	Carbamazepine 1,201
9	Primidone 2,637	Pregabalin 86	Levetiracetam 83	Primidone 613	Levetiracetam 513	Phenytoin 57	Primidone 804	Primidone 2,122	Pregabalin 431
10	Oxcarbazepine 1,482	Oxcarbazepine 65	Primidone 39	Oxcarbazepine 570	Primidone 331	Oxcarbazepine 25	Oxcarbazepine 722	Oxcarbazepine 1,204	Oxcarbazepine 262
11	Zonisamide 230	Tiagabine 19	Zonisamide 3	Tiagabine 59	Tiagabine 36	Zonisamide 6	Zonisamide 150	Zonisamide 190	Zonisamide 100
12	Tiagabine 194	Zonisamide 6	Tiagabine 2	Zonisamide 48	Zonisamide 31	Tiagabine 0	Tiagabine 83	Tiagabine 151	Tiagabine 22
Total	182,077	9,517	4,982	58,586	35,233	3,708	82,661	154,491	14,049

[a]Note. All patients are included.

FDA approved indication 79.7% (145,155/182,077)

Add additional recommendations 90.0% (163,848/182,077)

Table 3.

Frequency of Most Common Anticonvulsant Indication and Initiation Among Veterans with New Episodes of PTSD Care, 2004–2013[a]

	Overall	\\ Frequency of Medication Use by Fiscal Year (number of veterans), %										Change	
		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Abs.[b]	Rel.[c]
	(607,776)	(43,080)	(50,822)	(50,019)	(59,179)	(65,517)	(69,127)	(70,338)	(68,915)	(64,354)	(66,425)		
No Indication Identified													
Patients in Category	18.1%	22.0%	21.2%	20.8%	22.5%	18.0%	16.8%	16.8%	17.1%	16.7%	15.8%	−6.2%	−28.2%
Received Anticonvulsant	5.0%	5.2%	5.1%	5.0%	4.8%	5.1%	5.1%	5.0%	4.8%	5.1%	5.2%	0.0%	−0.4%
Comorbid Pain Disorders													
Patients in Category	70.5%	66.0%	67.6%	68.0%	82.3%	70.7%	71.4%	71.9%	71.5%	72.3%	73.1%	7.0%	10.7%
Received Anticonvulsant	17.0%	13.4%	12.9%	13.9%	15.7%	17.1%	18.5%	18.5%	17.6%	18.6%	20.3%	6.9%	51.4%
Comorbid Headache Disorders													
Patients in Category	26.3%	20.4%	20.9%	21.7%	28.0%	27.4%	28.8%	28.2%	27.6%	28.8%	30.4%	10.0%	49.1%
Received Anticonvulsant	25.1%	19.0%	20.0%	20.0%	23.2%	25.4%	26.6%	26.6%	25.5%	27.3%	29.0%	10.0%	52.4%
Comorbid Alcohol Use Disorders													
Patients in Category	26.2%	25.9%	24.8%	24.7%	29.6%	25.9%	27.5%	27.7%	27.1%	26.7%	26.0%	0.1%	0.4%
Received Anticonvulsant	18.4%	14.5%	14.1%	15.7%	17.4%	18.4%	19.7%	19.3%	19.1%	20.6%	21.9%	7.4%	51.2%
Comorbid Bipolar and Schizoaffective Disorders													
Patients in Category	5.2%	5.9%	5.3%	5.4%	6.4%	5.1%	5.3%	5.2%	4.8%	5.0%	5.0%	−0.9%	−14.5%
Received Anticonvulsant	40.7%	34.5%	35.7%	36.5%	40.4%	40.5%	42.0%	44.1%	42.9%	43.5%	43.1%	8.6%	24.9%

[a] Note. Excludes patients who received an anticonvulsant before their index PTSD diagnosis and comorbidities were established before the initiation of the anticonvulsant.

[b] Absolute change in frequency of use from fiscal years 2004 through 2013; negative values represent decreased frequency over time.

[c] Relative change in frequency of use from fiscal years 2004 through 2013; negative values represent decreased frequency over time.

Table 4.

Predictors of Anticonvulsant Initiation Among Patients who Received a Psychotropic Medication and had no Obvious Indication for an Anticonvulsant[a]

Regression Model Characteristics	All (n=87,626)	Received Specific AC (n=5,532)				
Inclusion Criteria for Model						
Dependent Variable (Received Agent)	Any AC	Gabapentin	Valproic Acid	Lamotrigine	Topiramate	Carbamazepine
Prescription Status, % (n)	6.31% (5,532)	41.6% (2302)	35.6% (1,969)	12.0% (665)	8.4% (465)	3.7%(204)
Model Performance	c=0.74	c=0.75	c=0.72	c=0.72	c=0.67	c=0.65
Notation	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Patient Characteristics						
Age >= 55	**0.81** **(0.76–0.86)**	**2.21** **(1.94–2.52)**	**0.54** **(0.48–0.62)**	0.84 (0.70–1.01)	**0.76** **(0.61–0.94)**	0.90 (0.67–1.23)
Men	**1.20** **(1.07–1.36)**	1.15 (0.87–1.51)	**2.79** **(2.12–3.67)**	**0.38** **(0.29–0.50)**	**0.31** **(0.23–0.43)**	1.47 (0.75–2.87)
Psychotic Disorders (Non-Schizoaffective)	**0.81** **(0.69–0.96)**	**0.49** **(0.33–0.71)**	**1.55** **(1.11–2.17)**	1.15 (0.72–1.83)	0.91 (0.50–1.63)	1.07 (0.50–2.25)
Unipolar Depressive Disorders	1.02 (0.96–1.08)	1.00 (0.88–1.13)	**0.77** **(0.68–0.87)**	**1.70** **(1.41–2.06)**	1.03 (0.84–1.26)	0.85 (0.63–1.15)
Anxiety Disorders	0.96 (0.90–1.03)	1.04 (0.90–1.20)	1.03 (0.90–1.18)	0.86 (0.71–1.05)	1.02 (0.82–1.28)	1.24 (0.90–1.71)
Personality Disorders	**1.53** **(1.28–1.84)**	0.71 (0.47–1.05)	**1.64** **(1.15–2.34)**	1.16 (0.73–1.84)	0.69 (0.37–1.29)	1.75 (0.90–3.41)
Non-Alcohol Substance Use Disorders	**0.91** **(0.86–0.98)**	**1.22** **(1.06–1.41)**	0.99 (0.85–1.14)	0.98 (0.80–1.19)	**0.73** **(0.57–0.94)**	**0.68** **(0.47–0.98)**
History of Traumatic Brain Injury	**1.35** **(1.18–1.56)**	0.77 (0.57–1.05)	**1.38** **(1.05–1.80)**	**0.63** **(0.41–0.97)**	**2.27** **(1.58–3.27)**	1.34 (0.73–2.45)
Service Use Characteristics						
Fiscal Years 2008–2013 (v. 2004–2007)	1.03 (0.97–1.09)	**1.49** **(1.32–1.70)**	**0.65** **(0.57–0.73)**	**1.71** **(1.41–2.06)**	**0.76** **(0.62–0.93)**	**0.65** **(0.47–0.87)**
5–13 Mental Health Visits (v. 4 or fewer)	**1.41** **(1.30–1.53)**	1.04 (0.87–1.24)	1.06 (0.89–1.27)	1.13 (0.87–1.49)	0.88 (0.67–1.17)	0.73 (0.49–1.07)
>= 14 Mental Health Visits (v. 4 or fewer)	**1.82** **(1.66–1.98)**	**1.25** **(1.04–1.52)**	0.95 (0.78–1.15)	**1.41** **(1.06–1.87)**	0.84 (0.62–1.14)	**0.60** **(0.39–0.93)**
One or More Inpatient Mental Health Admission	**1.70** **(1.48–1.94)**	**0.74** **(0.56–0.99)**	1.12 (0.86–1.45)	**0.67** **(0.46–1.00)**	0.81 (0.51–1.27)	**2.26** **(1.39–3.68)**

Regression Model Characteristics

Three or More Psychiatric Medications (v. 1 or 2)	**6.15** **(5.73–6.60)**	**0.81** **(0.69–0.96)**	1.12 (0.94–1.32)	**1.36** **(1.06–1.74)**	**1.37** **(1.01–1.84)**	**1.73** **(1.12–2.68)**
Any Recommended Medication for PTSD	**0.41** **(0.38–0.44)**	**1.22** **(1.03–1.45)**	1.08 (0.91–1.28)	**0.51** **(0.41–0.64)**	1.29 (0.96–1.73)	0.73 (0.49–1.07)
Measures that Apply to AC Population Only						
Plurality of AC Prescriptions from Mental Health	-	**0.24** **(0.21–0.28)**	**3.92** **(3.29–4.67)**	**3.69** **(2.74–4.97)**	**1.49** **(1.13–1.96)**	1.36 (0.92–1.99)
Plurality of AC Prescriptions from Primary Care	-	**1.64** **(1.34–2.02)**	**0.70** **(0.54–0.91)**	0.81 (0.52–1.28)	0.66 (0.43–1.01)	**0.48** **(0.25–0.94)**

[a]Note. AC=Anticonvulsant, M=mean, SD=standard deviation, C=C-statistic

OR and 95% CI less than 1

OR and 95% CI greater than 1