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Emergent Anxiety after Antidepressant Initiation: a Retrospective Cohort Study of Depressed VA Health System Patients

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Abstract

Background—Initiation of antidepressant treatment for depression may be associated with new onset (emergent) anxiety.

Objective—We assessed patient demographic and clinical factors associated with emergent anxiety following a new antidepressant start among depressed VA health system patients.

Methods—Using a retrospective cohort design, we obtained data from 328,888 depressed VA patients newly prescribed one of the seven most commonly used antidepressants between April 1999 and September 2004 from the VA National Depression Registry. We examined the prevalence of emergent anxiety, defined as either a new anxiety diagnoses or by new antianxiety medication starts, in the 12 weeks following new antidepressant start. In multivariate analyses, we assessed the hazard ratios for emerging anxiety associated with patient characteristics and specific antidepressant agents.

Results—Approximately 3% patients developed clinically significant anxiety within 12 weeks of starting an antidepressant. Younger age (age <45 years and 45–64 years) was associated with higher risks for emergent anxiety than older age (≥65 years) (HR: 1.72 and 1.55, 95% CI: 1.59–1.85, and 1.38–1.72, respectively). Female gender was associated with higher risks than male gender (HR: 1.17, 95% CI: 1.10–1.26), and white and other races compared with black race were associated with higher risks of emergent anxiety (HR: 1.49 and 1.13, 95% CIs: 1.30–1.59 and

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1.04–1.23, respectively). Finally, antidepressant fills occurring in years subsequent to 1999 were associated with lower risks of emergent anxiety.

Conclusions—Only a small proportion of patients developed emergent anxiety following a new antidepressant start, resulting in a new diagnosis or antianxiety medication use. Anxiety occurred more often in young adults, whites, and women.

1. Introduction

Depression and anxiety disorders are highly prevalent psychiatric disorders. Major depressive disorder affects about 5% to 12% of men and 10% to 25% of women in their lifetimes, while anxiety disorders affect approximately 18.1% of the population^(1, 2). The prevalence rates may be even higher among veterans, for example, 31% of veterans have significant depressive symptoms³, and a recent study found that 41.5% of depressed veterans also have anxiety disorder diagnoses⁴. The relationships between these two disorders are complex and have been a subject of much debate^(5–7). The two conditions are not mutually exclusive and often coexist in the same patient. Three previous studies have demonstrated that patients with comorbid depression and anxiety have poorer outcomes, including greater symptom severity and persistence, more severe role impairment, increased help-seeking behavior, and higher incidence of suicide related thoughts and behaviors^(8–10).

Unfortunately, antidepressant treatment for depression has been associated with increased anxiety, restlessness, and agitation in the early period following treatment initiation^(11–13). The outcomes associated with anxiety following antidepressant initiation are not fully understood; however, there have been concerns that emergent anxiety and related symptoms after antidepressant initiation might result in increased risks for suicide^(14, 15).

We sought to assess whether specific patient demographic variables, comorbid psychiatric disorders, and antidepressant agents were associated with the development of anxiety after antidepressant initiation. The study was conducted among Veteran Administration (VA) Health System patients with depression in order to better understand anxiety comorbidity in this population.

2. Patients and Methods

Study Data

Patient data were identified using the VA's National Registry for Depression (NARDEP), which is maintained by the VA Serious Mental Illness Treatment Research and Evaluation Center in Ann Arbor, Michigan. NARDEP includes detailed services and pharmacy data for over 2.2 million patients diagnosed with depressive disorders in VA facilities nationwide. VA administrative data are drawn from databases that support clinical activity and must be sufficiently accurate to track and schedule patient visits and to allow clinical personnel to order and dispense medications. Studies have indicated good concordance between VA chart notation of the diagnoses used in this study (particularly depression) and diagnoses recorded in VA administrative data¹⁶.

Patients who received at least two clinical diagnoses of depression (major depressive disorder, dysthymic disorder, or depressive disorder not otherwise specified), or one depression diagnosis followed by an antidepressant fill during the study period, between April 1, 1999 and September 30, 2004, were included in this study. Patients with a diagnosis of bipolar I disorder, schizophrenia, or schizoaffective disorder are excluded from the database (see Appendix for specific ICD9 diagnosis codes).

Our study sample was restricted to those with a new start of one of the following seven antidepressant agents: fluoxetine, sertraline, paroxetine, citalopram, venlafaxine, bupropion or mirtazapine; thus patients who did not start one of these antidepressant medications were excluded. These were the seven most commonly prescribed antidepressants during the study period and constituted the large majority of all antidepressant fills during this period. A new start of these antidepressant medications was defined as a fill of one of these agents following a 6-month period with no antidepressant fills, where the antidepressant fills were determined by administrative records.

Patients were also excluded from study analyses if they met one of the following conditions: 1) were given an antianxiety drug (buspirone or a benzodiazepine) in the 6-month period prior to the new antidepressant start, 2) had an anxiety disorder diagnosis, including PTSD, in the 12 months prior to the new antidepressant start, or 3) had a diagnosis of Bipolar II disorder in the 12 months prior to the new antidepressant start (Bipolar I patients were not included in the original database). This study was conducted with institutional review board approval from the VA Ann Arbor Health System.

We assessed baseline patient demographic characteristics, including age (<45, 45–65, ≥65), race (white, black, and other), gender, and Hispanic ethnicity (yes or no). We also assessed clinical patient characteristics for the year prior to the new start date, including physical comorbidities (Charlson score category¹⁷, 0, 1, 2, or >2), major depression diagnosis versus other depression diagnosis (yes or no), alcohol abuse or dependence (yes or no), other substance abuse diagnosis (yes or no), personality disorder (yes or no), number of inpatient psychiatry stays (0, 1, or >1), total number of inpatient psychiatry days, the number of psychotropic medicines (0, 1, or >1), and Medicare usage (yes or no). All diagnoses of mental disorders (including alcohol abuse or dependence) were based on ICD-9 codes. Also, we assessed whether patients had a service connected disability (VA-related disability from injuries or conditions that occurred or were exacerbated during military service) during the 3 years prior to the new antidepressant start date. Finally, we assessed whether different fiscal years of antidepressant fill (1999, 2000, 2001, 2002, 2003, 2004) are associated with different risks of emergent anxiety.

Emergent anxiety was defined by either a new anxiety diagnosis or a new antianxiety medication fill in the first 12 weeks following a new antidepressant fill. Either a new anxiety diagnosis or new prescription of an anxiolytic indicates that a clinician has taken some action for anxiety symptoms. The 12 week period following new antidepressant starts was the time period used by FDA to determine the prevalence of serious emerging antidepressant related adverse events, such as suicidal ideation, suicide attempts, and suicide¹⁸. In two sub-analyses, we looked separately at emergent anxiety defined only by diagnosis or only by medication.

We did not include social phobia and PTSD diagnoses as meeting criteria for a new anxiety disorder associated with antidepressant initiation because PTSD requires that the patient experience a traumatic event and social phobia requires the anxiety to occur in a specific social event. This makes these disorders less likely to be the sole result of antidepressant exposure. Moreover, if the antianxiety medication was prescribed for night time use only or it was clearly stated that it was prescribed for insomnia, it was also excluded as an indication for newly developed anxiety.

Data Analyses

We first used the Cox proportional hazards model¹⁹ to estimate the unadjusted hazard ratios (HRs), and their 95% confidence intervals (CIs) for emergent anxiety associated with patient characteristics and antidepressant agents in the 12 weeks following new antidepressant

starts. We then fitted a multivariate Cox proportional hazards model to estimate the HRs and their 95% CIs for emergent anxiety controlling for the patient demographic and clinical characteristics outlined above. In fitting the main model, emergent anxiety was determined by either a new anxiety diagnosis or an anxiety drug prescription.

In order to see if different choices of time period yield different results, we conducted two sensitivity analyses. In one sensitivity analysis, we examined emerging anxiety after antidepressant starts, however instead of censoring at 12 weeks, we censored at the time the antidepressant was discontinued or at the end of the study period. In another sensitivity analysis, we looked at early anxiety development in the first 4 weeks following a new antidepressant initiation instead of 12 weeks. We also conducted analyses in which we used narrower age ranges, i.e., <30, 30–45, 45–55, 55–65, 65–75, and over 75 years old.

3. Results

After applying our exclusion criteria, 328,888 veterans were included in our examination of emergent anxiety following an antidepressant start. Table 1 reports the demographic and clinical characteristics in our patient sample. Among the study subjects, the majority are male (91.3%) and white (74.8%); 17.6% were under the age of 45 years. A total of 58,204 (17.7%) had a major depressive disorder, 35,365 (10.8%) had alcohol abuse or dependence, and 21,948 (6.7%) had a diagnosis of other substance abuse, in the year prior to the new antidepressant start date.

Development of Emergent Anxiety

A total number of 9,170 (2.8%) patients developed anxiety in the 12 weeks after their first new start of antidepressant, as indicated by either a new anxiety disorder diagnosis or by the prescription of an antianxiety medication, with 4,352 (1.3%) having a prescription of antianxiety medication, 5,329 (1.6%) having an anxiety disorder diagnosis, and 511 (0.2%) having both.

Association between patient characteristics and emergent anxiety following AD starts

In multivariate analyses, for which results are listed in Table 2, we found that, compared with older age (age ≥ 65), the middle age (age 45–64) was associated with higher risks of emergent anxiety (HR=1.55, 95% CI: 1.38–1.72) and younger age (age <45) was associated with even higher risks (HR=1.72, 95% CI: 1.59–1.85). Moreover, female gender was associated with higher risks than male gender (HR=1.17, 95% CI: 1.10–1.26), white race was associated with higher risk than blacks (HR=1.49, 95% CI: 1.39–1.59), and other races were also associated with higher risks than blacks (HR=1.13, 95% CI: 1.04–1.23). Higher levels of medical comorbidity (i.e., higher Charlson scores) were associated with higher risk as was more severe depression as defined by a diagnosis of major depression rather than other depressive disorders (HR=1.40, 95% CI: 1.33–1.47). Having one or more inpatient psychiatric stays in the last 12 months was associated with higher risks for emergent anxiety (HRs are 1.29 and 1.46, and 95% CIs are 1.16–1.42 and 1.23–1.73, respectively), as was having one or more psychotropic medication fills in addition to an antidepressant fill (HRs are 1.23 and 1.27, 95% CIs are 1.16–1.30 and 1.14–1.42, respectively). A concurrent alcohol abuse disorder was also associated with slightly higher risks (HR=1.09, 95% CI: 1.02–1.17). However, personality disorder, Hispanic ethnicity and other substance use disorder diagnoses were not significantly associated with anxiety development after initiation of antidepressant treatment. Finally, compared with fiscal year 1999, the more recent fiscal years of antidepressant fill were associated with lower risks of emergent anxiety, with hazard ratios 0.88, 0.75, 0.76, 0.66, and 0.73, and 95% CIs 0.79–0.97, 0.68–0.83, 0.69–0.83, 0.60–0.72 and 0.66–0.81, for the years 2000, 2001, 2002, 2003 and 2004, respectively.

Antidepressant choice and emergent anxiety

Among the seven antidepressants, sertraline was the most commonly initiated antidepressant (27.7% of patients), followed by citalopram (26.0%), fluoxetine (15.0%), paroxetine (12.4%), bupropion (11.3%), venlafaxine (4.2%) and mirtazapine (3.4%). In exploratory analyses controlling for other demographic variables and psychiatric comorbidities, use of mirtazapine was associated with the highest risks for emergent anxiety. Compared with sertraline, the hazard ratios and their 95% CIs are as follows: 0.94 (95% CI: 0.87–1.01) for bupropion, 1.10 (95% CI: 1.04–1.16) for citalopram, 0.97 (95% CI: 0.90–1.04) for fluoxetine, 1.42 (95% CI: 1.28–1.58) for mirtazapine, 1.25 (95% CI: 1.17–1.34) for paroxetine, and 1.16 (95% CI: 1.05–1.28) for venlafaxine, respectively.

Sensitivity Analyses

In analyses that censored patient data at the end of antidepressant use or at the end of the study period rather than at 12 weeks, 4% of patients developed new anxiety. The average time to anxiety development was about 14 weeks using this method, and predictors of new anxiety were similar in these analyses as in the analyses examining emergent anxiety in the 12 weeks following antidepressant initiation. In analyses that censored patient data at the end of 4 weeks, 1.5% of patients developed emergent anxiety, and the significant predictors of emergent anxiety still remained the same.

In the two analyses in which we looked at anxiety defined by medication and anxiety defined by diagnosis separately, we obtained generally similar results to those described above. Finally, when we categorized age into narrower age groups, we found no significant differences between the 45–54 age group and younger age groups. However, all age groups older than age 54 had a significantly reduced risk of developing anxiety compared to the 45–54 age group.

4. Discussion

Using data from a large national cohort of veterans with depression, we found that about 3% of patients had emergent anxiety symptoms that resulted in anxiety diagnosis or treatment in the 12 weeks following antidepressant starts. Several factors were significantly associated with emergent anxiety. Most notably, we found younger age, sex, and severity of the psychiatric illness (defined by major depression versus other depression diagnoses, number of recent psychiatric hospitalizations and number of recent psychotropic medications) to be significantly associated with emergent anxiety. Although we also found some associations of emerging anxiety with specific antidepressant agents, these findings may be due to treatment selection by indication. That is, prescribers may have been more likely to prescribe certain medications, such as mirtazapine, to anxious patients (not on anxiety medications or with an anxiety diagnosis) who were then more likely to go on to receive an anxiety diagnosis or medication. Although personality disorder was previously found to be significantly associated with “activation syndrome” induced by antidepressants²⁰, we found that it was not significantly associated with emergent anxiety in this population.

Our finding that younger patient age was associated with increased risks of emergent anxiety after antidepressant use is consistent with epidemiologic studies that have reported higher rates of anxiety disorders in general among younger age groups when compared to the older age groups²¹. Although we did not use the same age categories, our finding of greater risks among younger patient groups for emergent anxiety is of interest, given the FDA meta-analysis of clinical trials in which they observed a differential risk of antidepressant-induced suicidality across the age spectrum, with a greater risk in younger adults and a declining risk with increasing age²². We found that patients with more severe depression, more psychiatric

hospitalizations and more psychotropic medications were associated with higher risks of anxiety development. In our prior analyses of completed suicide among veterans³, many of these factors were also associated with higher risks for suicide among depressed veterans.

The risks of emergent anxiety following antidepressant treatment initiation were significantly lower for patients who were prescribed sertraline, citalopram, bupropion, or fluoxetine than for patients prescribed venlafaxine, paroxetine, or mirtazapine. Although these analyses must be considered exploratory and potentially confounded by treatment selection, we note that sertraline, which was found to be associated with a reduced risk of emergent anxiety in our analyses, was also found to be associated with lower risks of suicide related thoughts and behavior in a FDA meta-analysis among adults following antidepressant starts¹⁸. Further research is needed in this area.

As the first limitation of the study, we note that our measure of medication use was identified using pharmacy data (antidepressant and antianxiety medication fills), and that patients may not have ingested medications they filled. We studied emergent anxiety among VA patients with depression and antidepressant use, and study findings may not generalize to other depressed populations. Moreover, our analysis was restricted to the population who filled one of the seven most commonly prescribed antidepressants. Finally, we censored subjects who died from suicide before anxiety development.

5. Conclusions

Emergent anxiety symptoms prompting a new clinician diagnosis or new antianxiety medication prescription occurred in about 3% of depressed veterans starting antidepressant medication. Younger age, white race, and female gender were associated with higher risks of emergent anxiety following antidepressant initiation.

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References

1. American Psychiatric Association, Work Group on Major Depressive Disorder. Practice Guideline for the Treatment of Patients with Major Depression. Washington,DC: American Psychiatric Association; 2000.
2. Kessler CR, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005; 62:617–627. [PubMed: 15939839]
3. Zivin K, Kim M, McCarthy JF, Austin KL, Hoggatt KJ, Walters H, Valenstein M. Suicide mortality-among individuals receiving treatment for depression in the veterans affairs health system: associations with patient and treatment setting characteristics. *Am J Public Health*. 2007; 97(12):2193–2198. [PubMed: 17971541]
4. Pfeiffer PN, Ganoczy D, Ilgen M, Zivin K, Valenstein M. Comorbid anxiety as a suicide risk factor among depressed veterans. *Depress Anxiety*. 2009; 26:752–757. [PubMed: 19544314]
5. Stavrakaki C, Vargo B. The Relationship of anxiety and depression: A review of the literature. *Br J Psychiatry*. 1986; 149:7–16. [PubMed: 3535981]
6. Gorman MJ. Comorbid depression and anxiety spectrum disorders. *Depress Anxiety*. 1997; 4:160–168. [PubMed: 9166648]
7. Kaufman J, Charney D. Comorbidity of mood and anxiety disorders. *Depress Anxiety*. 2000; 12 Supplement 1:69–76. [PubMed: 11098417]

8. Lamers F, van Oppen P, Comijs HC, Smit JH, Spinhoven P, van Balkom AJ, Nolen WA, Zitman FG, Beekman AT, Penninx BW. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA). *J Clin Psychiatry*. 2011; 72(3):341–348. [PubMed: 21294994]
9. Angst J, Angst F, Stassen HH. Suicide risk in patients with major depressive disorder. *J Clin Psychiatry*. 1999; 60 Suppl:57–62. [PubMed: 10073389]
10. Roy-Byrne PP, Stang P, Wittchen HU, Ustun B, Walters EE, Kessler RC. Lifetime panic-depression comorbidity in the National Comorbidity Survey: Association with symptoms, impairment, course and help-seeking. *Br J Psychiatry*. 2000; 176:229–235. [PubMed: 10755069]
11. Sinclair LI, Christmas DM, Hood SD, Potokar JP, Robertson A, Isaac A, Srivastava S, Nutt DJ, Davies SJ. Antidepressant-induced jitteriness/anxiety syndrome: systematic review. *Br J Psychiatry*. 2009; 194(6):483–490. [PubMed: 19478285]
12. Beasley CM, Saylor ME, Bosomworth JC, Wernicke JF. High-dose Fluoxetine: efficacy and activating-sedating effects in agitated and retarded depression. *J Clin Psychopharmacol*. 1991; 11(3):166–174.
13. Trindade E, Menon D, Topfer LA, Coloma C. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. *Canadian Medical Association Journal*. 1998; 159(10):1245–1252. [PubMed: 9861221]
14. Damluji FN, Ferguson MJ. Paradoxical worsening of depressive symptomatology caused by antidepressants. *J Clin Psychopharmacol*. 1988; 8(5):347–349.
15. Teicher HM, Glod RNC, Cole OJ. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry*. 1990; 147(2):207–210. [PubMed: 2301661]
16. Kramer TL, Owen RR, Cannon D, Sloan KL, Thrush CR, Williams DK, Austen MA. How well do automated performance measures assess guideline implementation for new-onset depression in the Veterans Health Administration? *Jt Comm J Qual Saf*. 29(9):479–489. [PubMed: 14513671]
17. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992; 45(6):613–619. [PubMed: 1607900]
18. Food and Drug Administration. Memorandum of Department of Health and Human Services Public Health Service. Center for Drug Evaluation and Research. 2006 November 16.
19. Cox DR. Regression models and life-tables. *Journal of the Royal Statistical Society Series B (Methodological)*. 1972; 34(2):187–220.
20. Harada T, Sakamoto K, Ishigooka J. Incidence and predictors of activation syndrome induced by antidepressants. *Depress Anxiety*. 2008; 25(12):1014–1019. [PubMed: 18781664]
21. Flint AJ. Epidemiology and comorbidity of anxiety disorders in the elderly. *Am J Psychiatry*. 1994; 151(5):640–649. [PubMed: 8166303]
22. Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, Hammad TA, Temple R, Rochester G. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ*. 2009; 339:b2880. [PubMed: 19671933]

Appendix: ICD9 codes for all the disorders mentioned in the paper

Other Anxiety diagnoses excluding social phobia: 30000, 30001, 30002, 30009, 30010, 30020, 30021, 30022, 30029

Social phobia: 30023

PTSD: 30981

Major depression: 2962, 2963

All other depression: 311, 2980, 3004, 3090, 3091, 29690, 29699, 29383, 30112

Schizophrenia or Schizoaffective: 2950, 2951, 2952, 2953, 2954, 2956, 2957, 2958, 2959

Bipolar I: 2960, 2961, 2964, 2965, 2966, 2967

Bipolar II: 2968

Personality disorders: 3010, 30120, 30122, 3017, 30183, 30150, 30181, 30182, 3016, 3014, 3019.

Alcohol dependence/abuse: 3030, 3039, 3050, but not 30303, 30393, 30503, which are remission codes

Substance dependence/abuse: 291, 292, 3042, 3040, 3047, 3043, 3041, 3044, 3045, 3046, 3048, 3049, 3056, 3055, 3052, 3053, 3054, 3057, 3058, 3059, but not 30423, 30403, 30473, 30433, 30413, 30443, 30453, 30463, 30483, 30493, 30563, 30553, 30523, 30533, 30543, 30573, 30583, 30593, which are remission codes

Table 1

Demographic characteristics and psychiatric comorbidities of depressed veterans without anxiety diagnosis in the prior year of starting an antidepressant treatment (N = 328,888)

Variable	N	%
Male	300293	91.3
Age group		
<45	57730	17.6
45–64	150542	45.8
>=65	120616	36.6
Race		
White	246013	74.8
Black	42639	13.0
Other	40236	12.2
Hispanic	14143	4.3
Alcohol abuse	35365	10.8
Other substance abuse	21948	6.7
Service connection^a	88438	26.9
Charlson score category		
0	178512	54.3
1	92205	28.0
2	37103	11.3
3	21068	6.4
Major depression	58204	17.7
Medicare usage	101386	30.8
Personality disorder	5186	1.6
Total inpatient psych stays^b		
0	310179	94.3
1	14234	4.3
2	4475	1.4
# of psychotropic medicines		
0	273065	83.0
1	45928	14.0
≥2	9895	3.0

^aService connection indicating some VA-recognized disability stemming from injuries or conditions that occurred or were exacerbated during military service in past 3 years

^bTotal number of inpatient stays for psychiatric disorder in the past 12 months

Table 2

Unadjusted and adjusted hazard ratios and their 95% confidence intervals (CIs) for anxiety development (anxiety indicated by either antianxiety medicine or anxiety diagnosis) (N=328,888)

	Unadjusted		Adjusted	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Antidepressants				
Bupropion	1.09 [*]	(1.02, 1.18)	0.94	(0.87, 1.01)
Citalopram	1.09 ^{**}	(1.04, 1.17)	1.10 [*]	(1.04, 1.16)
Fluoxetine	1.03	(0.97, 1.11)	0.97	(0.90, 1.04)
Mirtazapine	1.54 ^{**}	(1.39, 1.71)	1.42 ^{**}	(1.28, 1.58)
Paroxetine	1.28 ^{**}	(1.20, 1.37)	1.25 ^{**}	(1.17, 1.34)
Venlafaxine	1.30 ^{**}	1	1.16 [*]	1
Sertraline	1		1	
Age				
≥65	1	1	1	1
45–65	1.69 ^{**}	(1.44, 1.81)	1.55 ^{**}	(1.38, 1.72)
<45	2.04 ^{**}	(1.92, 2.13)	1.72 ^{**}	(1.59, 1.85)
Hispanic				
Yes	1	1	1	1
No	0.86 ^{**}	(0.78, 0.94)	0.95	(0.86, 1.04)
Service connection^a				
Yes	1	1	0.95	(0.86, 1.05)
No	0.98	(0.93, 1.02)	1	1
Charlson score				
0	1	1	1	1
1	0.77 ^{**}	(0.73, 0.80)	0.99	(0.95, 1.03)
2	0.72 ^{**}	(0.67, 0.77)	1.11 ^{**}	(1.05, 1.18)
3	0.63 ^{**}	(0.57, 0.69)	1.20 ^{**}	(1.12, 1.29)
Major depression				
No	1	1	1	1
Yes	1.66 ^{**}	(1.59, 1.74)	1.40 ^{**}	(1.33, 1.47)
Medicare				
Yes	1	1	1	1
No	1.58 ^{**}	(1.50, 1.65)	1.11 ^{**}	(1.04, 1.18)
Personality disorder				
No	1	1	1	1
Yes	1.72 ^{**}	(1.51, 1.97)	1.12	(0.98, 1.29)
Total inpatient psych stays^b				
0	1	1	1	1
1	1.71 ^{**}	(1.57, 1.86)	1.29 ^{**}	(1.16, 1.42)
2	1.90 ^{**}	(1.66, 2.18)	1.46 ^{**}	(1.23, 1.73)
Psychiatric disorder days^c				
	1.004 ^{**}	(1.002, 1.005)	1.00	(0.99, 1.00)
# psychotropic medicines in last 12 months				
0	1	1	1	1
1	1.23 ^{**}	(1.17, 1.30)	1.23 ^{**}	(1.16, 1.30)
2	1.31 ^{**}	(1.18, 1.46)	1.27 ^{**}	(1.14, 1.42)
Alcohol abuse				
No	1	1	1	1
Yes	1.43 ^{**}	(1.35, 1.52)	1.09 [*]	(1.02, 1.17)
Any other substance abuse				
No	1	1	1	1
Yes	1.44 ^{**}	(1.34, 1.55)	1.01	(0.92, 1.11)

	Unadjusted		Adjusted	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Gender	1		1	
Male	1.35**	(1.27, 1.45)	1.17**	(1.10, 1.26)
Female				
Race	1		1	
Black	1.33**	(1.21, 1.43)	1.49**	(1.39, 1.59)
White	1.05*	(1.01, 1.08)	1.13**	(1.04, 1.23)
Other				
Fiscal Year	1		1	
1999	0.86*	(0.78, 0.95)	0.88*	(0.79, 0.97)
2000	0.71**	(0.65, 0.79)	0.75**	(0.68, 0.83)
2001	0.71**	(0.65, 0.79)	0.76**	(0.69, 0.83)
2002	0.61**	(0.56, 0.67)	0.66**	(0.60, 0.72)
2003	0.68**	(0.62, 0.75)	0.73**	(0.66, 0.81)
2004				

^a Service connection indicating some VA-recognized disability stemming from injuries or conditions that occurred or were exacerbated during military service in past 3 years

^b Total number of inpatient stays for psychiatric disorder in the past 12 months

^c Total number of days of inpatient stay for psychiatric disorder in the past 12 months

* 0.0001 < p value < 0.05,

** p value < 0.0001