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Comorbid Anxiety as a Suicide Risk Factor Among Depressed Veterans

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Abstract

Background—Depressive disorders greatly increase suicide risk, however little is known about the contribution of comorbid anxiety disorders or anxiety symptoms to the risk of suicide death among depressed patients. We examined whether depressed veterans with comorbid anxiety had higher risks of suicide death.

Methods—Using VA administrative databases we identified 887,859 patients with depression. We then used univariate and multivariate logistic regression, controlling for demographics and substance use disorders, to determine the odds ratios of completed suicide associated with individual comorbid anxiety disorders, the presence of any comorbid anxiety disorder, the prescription of an antianxiety medication, or the prescription of a high dose of an antianxiety medication.

Results—In multivariate analyses, the odds of completed suicide were significantly increased for patients with panic disorder (OR 1.26, 95% CI: 1.04–1.53), generalized anxiety disorder (OR 1.27, 95% CI: 1.09–1.47), and anxiety disorder, not otherwise specified (OR 1.25, 95% CI: 1.12–1.38). The odds of completed suicide were also greater among patients who received any antianxiety medication (OR 1.71, 95% CI: 1.55–1.88), and were further increased among those who received high dose treatment (OR 2.26, 95% CI: 1.98–2.57). Odds of completed suicide were decreased among patients with comorbid posttraumatic stress disorder (OR 0.87, 95% CI: 0.77–0.97), and there was no statistically significant relationship between social phobia, obsessive-compulsive disorder, and all other anxiety disorders and suicide.

Conclusions—These findings emphasize the importance of comorbid anxiety disorders and symptoms in increasing suicide risk among depressed patients and may inform suicide prevention efforts among these patients.

Keywords

Introduction

Between 2 and 8% of depressed patients eventually die from suicide[1,2] which is 2–5 times the rate seen in the general U.S. population[3]. Several risk factors for suicide attempts among

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depressed patients have been identified and include: being unmarried, more severe depression, a co-occurring alcohol use disorder, and a history of prior suicide attempts[4–7]. Whether comorbid anxiety disorders or anxiety symptoms, which may occur in over half of depressed patients[8,9], are independent risk factors for suicidal behaviors has been somewhat controversial, and data on the contribution of comorbid anxiety to actual suicide death has been limited.

In the general population, studies using diagnostic data from the Epidemiologic Catchment Area (ECA) survey, National Comorbidity Survey (NCS), and National Comorbidity Survey-Replication (NSC-R) suggest that several, although not all, anxiety disorders are independent risk factors for suicide attempts. Obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and generalized anxiety disorder (GAD), but not panic disorder, were associated with increased risk for suicide attempts in these studies after controlling for other psychiatric comorbidities, including depression[10–13]. Analysis of the Netherlands Mental Health and Incidence Survey (NEMESIS), however, indicated that the presence of "any anxiety disorder" increased the risk for suicide attempts after controlling for a broad range of psychiatric conditions and increased the risk specifically among those with mood disorders[14].

Many of the studies examining the relationship between anxiety and suicide, both in the general population and in populations of individuals with depression, have assessed suicide attempts rather than mortality[6,7,10–18]. However, studies of suicide attempts may not generalize to suicide mortality as there are important differences between populations that have attempted versus died from suicide, notably with regards to gender and choice of suicide method[16,19,20]. Those who make suicide attempts may be more likely to have an anxiety disorder than those who die by suicide[21], raising the possibility that anxiety may be a stronger risk factor for suicide attempts than for suicide mortality. Panic symptoms and severe anxiety have been associated with suicide death in studies whose subjects included patients with depression as well as other psychiatric illnesses[22,23]. However these prior studies did not address the role of specific anxiety disorders. More work is needed to evaluate the contribution of specific anxiety disorders and anxiety symptoms on risks of suicide mortality in those with depression.

Using Veterans Affairs (VA) administrative and National Death Index (NDI) data, we examined whether depressed patients with comorbid anxiety disorders or treatment for anxiety symptoms had increased risks of suicide. This study builds on the work previously reported by Zivin et al. which examined suicide risk factors among depressed patients within the VA but did not address specific comorbid anxiety disorders (other than posttraumatic stress disorder) and did not address anxiety symptoms prompting treatment, with or without an anxiety disorder diagnosis[24].

Using a comprehensive, large VA database allowed us to address suicide mortality rather than suicide attempts, and also allowed us to use treatment with an antianxiety medication as a marker for anxiety symptoms, separate from disorder status. We used this additional method to address the impact of anxiety symptoms on suicide death as many depressed patients have significant co-occurring anxiety symptoms that do not meet criteria for a disorder and because comorbid anxiety disorders may be underdiagnosed during standard clinical care among depressed patients.

Methods

Subjects

Participant data used in our analyses were obtained from a national database of veterans in depression treatment (NARDEP), which is maintained by the Serious Mental Illness Treatment

and Evaluation Center (SMITREC) located in Ann Arbor, Michigan[25]. The study was conducted in concordance with institutional review board approval at the Veterans Affairs Ann Arbor Health system. To be included in the study, patients had to receive at least two clinical diagnoses of depression or one diagnosis followed by an antidepressant fill during the study period, between April 1, 1999 and September 30, 2004. Depression diagnoses included major depressive disorder, dysthymia, depressive disorder NOS, and bipolar II disorder. Patients with a diagnosis of bipolar I disorder, schizophrenia, or schizoaffective disorder were excluded from the study. As described previously, data on cause of death were obtained from the National Death Index (NDI) for patients in the cohort[24]. The NDI has been shown to be high quality database suitable for research purposes[26]. The study sample included 887,859 patients.

Study Measures

Demographic—The demographic characteristics that were examined include age (18–44, 45–64, ≥65), gender, marital status (married or not), ethnicity (Hispanic or not), and race (white, African-American, other). "Other" race includes patients of Asian, Native Hawaiian, Pacific Islander, or Native American race/ethnicity and patients who are multi-racial.

Clinical diagnosis—Comorbid anxiety disorders were determined from NARDEP treatment and administrative records and included posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), any panic disorder (panic disorder and agoraphobia with panic attacks), social phobia, obsessive compulsive disorder (OCD), anxiety disorder not otherwise specified (NOS), and any other anxiety disorders (all other phobias, hysteria, and "anxiety state, other"). The presence of any substance use disorder (except nicotine dependence) was also obtained from clinical and administrative records.

Prescription medication—Medication use was determined from outpatient VA pharmacy records contained in NARDEP and included a period of 6 months prior to patients' entry into the cohort. Antianxiety agents were defined as all commonly prescribed benzodiazepines (lorazepam, alprazolam, clonazepam, diazepam, temazepam, oxazepam, chlordiazepoxide, and chlorazepate), and buspirone. Antianxiety medications that were prescribed to be taken only at night were excluded as these may have been more likely to have been prescribed for sleep rather than for anxiety symptoms per se. "High dose" for each antianxiety agent was determined as any dose exceeding the 75th percentile dose for that medication within this cohort.

Suicide—Suicide mortality was determined from the cause of death contained in the NDI. A death was identified as a suicide using the International Classification of Diseases, tenth revision, codes X60-X84, Y87.0, and U03[27]. Cause of death data in the NDI is compiled from state-mandated death certificates[26].

Analyses

We used univariate logistic regression analysis to determine the odds of suicide associated with each individual anxiety disorder or with having any anxiety disorder. Logistic regression analyses were also used to determine the risk of suicide among those prescribed any antianxiety agent and among those ever prescribed a high dose of antianxiety medication. We also fit a series of separate multivariate logistic regression models to determine whether each individual anxiety disorder, any anxiety disorder, any antianxiety medication treatment, or high-dose antianxiety medication treatment were significant predictors of suicide after adjusting for age, gender, race, ethnicity, or the presence of any substance use disorder. Finally, in order to control for potential differences in antianxiety medication use among those with different anxiety disorders, we conducted a multivariate logistic regression model which included both the

individual anxiety disorders and receipt of any antianxiety medication, adjusting for demographic variables and substance use. We used STATA 10.0 to perform all analyses[28].

Results

Subjects

A total of 887,859 patients received treatment for depression within the VA during the study period and were eligible for study inclusion. Among these patients, 1,892 suicides occurred during the study period. The demographic characteristics, prevalence of comorbid anxiety disorders, and antianxiety medication use for these patients are reported in Table 1. The study sample was predominantly male (91.9%) and white (76.5%) and had a high prevalence of substance abuse disorders (22.1%).

We found that 41.5% of depressed veterans had a comorbid anxiety disorder diagnosis. PTSD was the most common diagnosis (22.5%) and anxiety disorder NOS was the second most common (20.0%). Panic disorder, GAD, social phobia, OCD, and all other anxiety disorders had prevalence rates of less than 10%. Twenty-four percent of depressed veterans were prescribed daytime doses of antianxiety medication during the study period. Forty-one percent of those with a comorbid anxiety disorder received an antianxiety agent compared to 12% of depressed veterans without a diagnosed anxiety disorder. Rates of antianxiety medication use by comorbid anxiety disorder were: 37% for PTSD, 50% for anxiety disorder NOS, 65% for panic disorder, 58% for GAD, 46% for social phobia, 46% for OCD, and 54% for all other anxiety disorders.

Relationship between comorbid anxiety and completed suicide

In separate unadjusted analyses, the following anxiety disorders were significantly associated with increased odds for suicide: any anxiety disorder (OR 1.13, 95% CI: 1.04–1.24), panic disorder (OR 1.40, 95% CI: 1.15–1.70), generalized anxiety disorder (OR 1.38, 95% CI: 1.19–1.60), and anxiety disorder NOS (OR 1.34, 95% CI: 1.21–1.49). Odds for suicide were higher for patients who ever received an antianxiety medication (OR 1.82, 95% CI: 1.65–2.00), and the odds were even greater among for those ever prescribed high doses of antianxiety medications (OR 2.63, 95% CI: 2.32–2.99) (Table 2).

After adjusting for gender, age, race, ethnicity, marital status, and substance use disorders, having "any anxiety disorder" was no longer significantly associated with increased odds for suicide. Panic disorder (OR 1.26, 95% CI: 1.04–1.53), GAD (OR 1.27, 95% CI: 1.09–1.47), and anxiety disorder NOS (OR 1.25, 95% CI: 1.12–1.38) continued to be significant predictors. PTSD was significantly associated with decreased odds of completed suicide (OR 0.87, 95% CI: 0.77–0.97). Having ever been prescribed an antianxiety medication (OR 1.71, 95% CI: 1.55–1.88) or a high dose antianxiety medication (OR 2.26, 95% CI: 1.98–2.57) also continued to be significant after controlling for other risk factors (Table 2).

A diagnosis of social phobia, obsessive compulsive disorder, or "any other" anxiety disorder was not associated with completed suicide in either unadjusted or adjusted analyses.

When the individual anxiety disorders and prescription of an antianxiety medication were included in the same logistic regression model, prescription of an antianxiety medication remained a significant predictor (OR 1.74, 95% CI: 1.57–1.93), however the only anxiety disorder which remained significant was PTSD (OR 0.79, 95% CI: 0.70–0.88).

Discussion

In a large national sample of U.S. veterans treated for depression we found high rates of diagnosed anxiety disorders and high rates of treatment with daytime doses of antianxiety medications. Fifty-three percent of VA patients in treatment for depression had either a diagnosed anxiety disorder or were prescribed daytime doses of a common antianxiety medication. Similarly high rates of comorbid anxiety with depression have been found in large epidemiologic studies and in other clinical populations of depressed patients, although we found considerably lower rates of social phobia and OCD than reported elsewhere[8,9,29].

We found that several, but not all, concurrent anxiety disorders were associated with increased risk of suicide mortality and we also found that treatment with antianxiety medications, considered separately from disorder status, was also associated with increased suicide mortality.

When anxiety disorders were aggregated and we considered whether "any anxiety disorder" resulted in increased risks of suicide among depressed patients, we found a small but significant OR of 1.13 in unadjusted analyses, however this association was not significant when adjusting for other patient factors. Individual comorbid anxiety disorders that were positively associated with suicide (panic disorder, generalized anxiety disorder, and anxiety disorder, NOS) had ORs of 1.25–1.27 for suicide death. These associations are smaller than the association reported by Sareen et al. who reported an OR of 4.15 (95% CI: 1.34–12.90) for suicide attempts among depressed patients with a comorbid anxiety disorder compared to those without these comorbidities[14]. As noted by Beautris et al, comorbid anxiety in aggregate may be a greater risk factor for suicide attempts than suicide deaths[21]. However, PTSD was also not included in Sareen's study of the relationship between "any anxiety disorders" and suicide attempts, and in our study comorbid PTSD was common and associated with a decreased risk for suicide death.

Among the individual anxiety disorder comorbidities, panic disorder, GAD, and anxiety disorder NOS were all associated with higher risk of suicide death among depressed patients whereas social phobia, obsessive-compulsive disorder, and all other anxiety disorders were not. These findings are generally congruent with the prior literature on these disorders and suicide attempts. Although panic disorder was not associated with an increase in suicide attempts in comorbidity-adjusted analyses of the ECA, NCS, or NCS-R (when both genders were considered together), panic disorder was associated with suicide attempts in the NCS-R among men[10–13]. As men comprised 92% of our population, our finding of a relationship between panic disorder and suicide death is congruent with the latter finding. Panic symptoms may also be a more prominent risk factor for suicide death than attempts in clinical populations[12,13,22].

Our finding of an increased risk for suicide death associated with comorbid generalized anxiety disorder is consistent with prior studies of risk factors for suicide attempts[13]. Social phobia and OCD were not significantly associated with increased suicide mortality in our study, however with less than 10,000 patients having either diagnosis, we had limited power to detect modest differences in suicide risk in these subpopulations. Analyses of the NCS-R also suggest that social phobia is associated with suicide attempts in women but not men, which may explain why there was not a significant association among our sample of mostly men[10].

The decreased risk associated with PTSD in this cohort was previously reported by Zivin et al. and hypothesized to be related to the higher levels of mental health services and income supports provided to patients with depression and PTSD in the VA[24]. PTSD is associated with increased risk for suicide attempts in general population surveys[10,13]. The contribution of PTSD to suicide deaths may vary by age, gender, co-morbid psychiatric conditions, and veteran

status, thereby underlining the need for further study of how PTSD fits into an overall suicide risk assessment.

Interestingly, we found that receipt of an antianxiety medication was a stronger predictor of completed suicide than any individual anxiety disorder diagnosis. When anxiety disorders and a prescription of an antianxiety medication were included in the same multivariate analysis, only antianxiety medication fills were significantly associated with increased suicide risk. This suggests that symptoms leading to prescription of antianxiety medications may be more salient than clinical diagnoses of anxiety disorders in predicting suicide death. The use of antianxiety medications among depressed patients may serve as a marker for more severe or treatment-resistant anxiety as these patients with depression may have received "antidepressant" medications (i.e. selective serotonin reuptake inhibitors) which are also effective for most anxiety disorders. Our finding that prescription of high dose antianxiety medication was associated with even greater odds of suicide mortality further supports the possibility that severity of anxiety symptoms may play a larger role than anxiety diagnosis with regards to suicide risk.

Benzodiazepine use has previously been associated with an increased risk for suicide attempts in a general patient population[30]. Our findings add to this work by showing a similar association for suicide deaths among depressed patients. However, limitations in our data do not allow us to determine whether suicide risks associated with antianxiety medication use are directly related to the anxiety symptoms prompting the prescription or are potentially due to direct effects of medications themselves (e.g. by causing disinhibition). Because we identified patients who filled a prescription for an antianxiety medication at any point during our observation period, patients may have been prescribed an antianxiety medication well before the time of suicide, further limiting our ability to assess a direct medication effect. A literature review conducted by Youssef and Rich sought to determine the evidence for sedative/hypnotics affecting suicide risk and found no conclusive evidence for these agents to either be protective or causative with regards to suicide[31]. Additional research to determine whether suicide risk differs among the individual antianxiety agents, or by patterns of use, may help clarify the relationship between antianxiety medication use and suicide risk. Irrespective of the nature of the relationship between antianxiety medications and suicide, future health services research on markers of suicide risk should consider examining antianxiety medications as part of a comprehensive suicide risk profile.

The generalizability of this study is limited by our sample of U.S. veterans which, in comparison to most depressed populations, is older and predominantly male. The use of clinical administrative data to assess the presence of comorbid anxiety disorders may also under or over identify these disorders. Thus even though 40% of our depressed patients had a comorbid anxiety diagnosis, certain anxiety disorders, such as social phobia, may have been under-diagnosed whereas anxiety disorder NOS may have been over-diagnosed among individuals simply having anxiety symptoms as part of their depressive syndrome[8]. The use of pharmacy data to determine medication use for purposes of ameliorating anxiety symptoms is also limited by the fact that antianxiety medications may be used for purposes other than anxiety (i.e. sleep, seizure disorders, as a muscle relaxant). However, we believe we addressed the most significant of these confounding indications by removing all antianxiety medications prescribed only at night and likely intended for sleep. The administrative dataset used for this study also does not contain reliable information regarding specific symptoms or levels of distress or impairment, unfortunately limiting our ability to explore what may underlie differences between the individual comorbid anxiety disorders.

In summary, among depressed veterans we found that comorbid panic disorder, generalized anxiety disorder, and anxiety disorder NOS were associated with increased odds of suicide

deaths, whereas PTSD and other anxiety disorders were not. Prescription of an antianxiety medication was a stronger predictor of completed suicide than any anxiety disorder diagnosis. These findings confirm the importance of some, but not all, anxiety disorders and the likely importance of anxiety symptoms warranting medical treatment, separate from disorder status, as risk factors for suicide death among the depressed patient population.

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Table 1

Characteristics of Depressed Veterans including Anxiety Disorders and Treatment (N = 887, 859)

Variable	N	%
Male	815,917	91.9
Age:		
18–44	142931	16.1
45–64	445108	50.1
>=65	299820	33.8
Race:		
White	678,829	76.5
African-American	110,125	12.4
Other	98,905	11.1
Married	482,312	54.3
Hispanic	41,457	4.7
Any Substance Abuse Disorder	196,345	22.1
Any Anxiety Disorder	368,709	41.5
PTSD	199,486	22.5
Anxiety Disorder, NOS	177,142	20.0
Panic disorder	37,567	4.2
GAD	68,470	7.7
Social Phobia	4,772	0.5
OCD	8,869	1.0
Any Other Anxiety Disorder	40,020	4.5
Ever Prescribed Antianxiety Medication	216,351	24.4
High Dose Antianxiety Medication	57,051	6.4

OCD= Obsessive-compulsive disorder, PTSD = Posttraumatic stress disorder, GAD = Generalized anxiety disorder, NOS = not otherwise specified

Table 2

Predictors of Completed Suicide Among Depressed Veterans (N = 887,859)

	Unadjusted		Adjusted[†]	
Variable	Odds Ratio	95% CI	Odds Ratio	95% CI
Any Anxiety Disorder	1.13[*]	1.04–1.24	1.07	0.98–1.18
PTSD	0.90	.80–1.00	0.87[*]	0.77–.97
Anxiety Disorder, NOS	1.34[**]	1.21–1.49	1.25[**]	1.12–1.38
Panic disorder	1.40[*]	1.15–1.70	1.26[*]	1.04–1.53
GAD	1.38[*]	1.19–1.60	1.27[*]	1.09–1.47
Social Phobia	0.79	.39–.57	0.59	0.29–1.18
OCD	1.22	.81–1.84	1.10	0.73–1.67
Any Other Anxiety Disorder	1.11	.90–1.36	1.05	0.85–1.29
Ever Prescribed Antianxiety Medication	1.82[**]	1.65–2.00	1.71[**]	1.55–1.88
High Dose Antianxiety Medication	2.63[**]	2.32–2.99	2.26[**]	1.98–2.57

[†]Separate logistic regressions adjusting for gender, age, race, ethnicity, marital status, and presence of a substance use disorder

[*]$p < .05$,

[**]$p < .001$

OCD= Obsessive-compulsive disorder, PTSD = Posttraumatic stress disorder, GAD = Generalized anxiety disorder, NOS = not otherwise specified