Predictors of Persistence of Comorbid Generalized Anxiety Disorder Among Veterans With Major Depressive Disorder

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ABSTRACT

Objective: A limited number of randomized clinical trials show that efficacious pharmacologic treatments exist for comorbid major depressive disorder (MDD) and generalized anxiety disorder (GAD). The aims of this effectiveness study were to describe the impact of a depression care management intervention on the persistence of comorbid GAD symptoms in a sample of primary care patients with MDD and to identify risk factors for persistent GAD.

Method: Data were collected from April 2003 to September 2005 for the Telemedicine-Enhanced Antidepressant Management (TEAM) study, a multisite, randomized effectiveness trial targeting US Department of Veterans Affairs (VA) primary care patients with depression. Veterans aged 26.59–88.36 years received either the TEAM intervention or usual care in small VA community-based outpatient clinics. The TEAM care management intervention focused on optimizing antidepressant therapy through patient education and activation, symptom monitoring, adherence promotion, and side-effect management. Veterans who screened positive for MDD using the Patient Health Questionnaire-9 (based on *DSM-IV* criteria) and who met the Mini-International Neuropsychiatric Interview criteria (maintaining consistency with *DSM-IV-TR*) for comorbid GAD at baseline were selected for the present study (N = 168). The primary outcome was persistence of GAD at 6 months and 12 months. All predictors available in the TEAM study data that were described in the literature to be associated with influencing GAD outcomes were examined.

Results: Persistence of depression was the strongest predictor of persistence of comorbid GAD at both 6 months (OR = 5.75; 95% CI, 2.38–13.86; $P < .05$) and 12 months (OR = 15.56; 95% CI, 6.10–39.68; $P < .05$). Although the TEAM intervention significantly reduced depression symptom severity, it was not significantly associated with GAD persistence. Insomnia was a significant protective factor for persistence of GAD at 6 months (OR = 0.66; 95% CI, 0.44–0.99; $P < .05$).

Conclusions: Early screening for presence of comorbid GAD among those with MDD may be valuable both for further research and for enhancing clinical management of GAD and MDD comorbidity.

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Epidemiologic studies find high rates of comorbidity between generalized anxiety disorder (GAD) and major depressive disorder (MDD).[1–3] Rates of comorbid GAD among patients with a principal diagnosis of MDD range from 20%–45%.[4–6] Compared to each disorder alone, depression-anxiety comorbidity is associated with poorer prognosis,[7,8] greater persistence and severity of illness,[9,10] lower rates of treatment response,[11–13] higher suicide risk,[14,15] greater risk of major cardiac events,[16] greater functional disability,[11,17,18] and lower quality of life.[19]

Although several drug classes have proven efficacious for GAD, antidepressant medications are more effective than other agents for GAD with comorbid MDD.[20] In a review of efficacy trials with antidepressants for GAD alone, Kapczinski et al[21] calculated the number needed to treat for antidepressants in GAD alone to be 5.15. However, the limited number of clinical trials among patients with comorbid depression and anxiety indicates that these patients are more treatment-resistant and more likely to drop out of treatment.[11,22] While data exist on effectiveness of benzodiazepines, tricyclic agents, azapirones, selective serotonin reuptake inhibitors, and psychosocial therapies for comorbid anxiety and depression,[23–25] a large number of patients with GAD continue to experience persistent and disabling symptoms of depression and anxiety.[26]

It remains difficult to predict reliably which patients with comorbid GAD will respond to treatment.[27] Although some data exist on predictors of persistent anxiety symptoms among patients with GAD alone,[28] there is a paucity of data on clinical correlates of persistence of GAD among patients with MDD who are treated with antidepressants. In the largest pooled analysis of efficacy study data (N = 1,839), several pretreatment factors were associated with treatment response in patients with GAD without MDD who received venlafaxine extended release (XR) or placebo. At 24 weeks, significant baseline predictors of poor treatment response with venlafaxine XR included restlessness, irritability, previous use of benzodiazepines and other anxiolytic medications, easy fatigability, male gender, and longer duration of current GAD episode.[29] Interestingly, pretreatment sleep disturbance was a significant predictor of better treatment response with venlafaxine XR at 24 weeks. History of panic disorder, substance abuse, and minor depressive symptoms and severity of baseline GAD symptoms were not significant predictors of treatment response at 24 weeks.[29]

Other studies[28,30] among patients with comorbid MDD and GAD in a primary care setting reported that GAD severity, duration of illness, lower education, less social support, substance abuse, panic, and history of abuse in childhood predicted persistence of GAD.[28,30] Favorable GAD outcomes have been associated with shorter duration of illness (GAD), presence of dysthymia,[31] and later onset of anxiety symptoms.[32] Functional imaging studies[33] reveal that patients with higher pretreatment amygdala activity may be particularly likely to respond well to such widely used treatments as selective serotonin reuptake inhibitor medications and cognitive-behavioral therapy.[33]

The purpose of this study was 2-fold. The first was to assess the effectiveness of the Telemedicine-Enhanced Antidepressant Management (TEAM) intervention (designed to optimize antidepressant management)

in improving persistence of comorbid GAD symptoms among primary care patients with MDD. The primary outcome measure for the present study was meeting diagnostic criteria for GAD at 6 and 12 months. Our second goal was to identify the potential risk factors for persistent GAD in this sample of primary care patients with MDD. We examined all predictors available in the TEAM study data that were described in the literature to be associated with influencing GAD outcomes. Specifically, we hypothesized that greater severity of MDD, less social support, substance use, absence of insomnia, fatigue, restlessness, and lower education level would be associated with greater persistence of comorbid GAD.

METHOD

Study Setting and Enrollment Procedures

Details about the TEAM intervention and evaluation methods are described in a previous article.[34] Briefly, the study was conducted from April 2003 to September 2005 in small US Department of Veterans Affairs (VA) community-based outpatient clinics, which are satellite facilities of "parent" VA medical centers that often lack on-site psychiatrists. Veterans with upcoming appointments were screened for depression using the Patient Health Questionnaire-9 (PHQ-9)[35] (based on *DSM-IV* criteria). We used a PHQ-9 cut-off score of ≥ 12 for a diagnosis of depression for inclusion in the study.[36] Exclusion criteria included a diagnosis of schizophrenia, current suicidal ideation, recent bereavement, pregnancy, having a court-appointed guardian, substance dependence, bipolar disorder, cognitive impairment, or receiving specialty mental health treatment. Using Veterans Health Information Systems and Technology Architecture (VistA) data, we excluded those who were seen in a specialty mental health clinic in the past 6 months or who had a future specialty mental health clinic appointment because inclusion of those receiving care in specialty mental health would have reduced the effectiveness of the intervention. Among eligible patients, 91.3% agreed to participate and were administered the baseline interview, and 91.9% attended their appointment and provided written informed consent (N = 395). The study sample had an age range of 26.59–88.36 years. Follow-up interviews were completed for 91.1% (N = 360) of the study participants at 6 months and 84.8% (N = 335) at 12 months. A subsample of those veterans who met the PHQ-9 criteria for MDD and the Mini-International Neuropsychiatric Interview (MINI) criteria for comorbid GAD at baseline was selected for the present study (N = 168). For the MINI questions about GAD, participants were instructed to consider a 6-month period while responding to the questions.

TEAM Intervention

Provider education (via interactive video and Web site) and patient education (via mail and Web site) were provided to both intervention and usual-care sites. Depression screening results were entered into the electronic medical record at both intervention and usual-care sites.

Patients who were randomized to the intervention received a stepped-care model of depression treatment for up to 12 months. Treatment intensity was increased for patients failing to respond to lower levels of care by involving a greater number of intervention personnel with increasing mental health expertise. The intervention involved 5 types of providers: (1) primary care providers located at VA community-based outpatient clinics, (2) consult telepsychiatrists located at parent VA medical centers, (3) an off-site depression nurse–care manager (RN), (4) an off-site clinical pharmacist (PharmD), and (5) an off-site supervising psychiatrist. The consult telepsychiatrist accepted consultations or referrals from primary care providers. The supervising psychiatrist provided clinical supervision to the care manager and clinical pharmacist via weekly face-to-face meetings.

The off-site intervention team focused on optimizing pharmacotherapy. Nurse–care manager telephone encounters with patients included monitoring of symptoms, medication adherence, and side effects. During the initial care management encounter, patients were (1) administered the PHQ-9 symptom monitoring tool, (2) educated and activated using a semistructured script,[37] and (3) assessed for treatment barriers using semistructured scripts for endorsed barriers.[37] Follow-up encounters to monitor symptoms, medication adherence, and side effects were scheduled every 2 weeks during acute treatment and every 4 weeks during watchful waiting or continuation treatment. The nurse–care manager also followed scripts to address specific reasons for nonadherence (eg, concern about addiction) and specific side effects.[38] Pharmacist telephone encounters with patients not responding to treatment included review of medication histories and ongoing side-effect management. A psychiatrist supervised the off-site team and provided consultations via interactive video.

Patients and providers could choose either watchful waiting or antidepressant treatment (step 1). If the patient did not respond to the initial antidepressant, the pharmacist conducted a medication history and provided pharmacotherapy recommendations to the primary care provider via an electronic progress note (step 2). The pharmacist also provided nonscripted medication management over the phone to patients experiencing severe side effects or problems with nonadherence. If the patient did not respond to 2 antidepressants trials, the protocol was to recommend a telepsychiatry consultation followed by additional treatment recommendations to the primary care provider (step 3).

Measures

Dependent variable. Among the 168 patients with MDD who also met the MINI criteria for GAD at baseline, we measured persistence of GAD at 6-month and 12-month time points. To maintain consistency with *DSM-IV-TR*, we defined the veterans as having persistent GAD if they met MINI criteria 1 and 2 for GAD and endorsed 3 of the 6 items for criterion 3. At each time point while administering the MINI, we asked the patients to respond to questions about GAD symptoms as pertaining to the last 6 months.

Independent variables. At baseline, demographic characteristics and depression history were measured using the Depression Outcomes Module.[39,40] Psychiatric comorbidity including GAD was measured using the MINI.[41,42] Health status was measured by the physical health and mental health component scores of the Veterans Short Form-12 Health Survey.[43,44] Social support was measured using the Duke Social Support and Stress Scale.[45–47] Depression severity was measured using the PHQ-9.[35] We used items from the Hopkins Symptom Checklist[48,49] to assess insomnia, fatigue, and restlessness. Veterans were identified as having persistent depression if they met 5 of the 9 MDD symptoms on the MINI during the previous 2-week period.

Statistical Analysis

Patients were the unit of the intent-to-treat analysis. Independent variables with missing values were imputed using multiple imputation. Sampling and attrition weights were calculated from administrative and baseline data, respectively, to adjust for the potential bias associated with nonparticipation and/or loss to follow-up. To estimate the effectiveness of the TEAM intervention on persistence of GAD symptoms among primary care patients with MDD, we performed logistic regression analyses with GAD persistence as the dependent variable. To find predictors of GAD persistence, we used our hypothesized predictor variables in logistic regressions with persistence of GAD specified as the dependent variable both at 6 and 12 months. In a second logistic regression analysis, we included persistence of depression at 6 and 12 months as a predictor variable with GAD persistence as the dependent variable at both time points. The study was approved by the Research and Development Committees of the Central Arkansas Veterans Healthcare System, Little Rock, Arkansas; the Overton Brooks VA Medical Center, Shreveport, Louisiana; and the G. V. (Sonny) Montgomery VA Medical Center, Jackson, Mississippi—and affiliated Institutional Review Boards at the University of Arkansas for Medical Sciences, Little Rock, and the University of Louisiana Health Sciences Center, Shreveport. All participants were informed of the risks and benefits of their participation in the study, and they signed written informed consent.

RESULTS

Socioeconomic and clinical characteristics of the sample are presented in Table 1. The substantial disease burden in this sample of middle-aged and elderly men is highlighted by their physical health status, which was 2 standard deviations below the US mean.[50] Of particular note is the extremely high number of physical comorbidities (a mean of 5.6 self-reported illnesses), eg, arthritis (72%), hypertension (61%), diabetes (33%), heart disease (31%), lung disease (18%), cancer (13%), and stroke (10%).

The mean number of prior depressive episodes was 3.8. Most patients (67%) had received prior depression treatment, and 44% were receiving depression treatment at the time of study entry.

Table 1. Baseline Sociodemographic and Clinical Characteristics

Characteristic	Overall, N = 395	GAD Plus MDD, n = 168
Sociodemographic		
Age, mean (SD), y	59.2 (12.2)	56.1 (11.3)
Sex, male, %	91.7	88.1
Race, %		
White	74.7	73.2
Black	18.2	21.4
Native American	3.0	2.4
Other	3.6	2.9
Annual household income < $20,000, %	51.7	54.3
Married, %	62.3	57.1
High school graduate, yes, %	76.0	76.8
Employed, %	21.9	26.5
Social support (0–1 continuous scale), mean (SD)	0.4 (0.2)	0.4 (0.2)
Clinical		
Patient Health Questionnaire-9 (depression screen score), mean (SD)	16.4 (3.4)	17.1 (3.5)
Physical component score of the Short Form-12, mean (SD)	30.0 (13.0)	30.2 (12.4)
Mental component score of the Short Form-12, mean (SD)	36.5 (12.3)	32.6 (9.7)
Chronic physical illnesses, mean (SD), no.	5.5 (2.8)	5.6 (2.8)
Family history of depression, %	45.2	48.2
Number of prior depression episodes, mean (SD)	3.7 (1.8)	3.8 (1.7)
Prior depression treatment, %	65.7	67.3
Current depression treatment, %	40.9	42.2
Current at-risk drinking, %	12.9	14.3
Diagnosis of posttraumatic stress disorder, %	23.8	29.8

Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder.

The TEAM intervention significantly reduced depression (50% decline in depression score from baseline) at 6 months as previously reported,[34] but it was not significantly associated with GAD persistence at either 6-month (OR = 0.74; 95% CI, 0.35–1.56; $P = .43$) or 12-month follow-up (OR = 0.59; 95% CI, 0.29–1.20; $P = .15$). For this reason, all subsequent analyses combined patients in both conditions (usual care and intervention). At 6 months, 69.7% of veterans were receiving antidepressant medications, compared to 79.6% at 12 months.

In the first multivariate logistic regression (model 1), we included only the variables we hypothesized to be associated with GAD persistence. We found that having a high school education at baseline was significantly associated with greater persistence of GAD at 6 months (Table 2). The direction of the association between high school education and GAD persistence was the opposite of what we hypothesized. As hypothesized, we found that presence of insomnia decreased the odds of GAD persistence (Table 2). None of the hypothesized variables predicted GAD persistence at 12 months (Table 3).

In a second multivariate logistic regression (model 2), we included the persistence of MDD at 6 and 12 months as an independent variable along with the other variables included in the first model. Veterans were identified as having persistent depression if they met 5 of the 9 MDD symptoms on the MINI. We found that persistence of MDD was significantly

Table 2. Variables Associated With Persistence of Generalized Anxiety Disorder at 6 Months as Diagnosed by the Mini-International Neuropsychiatric Interview

Variable	Model 1, Odds Ratio (95% CI)	Model 2, Odds Ratio (95% CI)
Education, high school graduate	2.36 (1.04–5.33)*	2.50 (1.06–5.93)*
Patient Health Questionnaire-9, depression severity score	1.03 (0.93–1.14)	1.04 (0.90–1.12)
Social support (0–1 continuous scale)	0.56 (0.10–3.01)	0.40 (0.07–2.50)
Hopkins Symptom Checklist-restlessness	1.19 (0.90–1.57)	1.23 (0.91–1.66)
Hopkins Symptom Checklist-fatigue	1.19 (0.80–1.75)	1.18 (0.78–1.79)
Hopkins Symptom Checklist-insomnia	0.66 (0.44–0.99)*	0.68 (0.35–0.85)*
Current at-risk drinking	0.81 (0.30–2.15)	0.81 (0.28–2.37)
Persistent major depressive disorder	…	5.75 (2.38–13.86)*

*$P < .05$.
Symbol: … = not included in model.

Table 3. Variables Associated With Persistence of Generalized Anxiety Disorder at 12 Months as Diagnosed by the Mini-International Neuropsychiatric Interview

Variable	Model 1, Odds Ratio (95% CI)	Model 2, Odds Ratio (95% CI)
Education, high school graduate	1.56 (0.67–3.63)	1.57 (0.57–4.30)
Patient Health Questionnaire-9, depression severity score	1.07 (0.97–1.20)	1.06 (0.94–1.21)
Social support (0–1 continuous scale)	0.99 (0.16–6.03)	1.78 (0.20–15.70)
Hopkins Symptom Checklist-restlessness	0.99 (0.74–1.33)	0.93 (0.65–1.32)
Hopkins Symptom Checklist-fatigue	1.35 (0.90–2.02)	1.19 (0.74–1.92)
Hopkins Symptom Checklist-insomnia	0.98 (0.67–1.43)	0.95 (0.59–1.52)
Current at-risk drinking	2.02 (0.64–6.36)	3.30 (0.82–13.17)
Persistent major depressive disorder	…	15.56 (6.10–39.68)*

*$P < .05$.
Symbol: … = not included in model.

associated with persistence of GAD at 6 months along with a high school education and absence of insomnia (Table 2). Persistence of MDD was the only significant predictor of GAD persistence at 12 months (Table 3).

Since many veterans with posttraumatic stress disorder can have GAD-like symptoms without having GAD, we performed a sensitivity analysis by including only veterans without posttraumatic stress disorder (n = 105). On repeating the first multivariate analysis, we found that, at 6 months, having a high school education (OR = 3.20; 95% CI, 1.12–9.27) and persistence of depression (OR = 5.09; 95% CI, 1.82–14.27) remained significantly associated with persistence of GAD; the magnitude of association remained similar. However, having insomnia did not remain statistically significant (OR = 0.70; 95% CI, 0.44–1.15) due to lack of power. At 12 months, similar to the main analyses (N = 168), none of the variables were significantly associated with persistence of GAD in model 1, and only persistence of MDD was a significant predictor of persistence of GAD in model 2, although the strength of association decreased somewhat (OR = 8.28; 95% CI, 2.90–23.57). Additionally, to examine intensity of treatment with antidepressant medications in our sample, we did a chart review among patients who filled a prescription for an antidepressant at any time during the 12-month follow-up period (n = 103). We found that 53.6% of the antidepressant prescriptions were for a minimally adequate dosage for GAD (greater than midrange of the recommended dose range for the prescribed antidepressant).

DISCUSSION

The primary finding of our investigation is that a primary care intervention designed to optimize antidepressant treatment for MDD did not improve GAD outcomes. Insomnia has been found to be a good prognostic indicator in the literature,[29,48] and this finding was replicated in this sample of predominantly male veterans. Insomnia was significantly associated with lower odds of having persistence of GAD at 6 months. Insomnia remained a significant predictor at 6 months even when persistent MDD was added as an independent variable to the model. Contrary to our hypothesis and the finding in the literature[28] that lower education is a poor prognostic factor for GAD outcomes, we identified having a high school education (or more) as a predictor of persistence of GAD at 6 months. At the 12-month time point, neither high school education nor insomnia predicted persistence of GAD.

When persistence of MDD was added as a predictor variable, it was highly predictive of persistence of GAD. The finding that the persistence of MDD at 6 and 12 months was a significant predictor of GAD persistence at both 6 months and 12 months suggests that if MDD symptoms improve, the GAD symptoms may respond as well. These data support the clinical practice to target depressive symptoms aggressively when MDD is comorbid with GAD and suggests that persistence of depression may be considered a target for interventions to improve GAD outcomes. Our results are also consistent with the results of a study by Anton et al,[8] which reported that poor outcomes of anxiety disorders result from comorbidity with MDD. However, the finding in our study that persistence of MDD predicts persistence of GAD contradicts 1 previous study[51] that found that response to anxiety symptoms was independent of response to depression symptoms. Our finding that persistence of MDD predicted persistence of GAD is consistent with the findings from genetic and twin studies[52,53] that support the notion that GAD and MDD are influenced by the same genetic factors but that expression of either disorder is the result of mostly environmental determinants.

The relationship between persistence of depression and GAD is important given the fact that the current *DSM-IV* criteria state that GAD may not occur exclusively during the course of a mood disorder. However, data from Zimmerman and Chelminski[54] showed that the 2 groups of

patients—(1) patients with MDD and comorbid GAD according to *DSM-IV* criteria and (2) patients with MDD with all GAD criteria except mood disorder exclusion—did not differ in their clinical characteristics from those with MDD alone. This finding suggests that the exclusion of GAD in the presence of mood disorder may not be valid. This finding also highlights the fact that comorbidity is largely the product of a nosologic system that classifies the mental disorders categorically, presupposing discrete diagnostic entities. Additionally, the *DSM-IV-TR* appendix also has a category for mixed subsyndromal anxiety and depressive disorder for further study of this comorbidity.[55] Regardless of how co-occurring symptom complexes are described, clinicians and researchers alike must continue to grapple with the challenges involved in assessing and treating patients with complex combinations of symptoms. Additionally, GAD and depression comorbidity has important treatment implications in that benzodiazepines may be less useful than antidepressants as the severity of comorbid depressive symptoms increases.[56]

The results reported here are limited in important ways. First, our outcome measure for GAD persistence was a categorical variable and therefore not as sensitive as a continuous symptom severity variable. Second, patients were predominantly male veterans with a high physical and mental health disease burden. Although this population is important because they constitute the majority of veterans receiving care at the VA, generalizability of results to other demographic groups may be limited. Third, we were able to test only a limited number of potential predictors because the data were primarily collected to assess outcomes of MDD and not GAD. Last, since the current *DSM-IV-TR* criteria call for presence of symptoms of GAD that do not occur exclusively during a mood episode, a MINI diagnosis of GAD does not confirm whether the GAD symptoms relate to MDD or represent a true diagnosis of GAD. Further diagnostic clarification regarding presence of MDD and GAD would require a structured clinical interview for GAD diagnosis. However, other investigators[57] have found differences in clinical response between patients with MDD alone and patients with MDD in conjunction with GAD symptoms. We therefore feel that examining the impact of MDD treatment on GAD symptoms is of interest.

Despite these limitations, our findings have several important clinical implications. First, awareness of the fact that persistence of MDD predicts persistent GAD in primary care settings may facilitate referral to specialty care settings where a broader array of interventions, including nonpharmacologic treatments, are available. Some data exist on effectiveness of benzodiazepines, tricyclic agents, azapirones, and selective serotonin reuptake inhibitors for comorbid anxiety and depression.[23–25] More research is clearly needed about strategies for treating persistent GAD among those with MDD. Most pharmacologic strategies are based on a limited number of controlled trials[58] and some small and open trials.[59] While some reviews[60] suggest that dose increase is an efficient strategy in the management of persistence of anxiety symptoms, American Psychiatric Association guidelines[61] recommend starting antidepressants at a lower dose to reduce an increase in antidepressant-induced anxiety symptoms and titrating to a relatively higher dose for patients with MDD who have comorbid anxiety symptoms.[61,62] Psychological treatments are underutilized despite evidence that cognitive distortions are core features of GAD and that psychosocial factors may be associated with persistence.[20]

On the basis of our findings that pharmacotherapy-focused interventions targeting depression did not reduce GAD persistence and the evidence from the literature about limited response to currently available management strategies for treating comorbid GAD, we would argue for screening for GAD among patients with MDD for the following reasons: (1) to estimate accurate prevalence of comorbid GAD in the presence of MDD given the fact that current *DSM-IV-TR* criteria state that GAD may not occur exclusively during the course of a mood disorder; (2) to begin to evaluate in a naturalistic manner the potential predictors of comorbid GAD outcomes and develop interventions targeted toward mutable factors; and (3) to know at the outset that, in the presence of GAD, the overall outcome is likely to be worse and to take steps such as more frequent visits, self-management, and earlier referral for specialty care.

Drug names: venlafaxine (Effexor and others).

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