Effects of Medical Comorbidity on Anxiety Treatment Outcomes in Primary Care

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Objective: To evaluate the effects of medical comorbidity on anxiety treatment outcomes. **Methods:** Data were analyzed from 1004 primary care patients enrolled in a trial of a collaborative care intervention for anxiety. Linear-mixed models accounting for baseline characteristics were used to evaluate the effects of overall medical comorbidity (two or more chronic medical conditions [CMCs] versus fewer than two CMCs) and specific CMCs (migraine, asthma, and gastrointestinal disease) on anxiety treatment outcomes at 6, 12, and 18 months. **Results:** At baseline, patients with two or more CMCs (n = 582; 58.0%) reported more severe anxiety symptoms (10.5 [95% confidence interval {CI} = 10.1–10.9] versus 9.5 [95% CI = 9.0–10.0], p = .003) and anxiety-related disability (17.6 [95% CI = 17.0–18.2] versus 16.0 [95% CI = 15.3–16.7], p = .001). However, their clinical improvement was comparable to that of patients with one or zero CMCs (predicted change in anxiety symptoms = −3.9 versus −4.1 at 6 months, −4.6 versus −4.4 at 12 months, −4.9 versus −5.0 at 18 months; predicted change in anxiety-related disability = −6.4 versus −6.9 at 6 months, −6.9 versus −7.3 at 12 months, −7.3 versus −7.5 at 18 months). The only specific CMC with a detrimental effect was migraine, which was associated with less improvement in anxiety symptoms at 18 months (predicted change = −4.1 versus −5.3). **Conclusions:** Effectiveness of the anxiety intervention was not significantly affected by the presence of multiple CMCs; however, patients with migraine displayed less improvement at long-term follow-up. **Trial Registration**: ClinicalTrials.com Identifier: NCT00347269 **Key words:** anxiety, medical illness, asthma, migraine, primary care, randomized controlled trial.

BSI-A = Brief Symptom Inventory; **CALM** = Coordinated Anxiety Learning and Management; **CBT** = cognitivebehavioral therapy; **CI** = confidence interval; **CMC** = chronic medical condition; **GAD** = generalized anxiety disorder; **IQR** = interquartile range; **MDD** = major depressive disorder; **MINI** = Mini International Neuropsychiatric Interview; **PD** = panic disorder; **PTSD** = posttraumatic stress disorder; **RCT** = randomized controlled trial; **SADD** = social anxiety disorder; **SDS** = Sheehan Disability Scale; **UC** = usual care.

INTRODUCTION

Anxiety disorders are strongly associated with many chronic medical conditions (CMCs (1–4)). Increased prevalence of anxiety disorders is observed in patients with a diverse array of CMCs, including cardiovascular disease (1,2), gastrointestinal disease (1,5), respiratory disease (1,6,7), migraine (1,8), chronic pain (1,9,10), and cancer (11). Many of these associations remain significant after controlling for multiple potential confounds (e.g., demographic variables, co-occurring mental disorders (1,2)). Overall degree of medical comorbidity demonstrates a "dose-response" relationship to prevalence of anxiety disorders, with odds of meeting criteria for an anxiety disorder increasing in a linear fashion as the number of CMCs increases (1,12).

Patients with anxiety disorders also display higher frequencies of certain CMCs than are observed in the general population (e.g., irritable bowel syndrome (13,14), asthma (7)) and report lower levels of health-related quality of life (15,16). Perhaps of greatest clinical significance, anxiety disorders have been shown to independently contribute to worse medical symptom severity and functional impairment in some CMCs (e.g., asthma (17), cardiovascular disease (18), diabetes (19)) and to increase risk for incidence or disease progression in others (e.g., cardiovascular disease (20,21)).

Medical comorbidity complicates assessment and, at times, may lead to underrecognition of anxiety disorders (22). Overlap between symptoms of anxiety disorders and CMCs can present a diagnostic challenge, even for clinicians specialized in anxiety assessment. Many of these challenging differential diagnoses involve panic disorder (PD), which is characterized by numerous somatic symptoms that could be attributable to medical illnesses (e.g., shortness of breath and dizziness). However, other anxiety disorders are also partly defined by symptoms that can also result from CMCs (e.g., hyperarousal associated with posttraumatic stress disorder [PTSD] and fatigue associated with generalized anxiety disorder [GAD]). Treatments for certain CMCs (e.g., oral corticosteroids) also can produce symptoms that mimic anxiety disorders (e.g., restlessness).

Medical comorbidity is also thought to complicate *treatment* of anxiety disorders (4,23). However, very few empirical investigations have quantified the impact of medical comorbidity on anxiety treatment outcomes. One exception is an analysis of outcomes from a randomized controlled trial (RCT) of a collaborative care intervention for PD in primary care (24). In that study, more medically ill patients had more severe anxiety at baseline but displayed reductions in anxiety, depression, and disability that were comparable to the reductions observed in the less medically ill group. The investigators concluded that the empirically supported treatments for PD used in the study

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Received for publication September 20, 2012; revision received May 13, 2013.
DOI: 10.1097/PSY.0b013e31829def54

0033-3174/13/7508–0713

TABLE 1. Baseline Patient Characteristics[a,b]

	All (n = 1004)	0 or 1 Chronic Medical Conditions (n = 422)	2+ Chronic Medical Conditions (n = 582)	p
Age, M (SD), y	43.5 (13.4)	37.7 (11.7)	47.7 (13.1)	<.001
Sex, % women	71.1 (714)	69.2 (292)	72.5 (422)	.252
Education				.033
<High school	5.5 (55)	3.6 (15)	6.9 (40)	
12 y	16.5 (165)	15.0 (63)	17.6 (102)	
>12 y	78.0 (782)	81.5 (343)	75.6 (439)	
Ethnicity				.048
Hispanic	19.5 (196)	22.0 (93)	17.7 (103)	
African American	11.6 (116)	8.8 (37)	13.6 (79)	
White	56.6 (568)	57.8 (244)	55.7 (324)	
Other	12.4 (124)	11.4 (48)	13.1 (76)	
Diagnoses[c]				
Panic disorder	47.3 (475)	48.6 (205)	46.4 (270)	.493
Generalized anxiety	75.3 (756)	73.2 (309)	76.8 (447)	.194
Social phobia	40.3 (405)	41.7 (176)	39.4 (229)	.452
Posttraumatic stress	18.0 (181)	12.8 (54)	21.8 (127)	<.001
Major depression	64.5 (648)	57.4 (242)	69.8 (406)	<.001
Type of health insurance[c]				
Medicaid	10.1 (101)	5.0 (21)	13.8 (80)	<.001
Medicare	12.4 (124)	3.6 (15)	18.7 (109)	<.001
Other government insurance[d]	3.5 (35)	3.8 (16)	3.3 (19)	.643
Private insurance	74.8 (749)	78.1 (328)	72.3 (421)	.039
No insurance	14.1 (141)	16.4 (69)	12.4 (72)	.069
Any opiate use	8.6 (86)	1.9 (8)	13.4 (78)	<.001
Any pain	43.9 (441)	26.3 (111)	56.7 (330)	<.001
Proportion assigned to CALM	50.1 (503)	51.7 (218)	49.0 (285)	.400
Baseline BSI-A, M (SD)	10.1 (5.2)	9.5 (5.1)	10.5 (5.3)	.003
Baseline SDS, M (SD)	17.0 (7.3)	16.0 (7.3)	17.6 (7.1)	.001

M = mean; SD = standard deviation; CALM = Coordinated Anxiety Learning and Management; BSI-A = Brief Symptom Inventory–Anxiety subscale (possible score range = 0–24); SDS = Sheehan Disability Scale (modified to capture anxiety-related disability; possible score range = 0–30).

[a] Data are reported as % (n) unless otherwise indicated.

[b] Baseline characteristics for patients with zero or one versus two or more chronic medical conditions were compared using t tests and χ^2 tests for continuous and categorical variables, respectively.

[c] Because patients could have more than one, n values may total more than 1004.

[d] Includes Veterans Administration benefits, TRICARE, county programs, or other government insurance.

(cognitive-behavioral therapy [CBT] and pharmacotherapy) worked equally well regardless of medical comorbidity.

The current study builds on the investigation of Roy-Byrne et al. (24) by evaluating the effects of medical comorbidity on outcomes from a large (n = 1004) RCT of the Coordinated Anxiety Learning and Management (CALM) intervention for a broad range of anxiety disorders (GAD, PD, PTSD, and social anxiety disorder [SAD]) in primary care (25). The CALM intervention was shown to be superior to usual care (UC) in reducing anxiety symptoms and anxiety-related disability during 18 months of follow-up (25,26). However, it is unknown whether co-occurring medical illness influenced treatment outcomes. The principal aim of the current study was to assess the effects of medical comorbidity on anxiety symptoms and anxiety-related disability measured during the 18-month study period. On the basis of prior results (24), we predicted that greater medical comorbidity would be associated with more severe anxiety symptoms and anxiety-related disability at baseline, but not with degree of improvement in symptoms and disability during the study follow-up period.

The secondary aim of this study was to explore whether distinct CMCs commonly associated with anxiety disorders have unique effects on anxiety treatment outcomes. To investigate this, we selected several specific CMCs that demonstrate strong associations with anxiety disorders, have widely recognized stress-related features, and were endorsed with sufficient frequency in this sample to justify separate evaluation of their potential interactions with treatment outcome. We limited these analyses to three CMCs to balance interest in evaluating disorder-specific effects with the risk of Type I error. The CMCs that best met our selection criteria were migraine, asthma, and gastrointestinal disease (1–8,13,14,17,27,28). Exploratory analyses examined whether these specific CMCs had similar or divergent influences on anxiety treatment outcomes.

METHODS

Participants

Participants were patients enrolled in the CALM study, an RCT conducted in 17 primary care clinics in four US regions (Seattle, WA; Los Angeles, CA; San Diego, CA; and Little Rock, AR). Patients provided informed consent to participate, and the study was approved by institutional review boards at all study sites. Patients were referred to the study by their primary care providers; in some clinics, referral was facilitated by a five-item anxiety screener (29).

Between June 2006 and April 2008, 1004 patients with GAD, PD, PTSD, and/or SAD aged 18 to 75 years who were English or Spanish speaking were enrolled in the study. Most co-occurring mental disorders were permitted; active suicidal intent or plan, psychosis, Bipolar I, and substance use disorders (except alcohol and marijuana abuse) were cause for exclusion. Table 1 reports the demographic and diagnostic characteristics of this sample.

Design of the CALM Study

The overall design of the CALM study has been described in prior reports (25,30). Briefly, eligible participants were randomly assigned to either CALM or UC; randomization was stratified by clinic and presence/absence of major depressive disorder (MDD). Blinded telephone assessments were performed by the RAND Survey Research Group at baseline and at 6, 12, and 18 months. Study retention was high and similar for the CALM and UC groups, with more than 80% of participants assessed at each follow-up evaluation point (6, 12, and 18 months).

Intervention

Patients assigned to UC received care as usual from their primary care provider, with no restrictions imposed (e.g., patients could receive pharmacotherapy from their primary care providers and/or in-house counseling if available, or they could be referred out for specialty care). Patients assigned to CALM met with an anxiety clinical specialist (ACS) and were given the choice of computer-assisted CBT delivered by the ACS, medication management, or both. Most patients assigned to CALM (n = 482; 95.8%) had at least one intervention contact with the ACS; of these, 166 (34.4%) had only CBT visits, 43 (8.9%) had only medication management visits, and 273 (56.6%) had both CBT and medication management visits (25).

Medication management was delivered by the primary care provider and supported by the ACS, who facilitated consultation with the CALM study psychiatrist as needed and encouraged medication adherence and healthy behaviors. Before the study enrollment period, a local study psychiatrist provided a one-time training to primary care providers at participating clinics focused on pharmacotherapy for anxiety disorders. The simple pharmacotherapy algorithm focused on first-line use of selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor antidepressants, dose optimization, and adverse effect monitoring; followed by second- and third-step combinations of two antidepressants or an antidepressant and a benzodiazepine for refractory patients.

Computer-assisted CBT was provided by the ACS and consisted of standard CBT elements such as self-monitoring, psychoeducation, breathing retraining, cognitive restructuring, exposure to feared internal and external stimuli, and relapse prevention (31). In cases where patients met the criteria for more than one of the four target anxiety disorders, CBT focused on the disorder the patient judged to be most distressing or disabling.

The initial treatment step (CBT, medication management, or both) was typically delivered during a 10- to 12-week period. For patients who did not respond fully to the initial treatment step, the CALM algorithm allowed for multiple treatment steps (up to four steps over the course of 12 months), which could include either "stepping up" (adding more of the same modality) or "stepping over" (switching to or adding the other modality). Once patients had achieved the criteria for remission (25) or improved to the degree where they did not want further treatment, they entered "continued care" where they received monthly telephone calls to reinforce CBT skills, medication adherence, or both, until the 12-month treatment period had elapsed. Detailed descriptions of the CALM intervention (25,31) and the training of the ACSs are provided elsewhere (32).

Measures

Diagnostic Assessment

Diagnoses of mental disorders were established using the Mini International Neuropsychiatric Interview (MINI), version 5.0 (33). The MINI was conducted

TABLE 2. Frequencies of Chronic Medical Conditions[a]

Chronic Medical Condition	Frequency Proportion (n)	Baseline BSI-A, M (SD)	Baseline SDS, M (SD)
Hypertension or high blood pressure	36.7 (368)	10.5 (5.3)	17.3 (7.5)
Back problems	33.0 (331)	10.8 (5.3)	17.8 (7.3)
Migraine headaches	28.6 (287)	10.5 (5.3)	17.7 (7.4)
Vision problems (despite use of corrective lenses)	24.3 (244)	11.5 (5.4)	18.7 (7.2)
Arthritis or rheumatism	24.0 (241)	10.3 (5.2)	17.7 (7.2)
Asthma	20.6 (207)	10.9 (5.5)	17.8 (7.1)
Gastrointestinal disease[b]	17.3 (174)	11.0 (5.5)	17.2 (7.6)
High blood sugar or diabetes	10.2 (102)	10.8 (5.5)	18.6 (7.1)
Thyroid disease	8.6 (86)	10.2 (5.4)	16.9 (7.6)
Heart disease	6.3 (63)	11.0 (5.9)	17.3 (7.4)
Chronic bronchitis or emphysema	5.2 (52)	11.0 (5.9)	17.0 (7.4)
Physical disability (birth defect; loss of limb, sight, hearing)	4.4 (44)	10.8 (4.7)	19.5 (6.4)
Cancer diagnosed within the last 3 y	3.5 (35)	10.5 (5.3)	17.2 (7.3)
Neurological condition	2.5 (25)	13.9 (5.1)	19.5 (7.5)
Stroke or major paralysis	2.0 (20)	11.9 (5.3)	18.6 (6.3)
Kidney failure	1.1 (11)	11.3 (5.7)	14.1 (7.4)

BSI-A = Brief Symptom Inventory–Anxiety subscale (possible score range = 0–24); M = mean; SD = standard deviation; SDS = Sheehan Disability Scale (modified to capture anxiety-related disability; possible score range = 0–30).

[a] Baseline BSI-A and SDS scores are presented as descriptive data only. Differences between the baseline scores for each chronic medical condition and the baseline scores for the total sample were not formally analyzed or interpreted because of a wide variation in the frequencies of specific chronic medical conditions.

[b] This category comprises patients who endorsed either the item "stomach ulcer" (10.2%; n = 102) or the item "chronic inflamed bowel, enteritis, or colitis" (9.4%; n = 94). These two items were counted separately in determining whether patients belonged to the high or low medical comorbidity group. The two items were collapsed into a general "gastrointestinal disease" category to increase power for subsequent analyses of the effect of gastrointestinal disease on treatment outcome.

in-person by the ACS at the participant's primary care clinic. Reliability and validity of anxiety disorder diagnoses established using the MINI are satisfactory (33).

Medical Comorbidity

Presence of medical conditions was assessed via patient self-report. Frequencies of many CMCs were high (see Table 2), and most of the sample endorsed at least one CMC (n = 801; 79.8%). The median number of CMCs endorsed was 2 (range = 0–11; interquartile range [IQR] = 3); this was the case for both the CALM (median = 2; range = 0–11; IQR = 3) and UC (median = 2; range = 0–9; IQR = 2) groups. Given that medical comorbidity was the rule rather than the exception in this sample, we opted to evaluate the effect of having multiple CMCs on treatment outcome (rather than evaluating the effect of having *any* medical comorbidity). Patients endorsing two or more CMCs (n = 582; 58.0%) comprised the high medical comorbidity group, whereas those endorsing zero or one CMC comprised the low medical comorbidity group (n = 421; 42.0%). We also evaluated the specific effects of migraine, asthma, and gastrointestinal disease on treatment outcomes. Positive status on these variables was defined as simply endorsing these items from the list in Table 2.

Anxiety Symptoms

Severity of anxiety symptoms was measured using the anxiety subscale of the well-validated Brief Symptom Inventory (BSI-A) (34). The BSI-A measures the severity of psychic anxiety, which is common across all anxiety disorders targeted in the study. BSI-A scores were measured during the RAND telephone assessments at baseline and at 6, 12, and 18 months.

Anxiety-Related Disability

Disability was assessed using the well-validated Sheehan Disability Scale (SDS) (35), which measures the degree to which symptoms disrupt work/school, social functioning, and family/home life. For the CALM study the instructions that precede each of the three ratings were modified to specifically target anxiety-related disability (e.g., "Anxiety, tension, and worry symptoms have disrupted your work/schoolwork…"). SDS scores were measured during the RAND telephone assessments at baseline and at 6, 12, and 18 months.

Statistical Analysis/Design of the Current Study

To estimate the effect of medical comorbidity over time, we jointly modeled the symptom-based and functional outcomes (BSI-A and SDS) at the four assessment points by treatment assignment (CALM versus UC), time (baseline and 6, 12, and 18 months), medical comorbidity (high versus low), and the interactions of treatment assignment, time, and medical comorbidity. In models where the three-way (treatment assignment × time × medical comorbidity) interaction was nonsignificant, we dropped the three-way interaction and refit the model including only the two-way interactions (treatment assignment × time, treatment assignment × medical comorbidity, and medical comorbidity × time). We also repeated the analyses replacing overall medical comorbidity with presence/absence of specific CMCs (asthma, migraine, and gastrointestinal disease). The objective of these additional analyses was to explore the potentially differential effects of specific CMCs that are commonly reported by individuals diagnosed with anxiety disorders. In all analyses, we modeled the effects of recruitment site, education level, sex, race/ethnicity, and age to control for potentially important demographic variables. Time was treated as a categorical variable in the analyses. To avoid restrictive assumptions, the covariance of the outcomes at the four assessment points was left unstructured.

We fitted the proposed model using a restricted maximum likelihood approach, which produces valid estimates under the missing-at-random assumption (36). This approach correctly handles the additional uncertainty arising from missing data and uses all available data to obtain unbiased estimates for model parameters (37). This is an efficient way to conduct intent-to-treat analyses because it includes all participants with a baseline assessment.

The statistical software used was SAS version 9 (SAS Institute Inc, Cary, NC). All p values were two tailed, and a conservative significance level of $p < .01$ was adopted to account for multiple comparisons in the analyses of study hypotheses.

RESULTS

Baseline Characteristics Related to Medical Comorbidity

Table 1 summarizes the characteristics of participants with high and low medical comorbidity. The high medical comorbidity group was older and more likely to be diagnosed as having PTSD and MDD, to have Medicaid or Medicare, and to report significant pain and opiate use (p values < .001). The high medical comorbidity group also endorsed higher anxiety symptom (10.5 [95% confidence interval {CI} = 10.1–10.9] versus 9.5 [95% CI = 9.0–10.0], p = .003) and anxiety-related disability (17.6 [95% CI = 17.0–18.2] versus 16.0 [95% CI = 15.3–16.7], p = .001) at baseline. A follow-up analysis revealed small but statistically significant correlations between the number of CMCs endorsed by patients and their anxiety symptom severity (Spearman ρ = 0.14, $p < .001$) and anxiety-related disability (Spearman $\rho = 0.12$, $p < .001$).

Table 2 presents the frequencies with which participants endorsed specific CMCs, as well as the baseline anxiety symptom and anxiety-related disability scores endorsed by patients with each CMC.

Effects of Overall Medical Comorbidity on Anxiety Treatment Outcomes

The three-way medical comorbidity × treatment assignment × time interaction effects on BSI-A (p = .64) and SDS (p = .44) were nonsignificant. We dropped the three-way interactions and refit the models including only two-way interactions; this also failed to reveal any significant medical comorbidity × time interaction effects on BSI-A (p = .47) or SDS (p = .61).[1] These results indicate that improvement in anxiety symptoms and anxiety-related disability was comparable for the high medical comorbidity and low medical comorbidity groups (predicted change in BSI-A = −3.9 versus −4.1 at 6 months, −4.6 versus −4.4 at 12 months, −4.9 versus −5.0 at 18 months; predicted change in SDS = −6.4 versus −6.9 at 6 months, −6.9 versus −7.3 at 12 months, −7.3 versus −7.5 at 18 months).

As expected, based on the group differences on baseline measures, there were significant main effects of medical comorbidity on BSI-A ($F(1,988) = 22.44$, $p < .001$) and SDS ($F(1,988) = 22.03$, $p < .001$), with the high medical comorbidity group displaying higher anxiety symptom and anxiety-related disability scores at all of the assessment points (see Fig. 1).

Effects of Specific CMCs on Anxiety Treatment Outcomes

The three-way asthma × treatment assignment × time interaction effects on BSI-A (p = .64) and SDS (p = .60) were nonsignificant. We dropped the three-way interactions and refit the models including only two-way interactions, which revealed a significant asthma × time effect on BSI-A (p = .004). Regardless of treatment assignment, those with asthma showed greater

[1]Results do not change substantially when "Number of CMCs" is used instead of high versus low medical comorbidity groups. The number of CMCs × treatment assignment × time and number of CMCs × time effects on BSI-A and SDS scores were nonsignificant (all p values > .25).

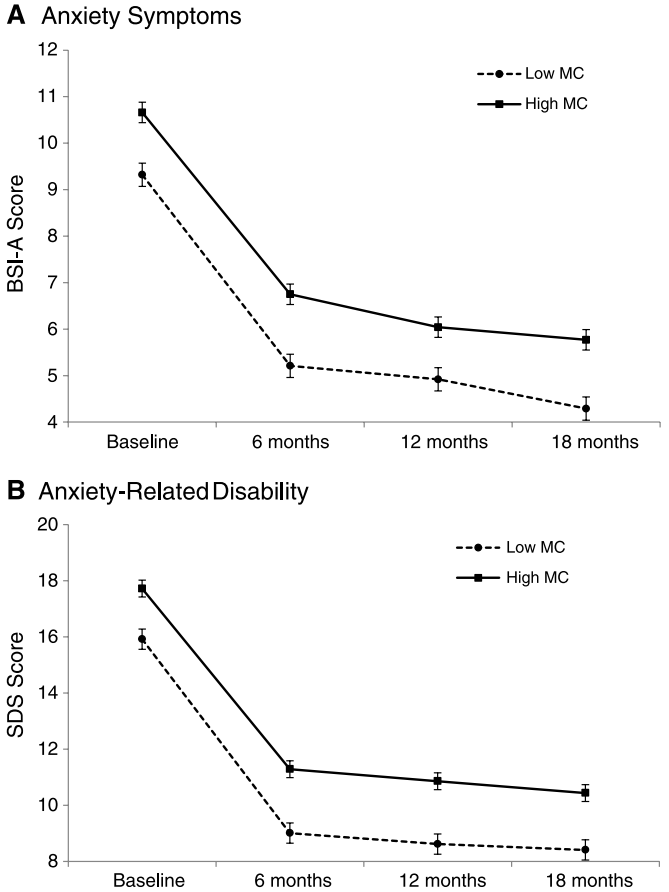

Figure 1. Predicted scores on the Brief Symptom Inventory–Anxiety subscale (BSI-A) (A) and Sheehan Disability Scale (SDS) (B) for the high and low medical comorbidity (MC) groups. There are significant main effects of MC on anxiety symptoms and disability, but no MC × time interaction effects. Results are not broken down by treatment assignment because there were no significant interaction effects involving treatment assignment and MC. Error bars represent the standard error of the predicted means.

improvement at 18 months than did those without asthma (predicted change in BSI-A = −5.8 versus −4.7 at 18 months, p = .010; see Fig. 2). Although those with asthma started the study with slightly higher BSI-A scores, by the 18-month follow-up, they endorsed slightly lower BSI-A scores than did participants without asthma (predicted mean BSI-A = 4.84 versus 5.23). Participants with asthma showed only a trend toward greater improvement at 12 months (p = .048) and comparable improvement at 6 months (p = .97), relative to those without asthma. There was no main effect of asthma on BSI-A (p = .41), nor was there a significant asthma × time effect on SDS (p = .056) or a main effect of asthma on SDS (p = .47).

The three-way migraine × treatment assignment × time interaction effects on BSI-A (p = .031) and SDS (p = .14) were nonsignificant. We therefore dropped the three-way interactions and refit the models including only two-way interactions. This also failed to reveal any migraine × time effects on BSI-A (p = .018) or on SDS (p = .073) that met our a priori criterion for statistical significance. However, the migraine × time effect approached significance for the BSI-A (F(3,991) = 3.39, p = .018) because those with migraine showed significantly less improvement in anxiety symptoms at 18 months (predicted change in BSI-A = −4.1 versus −5.3, p = .003) and tended to show less improvement at 12 months (predicted change in BSI-A = −3.8 versus −4.8, p = .014), regardless of treatment assignment (see Fig. 2). We also observed main effects of migraine status on BSI-A (p < .001) and SDS (p < .001), with participants with migraine displaying more severe anxiety symptoms and anxiety-related disability at all three follow-up points (p values = .001−.010) but not at baseline (p values = .17 and .079).

There were no significant effects of gastrointestinal disease on improvement in anxiety symptoms or anxiety-related disability. All three-way and two-way interactions involving gastrointestinal disease and time were nonsignificant (p values > .10).

DISCUSSION

The past decade has witnessed growing interest in the delivery of interventions for anxiety disorders in primary care. Collaborative care interventions that incorporate elements of empirically supported treatments have been shown to improve outcomes for primary care patients with anxiety disorders (25,38,39); however, questions remain about factors that influence treatment outcome. The results of the current study provide information pertaining

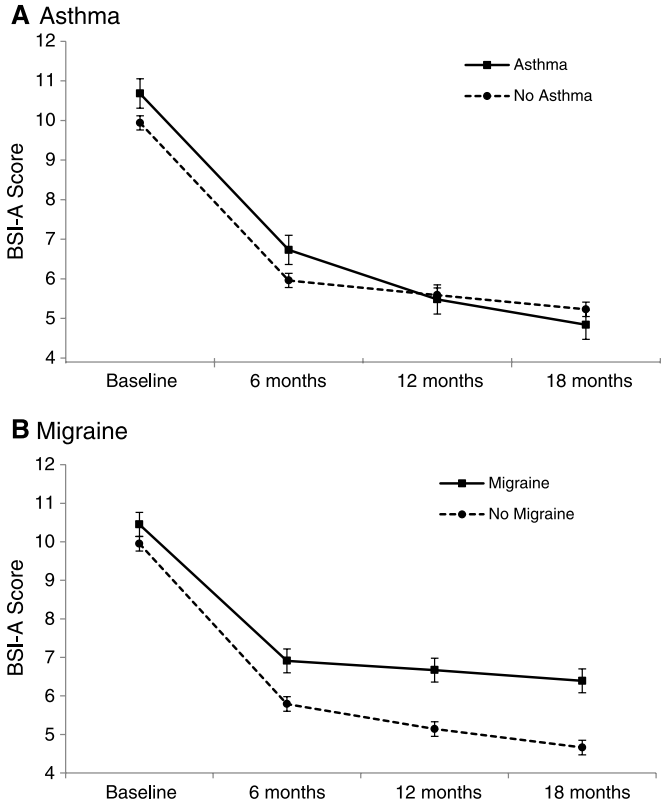

Figure 2. Predicted scores on the Brief Symptom Inventory–Anxiety subscale (BSI-A) for patients with and without asthma (A) and patients with and without migraine (B). Patients with asthma displayed greater improvement in anxiety symptoms at 18 months than did patients without asthma; whereas patients with migraine displayed less improvement in anxiety symptoms at 18 months compared with patients without migraine. Results are not broken down by treatment assignment because there were no significant interaction effects involving treatment assignment and asthma or treatment assignment and migraine. Error bars represent the standard error of the predicted means.

specifically to the effects of medical comorbidity on anxiety treatment outcome and more generally to the phenomenology of anxiety disorders in the context of medical illness.

First, descriptive analyses confirmed that frequencies of major CMCs are high in patients who seek treatment of anxiety disorders in primary care settings. Most of the CALM study sample endorsed two or more CMCs. Approximately one third of participants endorsed hypertension and back problems; one fourth endorsed migraine, vision problems despite use of corrective lenses, and arthritis; and one fifth endorsed asthma and gastrointestinal disease. Patients with multiple CMCs were older and more likely to be diagnosed as having PTSD and MDD, with nearly 70% of those with two or more CMCs meeting the criteria for MDD. Those with more medical comorbidity also endorsed more severe anxiety symptoms and anxiety-related disability at baseline. Taken together, the descriptive findings point toward a relatively complicated "typical" anxiety disorder presentation in primary care (multiple co-occurring CMCs, more severe anxiety, high likelihood of depression). These results highlight the need for continuing study of methods for optimizing assessment of anxiety and other mental health problems in primary care settings, as well as ways to facilitate treatment planning, delivery of interventions, and monitoring of outcomes.

Second, consistent with our hypotheses and previous findings in primary care patients with PD (24), overall medical comorbidity did not moderate the effects of the CALM intervention on anxiety symptoms or anxiety-related disability. This suggests that the advantages of CALM over UC are robust to differences in the level of medical comorbidity, broadly defined. In addition, reductions in anxiety symptoms and anxiety-related disability were comparable for the high and low medical comorbidity groups when considered, irrespective of treatment assignment. Considered in conjunction with prior results (24), these findings suggest that improvements of similar magnitude can be expected from interventions such as CALM and UC in patients with varying levels of overall medical comorbidity.

Although the degree of improvement was similar in patients with high and low medical comorbidity, absolute levels of anxiety symptoms and anxiety-related disability were higher at all assessment points for patients with two or more CMCs. Given the lack of significant interaction effects, these higher absolute scores seem attributable to baseline elevations in symptoms and disability (which carried forward to subsequent assessments). Higher baseline anxiety severity in patients with more medical comorbidity could be caused by a range of biopsychosocial factors. The stress of managing multiple CMCs could exacerbate anxiety disorder symptoms, whereas the need to address multiple CMCs could make anxiety disorder symptoms a lower treatment priority for both clinicians and patients. Symptoms of CMCs also could restrict patients' engagement in nontreatment activities that could assist in ameliorating anxiety symptom severity (e.g., exercise and activities that provide social support). It is also possible that in some cases of anxiety-CMC comorbidity, there could be shared biological substrates associated with increased severity of both types of conditions or increased susceptibility to medical conditions in patients with more severe anxiety (4). Finally, in the absence of objective confirmation of medical diagnoses, we cannot rule out the possibility that patients with more severe anxiety were more biased toward endorsing medical conditions because of hypersensitivity to physical symptoms and/or health-focused anxiety.

Although the CALM intervention produced similar degrees of clinical improvement regardless of medical comorbidity level, Figure 1 shows that there is room for further improvement in the absolute levels of anxiety symptoms and anxiety-related disability endorsed by patients with more medical comorbidity. Modification of standard interventions may be needed to accomplish further reductions in anxiety severity in these patients. This could include more tailoring of CBT to address possible interactions of anxiety and medical symptoms or augmentation with other empirically supported strategies (e.g., acceptance-based techniques (40)) that may aid patients in coping with symptoms of medical illness and anxiety.

Because different comorbid CMCs may influence anxiety treatment outcomes in distinct ways, we undertook exploratory analyses to examine treatment outcomes for patients who endorsed asthma, migraine, and gastrointestinal disease. We found preliminary evidence that these conditions have divergent effects on anxiety-related treatment outcomes. We did not observe any effects of gastrointestinal disease on improvement of anxiety symptoms or anxiety-related disability during the 18-month study period. In addition, asthma did not seem detrimental to treatment efficacy; in fact, patients with asthma showed more improvement than did patients without asthma at the 18-month follow-up. Although patients with asthma started the study with slightly more severe anxiety symptoms, by the end of the study, they had "caught up" with patients without asthma and reported comparably low anxiety symptoms. These results are encouraging, particularly in light of evidence suggesting that anxiety disorders and asthma can potentiate one another (27). Although symptom severity and functional impairment caused by anxiety and asthma may be interrelated, it seems that anxiety disorders can be just as successfully treated in patients with asthma as in other primary care patients. Furthermore, treatment of anxiety should be a priority in this subgroup because reduction in anxiety symptoms could conceivably improve asthma-related outcomes, as well (27).

Participants with migraine, on the other hand, displayed some evidence of poorer response to treatment. They tended to show less improvement in anxiety symptoms over time, and their anxiety symptoms were significantly less improved at the 18-month follow-up. Main effects also indicated that participants with migraine endorsed significantly higher absolute levels of anxiety symptoms and anxiety-related disability at all follow-up assessments. These effects were unlikely to be strictly caused by baseline elevations in anxiety-related symptoms and disability because patients with and without migraines did not differ significantly on these measures at baseline.

Several studies have found particularly strong associations between migraine headaches and anxiety disorders, with some reporting that migraine had the strongest association of all assessed CMCs (1,16). In addition, having an anxiety or mood

disorder diagnosis predicts worse outcome of migraine treatment (41). Our preliminary results suggest that anxiety-migraine comorbidity also may complicate the treatment of anxiety, with the negative impact observed most clearly in long-term follow-up. Several explanations for this finding are possible. To the extent that migraine headaches cause a restriction of activities, they may prevent the corrective learning experiences (and anxiety reduction) that occur with regular exposure to anxiety-provoking stimuli and situations. Such an effect could be expected to appear after treatment withdrawal (in this case, at 18 months) because at this point, patients no longer have the instruction, direct support, and accountability for exposure practice that results from regular contact with a clinician. However, an argument against this interpretation is that the other CMCs evaluated (particularly gastrointestinal disease) also can lead to a restriction of activities, and therefore, it is unclear why this detrimental effect would only be observed in relation to migraine. Alternatively, migraine may be a causal factor in certain types of anxiety (e.g., anxiety related to pain or the anticipation of pain[2]) that are less responsive to standard CBT or pharmacotherapy, or patients with anxiety-migraine comorbidity may have higher levels of neurobiological or temperamental diatheses (e.g., neuroticism and anxiety sensitivity) that predispose them to both conditions and make their anxiety symptoms more difficult to treat.

Limitations

This study evaluated the effects of medical comorbidity on outcomes from an RCT of a multifaceted intervention for a range of anxiety disorders. Owing to statistical power considerations, the study was not designed to evaluate higher level (four-way) interactions involving principal anxiety diagnosis (GAD, PD, PTSD, or SAD). In addition, patients were not randomized to receive specific treatment components (i.e., CBT and pharmacotherapy), and thus, we were unable to evaluate possible moderation effects of CMCs on patients' response to these components. The results reported here cannot be assumed to apply uniformly to each individual anxiety disorder or to CBT versus pharmacotherapy.

Statistical power considerations also limited our ability to examine the effects of specific CMCs on anxiety treatment outcomes; however, we undertook exploratory analyses of the effects of three high-frequency CMCs in this sample that were of conceptual interest and, when taken together, represent a broad range of medical comorbidity commonly found in patients with anxiety disorders. The divergent outcomes for patients with asthma, migraine, and gastrointestinal disease illustrate the limitations of examining medical comorbidity in the aggregate. Additional investigation is needed to further elucidate the effects of specific CMCs on treatments for anxiety disorders.

Measurement of medical comorbidity was based entirely on patients' self-report. Group membership (high versus low medical comorbidity) therefore depended on the accuracy of their answers to the survey questions focused on medical illnesses. It would have been ideal to corroborate diagnoses via examination of medical records; however, these data were not available to investigators. In addition, if more detailed assessment of medical conditions had been incorporated into the baseline assessment, we could have included variables related to the *severity* of medical illness. Future research should go beyond assessing the presence/absence of CMCs, with the aim of incorporating information about the severity of co-occurring medical illness into models of anxiety treatment response.

Finally, the results of this investigation may not generalize to groups of patients who were not well represented in the study sample (e.g., patients from underrepresented ethnic minority groups and patients with low levels of education). Future investigations should attempt to evaluate the effects of medical comorbidity on anxiety treatment outcome in more diverse samples.

CONCLUSIONS

Co-occurring CMCs are common in primary care patients with anxiety disorders and are associated with more severe baseline anxiety and higher frequencies of co-occurring MDD and PTSD. Nevertheless, patients with multiple CMCs achieve similar degrees of improvement in anxiety symptoms and anxiety-related disability compared to patients with one or zero CMCs. Different CMCs may have divergent effects on anxiety treatment outcomes. This study suggested that migraine was associated with poorer long-term improvement in anxiety symptoms. Future studies are needed to corroborate this finding and to further evaluate the effects of specific CMCs on anxiety treatment outcomes.

Although this study makes important contributions to the literature on anxiety disorders and medical comorbidity (especially in demonstrating that patients with multiple CMCs can benefit from anxiety treatment as much as those with low medical comorbidity), it also highlights the need for further study of interactions between medical conditions and the etiology, phenomenology, and treatment of anxiety disorders. The high prevalence of anxiety disorder/CMC comorbidity, the commonplace occurrence of complicated presentations (multiple CMCs, more severe anxiety, co-occurring depression), and the apparently divergent effects of distinct CMCs all indicate that better understanding of these relationships is crucial to maximizing the impact of primary care–based interventions for anxiety disorders.

Source of Funding and Conflicts of Interest: This work was supported by Grants U01 MH057858 (Dr. Roy-Byrne), U01 MH058915 (Dr. Craske), U01 MH 070022 (Dr. Sullivan), U01 MH070018 (Dr. Sherbourne), U01 MH057835 and K24 MH64122 (Dr. Stein), and K01 MH072952 (Dr. Chavira) from the National Institute of Mental Health, Bethesda, MD. Dr. Roy-Byrne is a consultant to Valant Medical Solutions (EMR Company) and is editor-in-chief of the Journal Watch Psychiatry, Depression and Anxiety, and UpToDate Psychiatry. Dr. Stein is paid for his editorial work on the journal Depression and Anxiety and the evidence-based medical information provider, UpToDate Psychiatry. The other authors have no disclosures.

[2]A post hoc analysis evaluated whether other pain-related CMCs had similar effects on anxiety outcomes; however, neither back problems nor arthritis showed any significant effects on improvement of anxiety symptoms or anxiety-related disability.

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