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Associations between anxiety disorders and physical illness

■ **Abstract** *Objective* In contrast to the literature on the association of depression with medical illness, less is known about the comorbidity among anxiety and somatic disorders. Although associations between anxiety disorders and medical illnesses have been reported, prior studies have not adjusted for the effects of gender, substance abuse/dependence, and depression. This study examined the patterns of comorbidity of anxiety disorders and physical illnesses. *Method* A total of 262 probands were selected from treatment settings or were randomly recruited from the community. DSM-III-R diagnoses were obtained based on direct interview (SADS) or family history information, and lifetime history of numerous medical illnesses were obtained. *Results* Patients with a lifetime anxiety disorder reported higher rates of several medical illnesses than did persons without anxiety. After controlling for the effects of gender, comorbid substance abuse/dependence and/or depression, significant associations were found between anxiety disorder and cardiac disorders (OR = 4.6), hypertension (OR = 2.4), gastrointestinal problems (OR = 2.4), genitourinary disorders (OR = 3.5), and migraine (OR = 5.0). A similar pattern was observed for probands with panic or generalized anxiety disorder (GAD). *Conclusions* Anxiety disorders were associated with a specific pattern of cardiac disorders, hypertension, gastrointestinal problems, genitourinary difficulties, and migraine; individuals presenting with anxiety disorders or medical illness need therefore to be evaluated carefully for comorbidity.

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Introduction

Recent epidemiological studies have revealed that anxiety disorders occur in approximately 12.6% to 17.2% of the population (12-month prevalence). The life-time prevalence of anxiety disorders is even higher (14.6% to 24.9%), mostly due to the high frequency of social phobia and simple phobias [14, 16, 22, 24, 31].

In contrast to the accumulating literature on the association of depression with medical illness [3, 15, 17, 20, 21, 23, 26], less is known about the comorbidity of anxiety disorders and somatic disorders or mixed anxiety-depression states [29]. Nonetheless, many investigators have reported an association between anxiety disorders and medical illnesses [8, 12, 27, 36]. Several studies relying on clinical or epidemiologic samples have shown higher rates of medical illnesses among patients with anxiety disorders compared to controls [10, 13, 18, 25, 33]. Studies that have investigated comorbidity according to specific subtypes of anxiety and medical illness reveal that the association is greater for panic disorder and generalized anxiety states than for phobias. Patients with panic are more likely to have specific comorbid medical disorders such as angina, mitral valve prolapse, idiopathic cardiomyopathy, labile hypertension, respiratory illnesses, migraine headaches, peptic ulcer disease, diabetes mellitus, or thyroid disease [3, 10, 12, 13, 18, 25, 27, 32].

It is not clear, however, whether the strength of the association between anxiety disorders and medical illness can be attributed to an increased frequency of treatment

seeking among those with such comorbidity. The nature of this association also remains unclear because of the heterogeneity of the anxiety and medical disorders and as well as the disparate methodologies (i. e., assessment methods, time window, sampling procedures) employed among the studies. Moreover, no studies have controlled for the effects of depression and substance abuse, which are highly comorbid with anxiety [19, 22, 30] and which have been linked to medical illness [20].

The present study investigates the co-occurrence of anxiety and medical disorders among a sample of probands with and without anxiety disorders who were recruited from clinic and community sources in the New Haven area (State Connecticut, U. S. A.). Because of the high comorbidity of substance abuse/dependence, depression, and anxiety disorders, we also examined the association between anxiety and medical disorders after adjusting for the effects of gender, depression, and substance use disorders. Based upon previous research we expect higher lifetime rates of cardiac disorders, hypertension, gastrointestinal problems, respiratory illnesses, dermatologic conditions, and migraine in probands with anxiety disorders compared to controls without anxiety disorders.

Method

■ Sample

The sample of 262 probands was composed of 169 probands with an anxiety disorder and 93 control probands with no evidence of an anxiety disorder according to DSM-III-R criteria. The probands were recruited from either treatment or community sources. Approximately 54 % of the probands were selected from outpatient specialty clinics for alcoholism and/or anxiety disorders at the Connecticut Mental Health Center (New Haven, Connecticut). The remaining probands were recruited through a random digit dialing procedure in which they were drawn from the same general population as those of the treatment-seeking probands. Approximately two-thirds of the probands with an anxiety disorder and all of the probands with no evidence of an anxiety disorder were recruited from treatment facilities. The rationale for including a combination of clinically referred probands and those recruited at random from the community was to minimize bias associated with treatment-seeking (e. g., Berkson's bias). By virtue of this design, the sample allows for the examination of the association between physical illness and anxiety disorders among probands who do and do not seek psychiatric treatment. All probands were interviewed directly according to the procedures described below. A full description of the study methodology can be found in Merikangas et al. [19].

Relying on DSM-III-R criteria, the probands were assigned to the anxiety group if they met criteria for lifetime presence of generalized anxiety disorder (GAD) (27.9 %), panic disorder with agoraphobia (24.4 %), panic disorder without agoraphobia (9.9 %), social phobia (32.1 %), simple phobia (33.6 %), or agoraphobia (8 %). Of the 169 probands with an anxiety disorder, 98 (58 %) had a comorbid lifetime history of drug and/or alcohol abuse/dependence, and 98 (58 %) had comorbid major depressive disorder or dysthymia. Although the 93 controls had no lifetime history of an anxiety disorder, 29 (21.5 %) had major depressive disorder or dysthymia and 46 (49.5 %) had a lifetime history of drug and/or alcohol abuse/dependence.

■ Interview procedures

Probands were interviewed blindly by experienced clinicians using the semi-structured Schedule for Affective Disorders and Schizophrenia (SADS), current and lifetime version [5], and the Family History-Research Diagnostic Criteria (FH-RDC) developed by Andreasen and colleagues [2]. Both types of assessments were modified to obtain DSM-III-R criteria [1]. The final psychiatric diagnoses were based upon all available information, including the diagnostic interview, family history reports, and medical records using a Best Estimate diagnostic procedure [19].

During the SADS interview the probands responded to numerous questions regarding their medical history. Respondents indicated whether or not they ever had in their lifetime any of approximately 50 medical illnesses. For each reported condition, respondents were asked their age when the condition developed, whether they currently had it, and, wherever relevant, the age when the condition stopped or remitted. In addition, more extensive information was collected on a subset of these disorders, including migraine headaches. For the purposes of this paper and for statistical reasons, many of the uncommon medical illnesses were collapsed into 14 categories of related conditions (see Table 1).

Table 1 Individual medical illnesses and their groupings

Groups of Illnesses	Individual Illnesses
Cardiac disorders	Angina, myocardial infarction, mitral valve prolapse
Hypertension	Hypertension
Metabolic disorders	Diabetes, hypercholesterolemia, hypoglycemia, gout
Gastrointestinal problems	Hepatitis/jaundice, liver disease other than hepatitis, ulcer, gallbladder problems, colitis, constipation, chronic enteritis, indigestion/nausea/nervous stomach
Genitourinary disorders	Kidney disease
Anemia	Anemia
Infectious diseases	AIDS, seropositive for AIDS, rheumatic fever, tuberculosis, Herpes
Dermatological disorders	Acne, psoriasis, eczema
Respiratory disorders	Bronchitis, chronic cough, asthma, emphysema
Allergies	Allergies
Neurological disorders	Convulsions, seizures, epilepsy, encephalitis, meningitis, polio, palsy, paralysis, stroke
Arthritis	Arthritis, rheumatism
Migraine	Migraine headaches
Back Pain	Low back pain

■ Training and reliability of interviewers

The interviewers were either psychologists or psychiatric social workers with clinical experience in psychiatric settings. Extensive effort was devoted to establishing the reliability of the diagnostic assessments until satisfactory levels of agreement were obtained. Kappas derived from joint ratings of individual interviews were generally higher for substance abuse (0.72–0.94) than for anxiety or affective disorders which ranged from (0.54–0.78) across the first three series of training sessions.

■ Statistical Analyses

Data analysis included standard chi-square tests for two-way contingency tables of categorical variables and analyses of variance (ANOVA) for continuous data. The associations between DSM-III-R diagnosis of anxiety and medical illnesses were analyzed via logistic regression (PROC LOGISTIC, SAS Version 6.12). This type of categorical analysis allows an independent assessment of the contribution of several potential predictors on a binary outcome variable, such as the presence or absence of a specific medical illness. Because gender, substance use disorder, and depression have been identified as predictors of physical illness [6, 20, 23, 26], the effect of having an anxiety disorder on the risk of medical conditions was examined in two models: (a) adjusting for gender and lifetime history of substance use disorder, and (b) adjusting for gender, lifetime history of substance use disorder, and lifetime diagnosis of depression. Logistic analyses were run for each of the 14 groups of medical conditions presented in Table 1.

We anticipated higher lifetime rates for cardiac disorders (e.g., angina attacks, mitral valve prolapse), gastrointestinal problems (e.g., ulcer, colitis, indigestion), respiratory illnesses, hypertension, dermatologic conditions (psoriasis, eczema), and migraine in probands with anxiety disorders [10, 18, 25, 32] compared to controls without an anxiety disorder. Furthermore, we predicted particularly high lifetime rates of these medical illnesses among probands with panic disorder or GAD compared to probands without panic disorder or GAD [11, 13, 27, 36].

Results

Demographic characteristics of the probands are presented in Table 2. Although there were no significant differences between groups for age and socioeconomic status, probands in the anxiety disorder group were more likely to be female and less likely to be married or remarried.

Lifetime rates of medical disorders among probands with anxiety and controls are presented by gender in Table 3. For both males and females, the rates of numerous medical disorders are higher among probands with an anxiety disorder than among controls. In particular, males with an anxiety disorder have higher rates of cardiac disorders, hypertension, metabolic, gastrointestinal

disorders, genitourinary problems, dermatological disorders, respiratory illnesses, allergies, arthritis, migraine, and back pain. Females with an anxiety disorder report elevated rates of cardiac, hypertensive, metabolic, gastrointestinal, genitourinary, dermatological, and respiratory disorders as well as allergies, arthritis, migraine and back pain. Of these elevated rates among probands with an anxiety disorder, the differences were statistically significant for gastrointestinal problems ($\chi^2 = 7.77$, df = 1, p = 0.005) and migraine among males ($\chi^2 = 8.45$, df = 1, p = 0.004) and cardiac disorders ($\chi^2 = 4.20$, df = 1, p = 0.040), hypertension ($\chi^2 = 4.61$, df = 1, p = 0.032), gastrointestinal problems ($\chi^2 = 5.96$, df = 1, p = 0.015), respiratory disorders ($\chi^2 = 5.36$, df = 1, p = 0.037), and migraine ($\chi^2 = 5.96$, df = 1, p = 0.015) among females.

Table 3 also presents results employing logistic regression models in which the presence or absence of a medical illness was predicted from the presence or absence of an anxiety disorder. Odds-ratios and 95% confidence intervals are presented for each of two logistic models; the first controls for gender and comorbid substance use disorder and the second controls for gender, comorbid substance use disorder, and comorbid depression. After adjusting for the effects of gender and a substance use disorder (model 1), probands with an anxiety disorder were 4.4-times more likely to have a cardiac disorder ($\chi^2 = 5.28$, df = 1, p = 0.0216), 2.8-times more likely to suffer from gastrointestinal problems ($\chi^2 = 11.81$, df = 1, p = 0.0006), 3.4-times as likely to have a genitourinary disorder ($\chi^2 = 4.44$, df = 1, p = 0.0352), and 4.8-times more likely to experience migraine headaches ($\chi^2 = 12.68$, df = 1, p = 0.0004) than were probands without an anxiety disorder. Similar results were obtained from the second model in which gender, substance use disorder, and depression were controlled (model 2). Specifically, probands with an anxiety disorder were at a 4.6-fold risk for cardiac disorders ($\chi^2 = 5.30$, df = 1, p = 0.0213), a 2.4-fold risk for hypertension ($\chi^2 = 4.47$, df = 1, p = 0.034), a 2.4-fold risk for gastrointestinal problems ($\chi^2 = 7.98$, df = 1, p = 0.0047), a 3.5-fold risk for genitourinary disorders ($\chi^2 = 4.42$, df = 1, p = 0.0355), and a 5-fold risk for migraine ($\chi^2 = 12.53$, df = 1, p = 0.0004) than were probands without an anxiety disorder.

When the analyses contrasted the probands with panic disorder or GAD to the probands without panic or GAD, modest increases in the rates of several medical illnesses were observed for both males and females. As shown in Table 4, male probands with panic or GAD reported significantly higher lifetime prevalence rates for cardiac problems ($\chi^2 = 4.85$, df = 1, p = 0.028), gastrointestinal problems ($\chi^2 = 8.62$, df = 1, p = 0.003), and dermatological disorders ($\chi^2 = 4.77$, df = 1, p = 0.029). Similarly, females with panic or GAD had elevated rates of cardiac problems ($\chi^2 = 6.29$, df = 1, p = 0.012) and gastrointestinal problems ($\chi^2 = 14.16$, df = 1, p < 0.001), but unlike the males, the females also had elevated rates of respiratory disorders ($\chi^2 = 8.40$, df = 1, p = 0.004) and migraine ($\chi^2 = 5.87$, df = 1, p = 0.027).

Table 2 Demographic characteristics of the probands, by group

	Anxiety (N = 169)	Control (N = 93)	Test for homogeneity of percentages or means
Age	39.2 (6.0)	40.5 (6.2)	$F_{(1.261)} = 2.83$, p = 0.0940
Females (%)	58.6	35.5	$\chi^2_{(1)} = 12.80$, p < 0.001
Socioeconomic Status, Hollingshead > 3, %	42.3	34.9	$\chi^2_{(1)} = 1.28$, p = 0.259
Married or remarried, %	71.6	85.0	$\chi^2_{(1)} = 5.92$, p = 0.015

Table 3 Rates of medical illness among male and female probands with and without an anxiety disorder

Medical illness	Males		Females		Odds-ratio (C. I.) adjusted for sex & substance use disorder	Odds-ratio (C. I.) adjusted for sex, substance use disorder & depression
	Anxiety (%) N = 70	Control (%) N = 60	Anxiety (%) N = 99	Control (%) N = 33		
Cardiac disorders	8.6	3.3	17.2	3.0	4.36 (1.24–15.30)*	4.59 (1.25–16.8)*
Hypertension	24.6	16.7	18.2	3.0	2.12 (0.99–4.55)	2.35 (1.06–5.17)*
Metabolic disorders	17.4	8.3	17.2	12.1	1.72 (0.75–3.92)	1.55 (0.66–3.66)
Gastrointestinal problems	50.7	26.7	48.5	24.2	2.74 (1.54–4.87)***	2.38 (1.30–4.34)**
Genitourinary disorders	11.6	5.0	13.1	3.0	3.36 (1.09–10.38)*	3.51 (1.09–11.29)*
Infections	2.9	3.3	4.0	0.0	1.67 (0.31–8.88)	1.06 (0.18–6.34)
Anemia	4.4	5.2	22.5	21.2	0.95 (0.41–2.20)	0.74 (0.30–1.84)
Dermatological disorders	41.4	36.7	34.3	21.2	1.42 (0.81–2.49)	1.37 (0.76–2.47)
Respiratory disorders	20.0	16.7	26.5	9.1	1.85 (0.91–3.76)	1.40 (0.66–2.98)
Allergies	37.1	31.7	42.4	30.3	1.38 (0.79–2.41)	1.29 (0.72–2.32)
Neurological disorders	7.1	6.7	4.0	0.0	1.18 (0.33–4.23)	0.88 (0.24–3.27)
Arthritis	15.9	10.0	8.3	3.0	1.82 (0.71–4.65)	1.63 (0.61–4.36)
Migraine	23.2	5.0	34.3	12.1	4.75 (2.02–11.21)***	5.01 (2.05–12.22)***
Back Pain	47.1	36.7	41.4	27.3	1.63 (0.94–2.82)	1.30 (0.73–2.34)

* p < 0.05; ** < 0.01; *** < 0.001

Table 4 Rates of medical illness among male and female probands with and without panic or GAD

Medical illnesses	Males		Females		Odds-ratio (C. I.) adjusted for sex & substance use disorder	Odds-ratio (C. I.) adjusted for sex, substance use disorder & depression
	Panic/GAD (%) N = 37	Control (%) N = 93	Panic/GAD (%) N = 74	Control (%) N = 58		
Cardiac disorders	13.5	3.2	20.3	5.2	5.08 (1.89–13.70)**	5.90 (2.04–17.06)***
Hypertension	27.8	18.3	17.6	10.3	1.62 (0.81–3.23)	1.73 (0.85–3.52)
Metabolic disorders	13.5	13.0	20.3	10.3	1.39 (0.67–2.90)	1.25 (0.58–2.69)
Gastrointestinal problems	59.5	31.5	56.8	24.1	3.49 (2.01–6.06)****	3.12 (1.76–5.54)****
Genitourinary disorders	13.5	6.5	10.8	10.3	1.56 (0.65–3.73)	1.52 (0.60–3.88)
Infections	2.7	3.3	5.4	0.0	2.42 (0.52–11.21)	1.72 (0.34–8.69)
Anemia	5.4	4.4	23.3	20.7	1.11 (0.52–2.41)	0.90 (0.39–2.08)
Dermatological disorders	54.1	33.3	33.8	27.6	1.73 (1.00–3.00)	1.70 (0.95–3.02)
Respiratory disorders	24.3	16.1	31.5	10.3	2.56 (1.33–4.91)**	2.07 (1.04–4.12)*
Allergies	35.1	34.4	44.6	32.8	1.28 (0.75–2.18)	1.19 (0.68–2.09)
Neurological disorders	5.4	7.5	5.4	0.0	1.15 (0.34–3.88)	1.05 (0.31–3.61)
Arthritis	19.4	10.8	8.2	5.3	1.75 (0.73–4.17)	1.59 (0.65–3.91)
Migraine	19.4	12.9	36.5	19.0	2.15 (1.14–4.06)*	2.13 (1.08–4.20)*
Back Pain	43.2	41.9	44.6	29.3	1.41 (0.83–2.40)	1.13 (0.64–1.99)

* p < 0.05; ** < 0.01; *** < 0.001; **** < 0.0

The last two columns of Table 4 provide the results of the logistic regression models that predicted a medical illness from the presence or absence of panic disorder or GAD. After accounting for gender and a comorbid substance use disorder (model 3), probands with panic or generalized anxiety disorder experienced a 5.1-fold increased risk of cardiac problems ($\chi^2 = 10.33$, df = 1, p = 0.0013), a 3.5-fold increased risk of gastrointestinal problems ($\chi^2 = 19.72$, df = 1, p < 0.0001), a 2.6-fold increased risk of respiratory disorders ($\chi^2 = 7.94$, df = 1, p = 0.0048), and a 2.2-fold increased risk of migraine ($\chi^2 = 5.54$, df = 1, p = 0.0186). Even after controlling for comorbid depression in addition to gender and substance abuse (model 4), probands with panic or generalized anxiety disorder, compared to the controls, were 5.9 times more likely to have cardiac disorders ($\chi^2 = 10.74$, df = 1, p = 0.001), 3.1 times more likely to experience gastrointestinal problems ($\chi^2 = 15.05$, df = 1, p < 0.0001), 2.1 times more likely to have respiratory difficulties ($\chi^2 = 4.29$, df = 1, p = 0.0383), and 2.1 times more likely to suffer from migraine headaches ($\chi^2 = 4.75$, df = 1, p = 0.0294).

Consistent with the findings reported above, the probands with an anxiety disorder perceived themselves to be in poorer physical health than did the controls. Specifically, when asked to describe their health in general (i. e., "Would you say that you are never ill, rarely ill, occasionally ill, frequently ill, or continually ill?"), probands with an anxiety disorder compared to controls were more likely to report that they were at least "occasionally ill" ($\chi^2 = 19.70$, df = 1, p < 0.001). Even after controlling for gender, comorbid substance use disorder, and comorbid depression, probands with an anxiety disorder were 3.6 (95 % C. I. = 1.82–7.03) times more likely than the controls to perceive themselves to be in poor health ($\chi^2 = 13.67$, df = 1, p = 0.0002). The perception of being at least "occasionally ill" was even greater among probands with panic disorder or GAD compared to probands without panic disorder or GAD ($\chi^2 = 24.55$, df = 1, p < 0.001). After adjusting for the effects of gender, comorbid substance use disorder, and comorbid depression, probands with panic disorder or GAD were 3.5 (95 % C. I. = 1.93–6.36) times more likely than the controls to perceive themselves to be at least "continually ill" ($\chi^2 = 16.90$, df = 1, p < 0.0001).

In addition to examining the lifetime prevalence of medical illnesses among probands with anxiety disorders, we were able to establish the temporal ordering of the anxiety and medical disorders for a subsample of cases. Based upon self-reported information concerning age of onset, simple phobia (mean = 12.4 years, SD = 7.4) and social phobia (mean = 12.2 years, SD = 6.3) tended to precede each of the physical conditions for which there was an increased risk: migraine headaches (mean = 21.8 years, SD = 11.0), gastrointestinal problems (mean = 22.4 years, SD = 10.8), genitourinary disorders (mean = 28.6 years, 10.3), and cardiac illness (mean = 29.9 years, SD = 9.0). Indeed, the onset of these physical illnesses postdated that of simple phobia and social phobia in 79 % and 63 % of the cases, respectively. In contrast, although the mean age of onset of panic (mean = 23.6 years, SD = 9.0) and GAD (mean = 25.6 years, SD = 9.1) followed the onset of the physical illnesses overall, the age-of-onset patterns differed somewhat by the type of physical illness. The onset of panic predated that of genitourinary (60 %), cardiac (60 %), and respiratory illnesses (55 %), though most often postdated the onset of migraine headaches (61 %) and gastrointestinal conditions (63 %). With respect to the age of onset of GAD, it preceded the onset of cardiac illness in 62 % of the cases, came after that of migraine and gastrointestinal problems in 56 % and 57 % of the cases, respectively, and was equally likely to precede or follow both genitourinary and respiratory illnesses.

Summary and Discussion

The present study supports findings from previous research showing an association between anxiety disorders and lifetime history of medical illnesses. We found that probands with a lifetime diagnosis of panic attacks with and without agoraphobia, generalized anxiety disorder, simple phobia, or social phobia report higher lifetime rates of numerous medical conditions compared to persons without an anxiety disorder. Indeed, patients with anxiety disorders studied by Rogers and colleagues [25] reported rates of hypertension (18 %), respiratory disorders (16 %), migraine (29 %), and allergies (46 %) that were similar to those reported by probands in the current study. Our study, however, extends prior research by accounting for gender, comorbid substance use disorder, and comorbid depression when investigating the relation between anxiety and medical disorders. After adjusting for gender and substance abuse, having an anxiety disorder significantly predicted cardiac disorders, gastrointestinal problems, genitourinary disorders, and migraine. Even when comorbid major depression or dysthymia was included as an additional covariate, probands with an anxiety disorder were significantly more likely to suffer from each of these medical disorders as well as hypertension.

Furthermore, data from the present study concur with previous studies indicating that persons with panic disorder or GAD tend to have especially high rates of medical illnesses [11, 36]. For most of the medical disorders, rates among probands with panic or GAD exceeded those of probands without panic or GAD. The rates of cardiac disorders, gastrointestinal problems, respiratory illness, and migraine were significantly greater among probands with panic or GAD, compared to those without, after adjusting for gender and lifetime history of substance use disorder. When comorbid lifetime depression/dysthymia was included into the model along with gender and lifetime substance abuse, panic disorder or GAD remained significantly associated with cardiac disorders, gastrointestinal problems, respiratory problems, and migraine.

In addition to these findings, some interesting patterns emerged upon further inspection of the rates of medical illness by the specific types of anxiety disorders (i. e., GAD, panic, simple phobia, and social phobia). Among the males, particularly high rates were found for cardiac problems among subjects with GAD (20 %), dermatologic (75 %) and arthritic (27.3 %) conditions among those with panic, and migraine headaches (35.7 %) among males with social phobia. In females, elevated rates were found for cardiac disorders (26.9 %) and infections (7.7 %) among those with panic, metabolic disorders (27.1 %), gastrointestinal problems (62.5 %), allergies (52.1 %), neurologic disorders (8.3 %), migraine (41.7 %), and back pain (50 %) among subjects with GAD, and kidney disease (22.7 %) among females with simple phobia. Although these rates should be evaluated cautiously because of the small number of subjects per cell (specific anxiety disorder by medical illness), the data offer modest support for specificity between type of medical illness and type of anxiety disorder, and that such a pattern varies by gender. For example, the rate of migraine appeared particularly high

among males (but not females) with social phobia and females (but not males) with GAD.

The interaction between anxiety disorders and medical illness is complex [25], as medical disorders can produce anxiety directly or indirectly. Some medical disorders (e. g., tumors of the temporal lobe, hyperthyroidism) have specific effects on neurotransmitter systems or on neuroanatomic sites associated directly with the production of anxiety [8]. Other medical disorders produce anxiety indirectly through autonomic arousal, which the patient interprets as a psychological state.

Panic disorders may sometimes exacerbate an underlying medical illness, as in the case of a panic attack that triggers angina in patients with underlying coronary heart disease [25, 36]. Alternatively, panic disorder may mimic symptoms of a medical disorder. Indeed, individuals with anxiety disorders, particularly panic, may be heavy users of primary health care services, have lower health-related quality of life, and increased functional disability [4, 7, 12, 25, 36]. Consistent with these reports, after controlling for gender, lifetime substance use disorder, and lifetime depression/dysthymia, probands with an anxiety disorder were three times more likely than the controls to perceive themselves to be in poor health.

Panic disorder has been postulated to occur because of dysregulation of key neuroregulatory centers of the central nervous system. A cluster of noradrenergic neurons in the locus coeruleus that appears to be involved in the fight-or-flight response to real or imagined signals of danger has been intensively studied [36]. In response to external events such as stressful life events, synaptic transmission in the locus coeruleus may alter, so that false alarms resembling panic attacks may occur even in the absence of any real danger. In addition to external stimuli, it has been shown that internal changes in the homeostasis in several organ systems may increase the firing rate of noradrenergic neurons in the locus coeruleus, leading to symptoms of anxiety [13, 28]. Severe medical illness and resulting changes in cardiorespiratory, digestive, and urinary tract system may activate the alarm system, thus, precipitating panic disorder much like external stressors predate panic attacks [13, 36]. Once the alarm system is activated severe physiologic stress, synaptic transmission may be altered so the panic attacks develop a life of their own separate from the original insult. Moreover, a vicious cycle may occur: severe external stress causes change in the function of the locus coeruleus, increased anxiety and a psychophysiologic disorder like ulcer disease. Then peptic ulcer may cause peripheral signaling to the coeruleus system, adding to the mental stress of the individual and further overwhelming coping mechanisms [13, 36].

■ Strengths and limitations

Several aspects of the design and methods of the present study enhance its contribution to current knowledge regarding the comorbidity of anxiety disorders and medical illnesses, and serve to enhance the validity and generalizability of the findings. First, by selecting the probands from both clinical and community settings, we have removed some of the selection bias associated with analyzing clinical treatment samples. Second, the probands used in the present study were selected from anxiety or substance abuse clinics rather than medical clinics; they are not necessarily seeking treatment for medical illnesses.

By virtue of the sampling design, it was possible to examine the association between physical illness and anxiety disorders among probands who did versus did not seek psychiatric treatment. Post hoc analyses revealed some similarities and differences that warrant mention. Compared to community controls, both clinic- and community-recruited probands with an anxiety disorder were more likely to report having migraine (O. R. = 5.9, 1.4–25.0; O. R. = 5.0, 1.6–16.2, respectively) and gastrointestinal complaints (O. R. = 3.8, 1.0–15.1; O. R. = 5.5, 1.6–19.2, respectively). The association between anxiety and gastrointestinal problems in the clinic probands was due, however, largely to comorbid affective disorder (O. R. = 2.7, 1.1–6.5). In terms of robust differences by source of recruitment, mitral valve prolapse was elevated among the clinic-recruited anxious probands (O. R. = 6.3, 1.1–36.7).

Third, the present study utilized a comprehensive psychiatric evaluation of probands using standardized diagnostic criteria for psychiatric disorders and rigorous diagnostic reviews. Finally, the use of multivariate techniques made it possible to control for potential confounding variables (i. e., gender, substance use disorder, and depression/dysthymia) whose association with medical illness has been well documented.

Despite these strengths, limitations inherent to the study suggest that caution be taken when interpreting the findings. The reliance on self-reported information for medical disorders, without validation from medical records, may have produced imprecise rates due to over- or underreporting and retrospective bias. Similarly, the use of self-reported medical conditions in the absence of medical records may have misidentified or misclassified some medical conditions. However, studies show that self-reported medical conditions compared with physical examinations are a) rather accurate (e. g., in diabetes: sensitivity rate 85.2 %, specificity rate 98.3 %) or b) tend to be underestimated (e. g., in hypertension: sensitivity rate 49.4 %, specificity rate 95.3 % [9]). Other studies show higher accuracy levels in hypertension (sensitivity ranges from 64 % to 91 %) [for more information, see 9].

The findings presented here have implications for the course and treatment of anxiety disorders and medical illnesses. The elevated rates of medical illnesses among probands with an anxiety disorder suggest that clinicians should evaluate systematically medical illness among patients with anxiety disorders. Likewise, primary care physicians should seek psychiatric consultation or regularly make use of screening instru-

ments designed to identify anxiety disorders [31, 34, 35]. Treatment strategies that consider anxiety disorders while addressing medical conditions may ultimately yield greater efficacy than those that focus solely on the index condition for which the subject sought treatment. Indeed, because the course of medical illness is often worse in the presence of psychiatric disorders, the co-morbidity of medical illnesses and anxiety disorders may affect the evaluation of individuals with these conditions, irrespective of the disorder for which they seek treatment. Although treatments for anxiety disorders, especially panic disorders and phobias, appear equally successful whether or not there is comorbid medical illness, medical symptoms typically desist and escalate until the anxious disorder is adequately treated [13]. Hence, physicians who routinely consider the comorbidity of medical and psychiatric disorders may place themselves in the advantageous position of reducing unnecessary suffering, costly medical procedures, and ineffective treatment approaches.

We suggest that future studies examine the onset and clinical course of specific medical conditions and psychiatric disorders by using prospective designs so as to more fully understand the process by which the associations reported here develop over time, to ascertain the full range of comorbid medical illnesses associated with anxiety disorders and to help clarify pathophysiologic mechanisms underlying their association.

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