Anxiety Disorders and Comorbid Medical Illness

Peter P. Roy-Byrne, M.D.
Karina W. Davidson, Ph.D.
Ronald C. Kessler, Ph.D.
Gordon J.G. Asmundson, Ph.D., R.D., Psych.
Renee D. Goodwin, Ph.D., M.P.H.
Laura Kubzansky, Ph.D.
R. Bruce Lydiard, Ph.D., M.D.
Mary Jane Massie, M.D.
Wayne Katon, M.D.
Sally K. Laden, M.S.
Murray B. Stein, M.D., M.P.H., F.R.C.P.C.

Objective: To provide an overview of the role of anxiety disorders in medical illness. **Method:** The Anxiety Disorders Association of America held a multidisciplinary conference from which conference leaders and speakers reviewed presentations and discussions, considered literature on prevalence, comorbidity, etiology and treatment, and made recommendations for research. Irritable bowel syndrome (IBS), asthma, cardiovascular disease (CVD), cancer and chronic pain were reviewed. **Results:** A substantial literature supports clinically important associations between psychiatric illness and chronic medical conditions. Most research focuses on depression, finding that depression can adversely affect self-care and increase the risk of incident medical illness, complications and mortality. Anxiety disorders are less well studied, but robust epidemiological and clinical evidence shows that anxiety disorders play an equally important role. Biological theories of the interactions between anxiety and IBS, CVD and chronic pain are presented. Available data suggest that anxiety disorders in medically ill patients should not be ignored and could be considered conjointly with depression when developing strategies for screening and intervention, particularly in primary care. **Conclusions:** Emerging data offer a strong argument for the role of anxiety in medical illness and suggest that anxiety disorders rival depression in terms of risk, comorbidity and outcome. Research programs designed to advance our understanding of the impact of anxiety disorders on medical illness are needed to develop evidence-based approaches to improving patient care.

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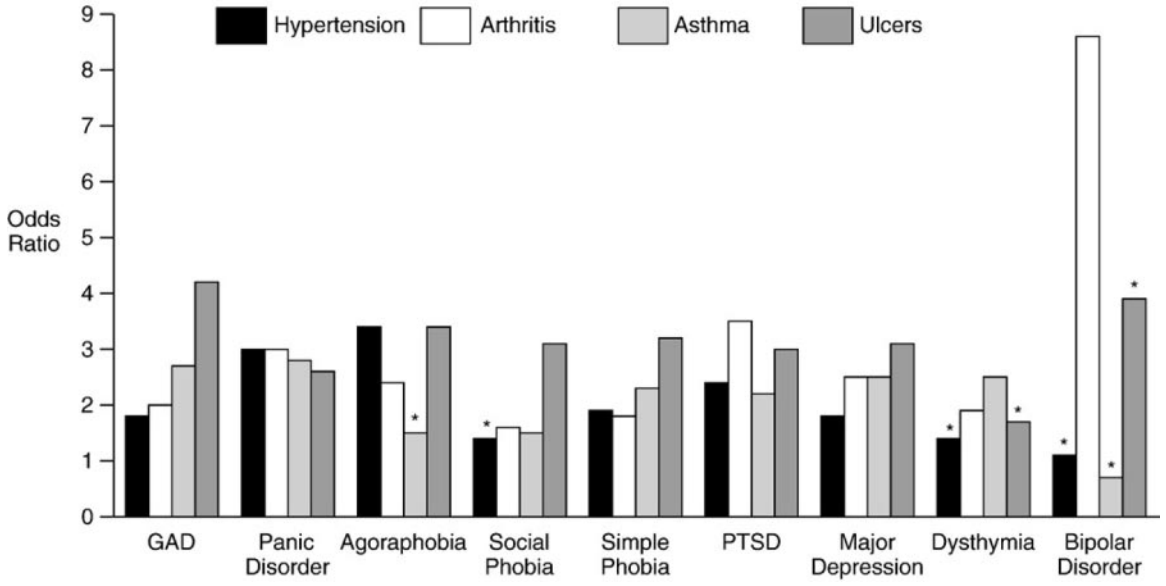
Introduction

Mental disorders occur with chronic medical conditions in many patients, causing significant role impairment, work loss and work cut-back (1, 2). Depression increases symptom burden and functional impairment and worsens prognosis for heart disease, stroke, diabetes mellitus, HIV/AIDS, cancer and other chronic illnesses (3–5). One nationally representative survey of over 130,000 Canadian adults demonstrated that depression independently increased role impairment by 21% compared to healthy controls. However, when depression occurred along with chronic lung disease, diabetes mellitus or heart disease, the rate of disability increased by over 50% (5). A more complete understanding of the adverse effect of depression on biological and self-care (e.g., adherence to diet, smoking cessation, exercise, medications) mechanisms and findings from treatment studies is emerging to guide patient care (6–14). These data paint a compelling picture of the importance of depression in medical illness.

Much less is known about the impact of anxiety disorders on function and outcome in persons with chronic medical illness. There is convincing evidence that anxiety is associated with high rates of medically unexplained symptoms and increased utilization of healthcare resources (4, 15–19). Moreover, anxiety disorders are strongly and independently associated with chronic medical illness (20, 21), low levels of physical health-related quality of life, and physical disability (21–24). Indeed, the disability and related poor physical and economic outcomes associated with anxiety disorders may be as great as with depression. In a sample of 480 primary care patients, the probability of missing time from work in the prior month for persons with an anxiety disorder (OR: 2.22) was as great as for persons with major depression (OR: 2.15) (25). In patients with diabetes, comorbid panic disorder had a significant adverse effect on symptom bur-

Figure 1. Associations (Odds Ratios) of *DSM-III-R* Mental Disorders Among NCS-R Respondents With Chronic Physical Disorders

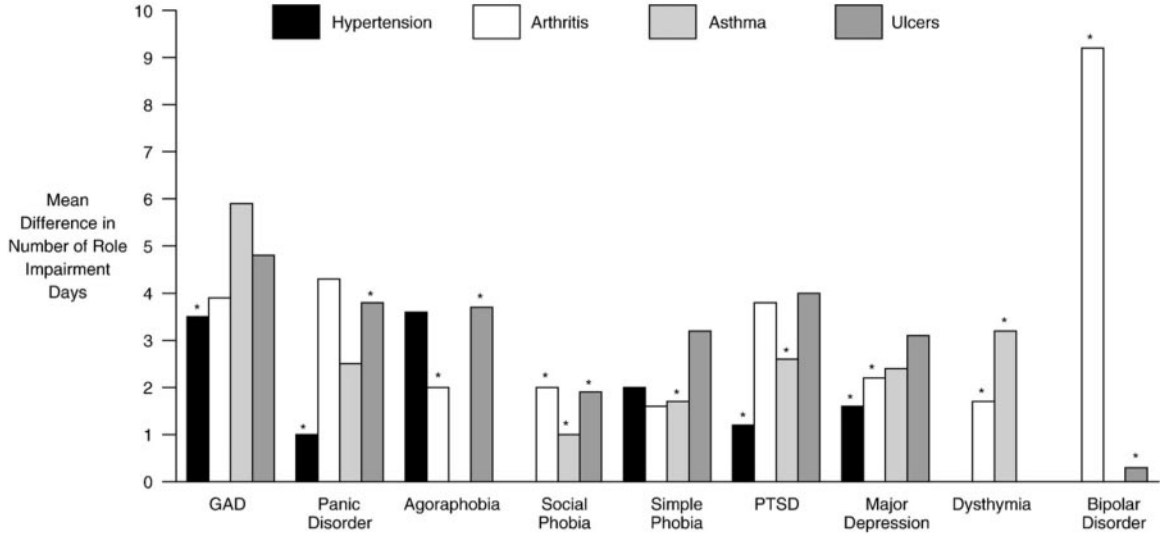


* indicates not statistically significant at $P \geq .05$) [1].

den, functional impairment and HbA_{1c} levels after controlling for depression (23). In the National Comorbidity Survey-Replication (NCS-R), Kessler et al. (1) reported that various anxiety disorders had equal or greater association than depression with four chronic physical disorders (i.e., hypertension, arthritis, asthma, ulcers) (Fig. 1). Similarly, the number of 30-day role impairment days associated with anxiety disorders among respondents with these four chronic medical disorders was similar or greater to that seen in association with depression and dysthymia (Fig. 2) (1).

In recognition of the need to better understand and illustrate the effect of anxiety disorders on persons with chronic medical illnesses and with the hope of developing treatment strategies, the Anxiety Disorders Association of America (ADDA) convened a multidisciplinary conference on January 30

Figure 2. Number of 30-Day Role Impairment Days Associated With Comorbid *DSM-III-R* Mental Disorders Among NCS-R Respondents With Chronic Physical Disorders



*indicates not statistically significant at $P \geq .05$. [1]

31, 2006, to review current data on the relationship between anxiety disorders and specific medical illnesses. Presenters and discussants included clinicians and researchers in psychiatry, psychology, primary care, healthcare systems, epidemiology, public health, healthcare policy and advocacy. The proceedings of the conference are summarized in this paper, which reviews anxiety disorders in the context of functional gastrointestinal disorders, asthma, heart disease, cancer and chronic pain. These selective reviews mainly focused on anxiety disorders per se and did not investigate numerous studies focused on "stress". In addition, specific recommendations are made for furthering the basic science and clinical research agenda to better understand the impact of anxiety disorders on medical illness and improve clinical outcomes and patient care.

ANXIETY DISORDERS AND COMORBID MEDICAL ILLNESS

FUNCTIONAL GASTROINTESTINAL DISEASES

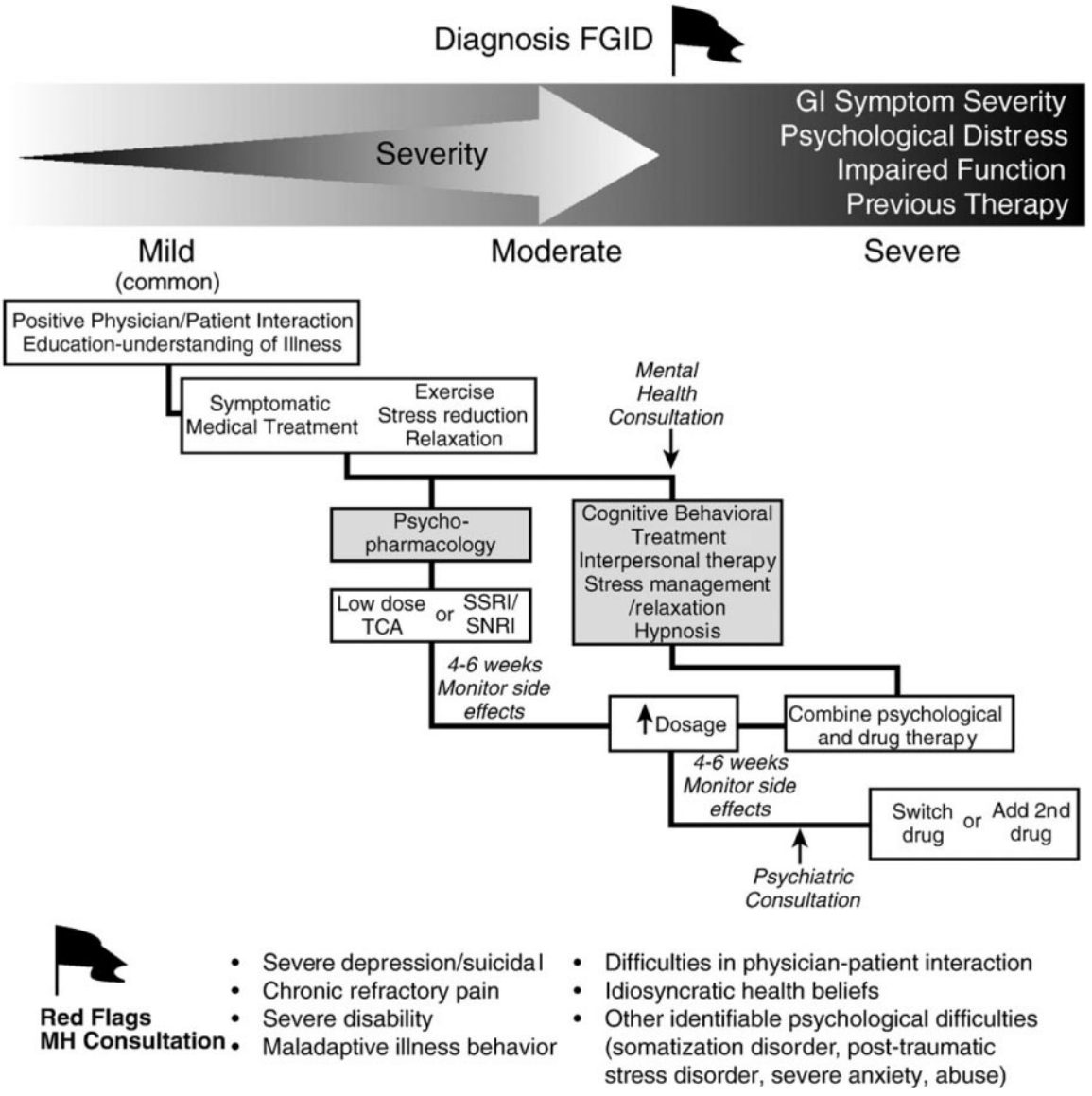
Epidemiology. Irritable bowel syndrome (IBS) is characterized by chronic, unexplained abdominal pain or discomfort associated with diarrhea, constipation, or both (26). It is one of the most common and well studied of the 28 functional gastrointestinal disorders (FGIDs) (27), affecting an estimated 10% to 25% of the population and occurring in women twice as frequently as in men. A key feature of IBS is visceral hyperalgesia, defined as abnormally exaggerated visceral pain responses from gut events (e.g., experimental colonic distension, meals, infection/inflammation) (27–29). Stress reactivity is considered an extremely important non-diagnostic feature of IBS (27, 29) and is characteristic of other disorders with which IBS most frequently overlaps, such as anxiety disorders, mood disorders and other functional somatic disorders.

There is a strong association between IBS and psychiatric diagnoses, particularly anxiety disorders (30). Rates of psychiatric diagnoses range from 54% to 94% in treatment-seeking patients with IBS (31, 32). Rates of anxiety and mood disorders in patients with IBS are significantly higher than in patients with inflammatory bowel disease (33). When psychiatric disorders co-exist with IBS, gastrointestinal symptoms are typically more severe and disabling. In a survey of university students. IBS was associated with high rates of generalized anxiety disorder (GAD) and higher levels of neuroticism, visceral anxiety, anxiety sensitivity and worry than in those without (34). A community-based survey of 3911 adults in the USA found that rates of panic disorder, generalized social anxiety disorder, posttraumatic stress disorder (PTSD) and major depression were significantly higher in respondents with IBS than in those without IBS, but that rates of psychiatric diagnoses in treatment-seekers were remarkably similar to non-treatment-seeking persons with IBS. Both treatment-seeking and non-treatment-seeking groups with IBS reported greater levels of functional impairment than non-IBS groups (35, 36). In a re-analysis of the Epidemiologic Catchment Area study (N = 13,537), respondents with panic disorder were nearly five times as likely to have IBS-like symptoms than those with no psychiatric diagnosis (37). The rate of IBS among persons with panic disorder appears to be over twice that of those without panic disorder (37). The temporal relationship between onset of anxiety disorders and IBS is not well studied, although one study found that IBS subjects with anxiety disorders were significantly more likely to report that the anxiety disorder preceded the onset of IBS (39). Up to one-third of IBS patients have PTSD (40), and prior physical/sexual abuse and PTSD are more frequent in women with IBS than in those with equally severe organic gastrointestinal disorders and are predictive of increased vulnerability for the onset or worsening of IBS (41, 42).

Pathophysiology. There are multiple, nonexclusive potential etiologies for IBS, including inherited risk, infection/inflammation, severe traumatic events and psychiatric disorders, all of which may play a role in the onset or exacerbation of existing IBS symptoms (27, 43). Psychosocial stress is increasingly recognized as playing an important role in the onset, persistence and severity of IBS, regardless of presumed etiology (i.e., infections, stress-related, inherited risk) (44, 45). Sensitized central stress circuits may be important mediators of the distorted visceral perception/hyperalgesia and stress reactivity observed in IBS (45, 46), consistent with preclinical and clinical evidence that anxiety and stress can induce or worsen existing visceral hyperalgesia (47, 48).

The neural pathways that process visceral pain signals also regulate the stress response, anxiety, mood and gastrointestinal function (28). A key mediator of these pathways is the neuropeptide corticotropin-releasing factor (CRF). Exposure to prolonged or severe stress, especially in vulnerable individuals, can result in persistent changes in CRF activity with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, extra-hypothalamic and peripheral CRF neural systems that mediate

Figure 3. Rome III Guidelines for the Medical and Psychological Treatment of IBS.



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responses to stress, visceral hypersensitivity, colonic motility, immune response and fear conditioning (28, 38). If stress is sufficiently severe or persistent, the stress response may not be completely terminated, leading to continued CRF hyperactivity and release of stress mediators, including pro-inflammatory cytokines and catecholamines, resulting in sustained excessive inflammatory activity. There is some evidence, although not entirely consistent in direction, for HPA abnormalities and altered pro-inflammatory cytokine activity in IBS (45, 49) and several disorders commonly overlapping with IBS (e.g., fibromyalgia, chronic fatigue, anxiety disorders, including PTSD, and mood disorders) (50). Thus, CRF dysregulation may be one potential neurobiological link among these seemingly unrelated, stress-reactive conditions (45, 46, 50). Antidepressants (51) and cognitive behavioral therapy (CBT) (52), both of which are effective in IBS and in reducing stress reactivity, may reduce circulating pro-inflammatory cytokines or improve immune function in individuals with stress-related disorders.

An emerging neuroimaging literature suggests that, compared to healthy controls, experimental rectal distension is associated with altered reactivity of the anterior cingulate cortex, a brain region im-

plicated in pain perception, anxiety, stress and prior trauma in persons with IBS (53). Recognition of the shared neurobiological underpinnings theoretically linking anxiety and stress may eventually provide the basis for mechanism-based psychotherapeutic and psychopharmacologic treatments for IBS (35).

Treatment. Patients with mild IBS symptoms are generally seen in primary care settings and do not have significant functional impairment or psychological symptoms. Treatment for mild IBS focuses on education about the causes and course of IBS, reassurance of patients' concerns, and restrictions of foods and medications that exacerbate symptoms. Psychological treatments are usually reserved for patients with moderate or severe IBS symptoms and for patients with pain (Fig. 3) (27, 54). A meta-analysis of 32 psychotherapy trials in patients with IBS concluded that, despite the small sample sizes and nonstandardized methods, evidence exists to support the efficacy of psychological treatments in reducing IBS symptom severity compared to control conditions. Cognitive-behavioral therapy, which is the best studied intervention, teaches patients to regulate symptoms of IBS and alter behavior that reinforces or exacerbates symptoms (55, 56). Different psychotherapeutic techniques, including CBT, relaxation training, interpersonal psychotherapy and hypnotherapy, can be used in combination (54).

Antidepressants and anxiolytics are prescribed for patients with IBS for their effects on anxiety and mood as well as for direct analgesic effects. In their summary of the psychopharmacologic treatment literature, Levy et al. (54) suggested that the tricyclic antidepressants (TCAs) are more beneficial than the selective serotonin reuptake inhibitors (SSRIs), possibly due to the central analgesic actions associated with the noradrenergic properties of the TCAs. Nonetheless, the SSRIs are effective for underlying anxiety and depression, and there is emerging evidence that these newer agents are effective for IBS sufferers without psychiatric disorders (57). The benzodiazepines have had a limited place in the treatment of IBS because of concern over potential abuse and withdrawal. However, the limited available literature suggests that benzodiazepine treatment of anxiety is associated with improvement in anxiety and IBS (58, 59). The nonbenzodiazepine anxiolytic agent, buspirone, may have a role in the treatment of IBS, but studies are needed to support its use in this population. As in the treatment of anxiety disorders and depression, psycho-pharmacologic treatment should not be abandoned until the dose and duration of therapy are optimized (54).

ASTHMA

Epidemiology. Asthma is a chronic lung condition characterized by episodic inflammation and small airway constriction that can occur in response to environmental and other triggers. More than 30 million Americans have asthma, of whom 30% are children under the age of 18. Asthma ranges in severity from mild to life-threatening with an intermittent or persistent course. Age-adjusted mortality in 2003 was 1.4/100,000 population, with higher rates in African-Americans, women and the elderly. The prevalence of asthma has increased substantially over the past several decades, making it the most common chronic disease among youth worldwide, though the causes of this increase are unknown. Although death rates are stabilizing or decreasing, possibly due to improvements in medical care, asthma continues to pose a substantial economic burden. The total cost of asthma in 2004 was US$16 billion, US$11.5 billion due to direct healthcare costs (including US$5 billion in prescription drug costs) and US$4.6 billion in indirect costs associated with lost productivity at work and school and mortality (60). While there is no cure for asthma, the vast majority of persons with asthma can live symptom-free and without functional impairment with adequate routine medical care and adherence to asthma treatment. Yet, poor asthma control remains a problem among a substantial proportion of the population. As such, ongoing research aims to identify factors associated with poor asthma control. Recent evidence suggests that mental disorders may play a role in various aspects of onset and course of asthma and are the subject of studies designed to better understand this relationship.

Findings from community-based epidemiologic studies in youth and adults demonstrate a strong and consistent association between asthma and anxiety disorders (61–66). In contrast, available evidence on the link between asthma and depression is somewhat mixed (63, 67–69). The majority of studies to date on the link between mental disorders and asthma have relied on patient self-reports or parental reports of asthma. However, one study that examined the relationship between physician-diagnosed asthma and mental disorders found that anxiety disorders were significantly associated with both nonsevere [OR: 1.51 (1.00–2.32); $P<.05$) and severe asthma [OR: 2.09 (1.30–3.36); $P<.05$] (64), in contrast to the weaker and nonsignificant associations for mood disorders with lifetime nonsevere [OR: 1.44 (0.94–2.19)] or severe asthma [OR: 1.21 (0.75–1.98)]. Of note, nonsevere asthma (past 4 weeks) was significantly associated

with increased likelihood of any affective disorder [OR: 2.42 (1.03–5.72); $P<.05$], while bipolar disorder was very strongly associated with lifetime severe asthma [OR: 5.64 (1.95–16.35); $P<.05$]. Panic disorder, panic attacks, GAD and phobias appear to be the anxiety disorders most strongly associated with asthma (64). Another study compared 769 youth with physician-diagnosed asthma to 582 age-matched controls and found an approximately twofold increase in the prevalence of one or more anxiety or depressive disorders, with greater rates of anxiety compared to mood disorders, and a significant correlation between anxiety sensitivity and asthma severity (70).

Clinical studies assessing the rates of mental disorders in patients with asthma, although largely limited to relatively small sample sizes and self-reported asthma status, have consistently found high rates of anxiety disorders in children, adolescents and adults (Table 1). Few studies have been able to control for potentially confounding or mediating factors in the links between asthma and mental disorders, such as smoking or use of asthma medications (78). One study found that adolescents with a history of life-threatening asthma attacks are more likely to have symptoms of PTSD, which was directly related to the life-threatening experiences associated with asthma, compared to less severely ill patients or healthy controls (73). Another study examined the relationship between PTSD symptoms and asthma among male twins and found the association was not explained by common genetic factors (79).

One study of adolescents with asthma found that, after controlling for severity of asthma, the presence of an anxiety or depressive disorder was associated with an increased number of days with asthma symptoms in the past 2 weeks (mean: 5.4 days) compared to adolescents without these psychiatric diagnoses (mean: 3.5 days; $P<.001$), and that the number of anxiety-depressive symptoms was strongly associated with higher levels of asthma symptoms ($P < .001$) (80). The presence of anxiety disorders or other psychiatric diagnoses did not correlate with asthma severity in two studies of adult patients in asthma clinics (76, 81) or one large, primary care-based study (70). Findings for depression are somewhat equivocal, with some studies suggesting that depression is prevalent (74–77).

Nonetheless, poor asthma control, increased functional impairment, decreased quality of life, and utilization and cost of healthcare resources have been shown to be strongly associated with anxiety and mood disorders among persons with asthma (80, 82). Patients with comorbid asthma plus anxiety or mood disorders are more likely to use bronchodilators in the previous week ($P<.02$), have lower scores on asthma-control rating scales ($P<.001$) (e.g., nocturnal waking, activity limitation, wheezing, increased use of asthma medications, pulmonary function tests) (81) and lower quality of life as measured by activity limitation, asthma symptoms, environmental stimuli and emotional distress ($P<.001$) (81). Patients with asthma and a comorbid psychiatric diagnosis, including an anxiety disorder, are 4.9 times more likely to use an emergency room and 3.8 times more likely to be hospitalized (76), but few patients are treated for their mental disorder (81). Despite these robust data, comorbid anxiety and depressive disorders are only accurately diagnosed in approximately 40% of asthmatic patients in primary care (83). There are also a number of clinical and community-based studies that have found links between asthma and suicidal ideation (63, 84), suicide attempts and completed suicide (84). As suicide behavior has also been linked with anxiety disorders (85), further investigation into the risk of suicide behavior among individuals with asthma and anxiety disorders is needed.

Smoking is a particularly problematic health behavior in youth with asthma, leading to higher symptom burden and treatment resistance. *DSM-IV* anxiety/depressive disorders in a sample of adolescent patients with asthma in one healthcare system have been found to be present in 14.5% of nonsmokers, 19.8% of susceptible nonsmokers and 37.8% of smokers. After controlling for several covariates, youth with comorbid anxiety and depressive disorders and asthma had a two-fold increased likelihood of smoking compared to those without. Youth with asthma who smoked reported significantly more asthma symptoms, reduced functioning due to asthma, less use of controller medication and more use of rescue medications compared to those who did not smoke (86).

Pathophysiology. The mechanisms underlying the association between asthma and anxiety disorders are not known. It may be that there is a causal link between asthma and anxiety disorders; yet, increasingly, evidence supports the possibility that one or more outside factors, either environmental or genetic, may influence the risk of both (87). One longitudinal study that tracked children from ages 3 through 18 and assessed temperamental and illness factors found that a history of self-reported poor respiratory health at age 15 predicted panic disorder/agoraphobia at ages 18 to 21 compared to participants without a history of respiratory problems (88). Another longitudinal, community-based study followed 591 young adults for 20 years, beginning at age 19, and examined the relationship

Table 1. Anxiety Disorders in Clinical Samples of Patients With Asthma

Reference	Clinical population	Control population	Findings
Bussing et al, 1996 (71)	37 asthmatic children	31 HC	Anxiety disorder prevalence: Asthmatics—43% HC—19% ($P < .04$)
Vila et al, 1999 (72)	93 asthmatic children	93 children with Type 1 diabetes	Anxiety symptoms more common in asthmatics vs diabetics ($P < .05$) Anxiety disorder prevalence in asthmatics: GAD 26% Separation anxiety disorder 14% Social phobia 10% Panic disorder or agoraphobia 1%
Goodwin et al, 2005 (89)	74 inner-city children with asthma	No control group	4-week prevalence: Any psychiatric disorder—22% Panic disorder—15% Separation anxiety disorder—8% Agoraphobia—5% GAD—4% Major depression—3%
Kean et al, 2006 (73)	49 adolescents with life-threatening asthma attack	71 asthma controls 80 HC	PTSD prevalence: Life-threatening attack group—20% Asthma controls—11% HC—8%
Nascimento et al, 2002 (74)	86 adults with asthma	No control group	Any psychiatric disorder—62% ≥ 1 anxiety disorder—52% Panic disorder±agoraphobia—14% Agoraphobia—27% GAD—24% Social phobia—9% Major depression—34%
Goodwin et al. 2003 (63)	998 adults in inner-city primary care clinic were screened for psychiatric disorders	No control group	OR for anxiety disorders in asthmatic adults: Panic attack—1.7 Suicidal ideation—1.9 Major depression, GAD, substance abuse—NS
Lavoie et al. 2006 (75)	504 adults with asthma	No control group	≥ 1 psychiatric disorder—31% Any anxiety disorder—23% Panic disorder—11% GAD—5% Social phobia—4% Any mood disorder—20%
Feldman et al, 2005 (76)	85 inner-city adults with asthma	No control group	≥ 1 psychiatric disorder—48% Anxiety disorder—45% Mood disorder—51%
Valença et al, 2006 (77)	62 adults with asthma	No control group	≥ 1 psychiatric disorder—44% GAD—21% Panic disorder/agoraphobia—13% Agoraphobia—5% OCD—3% Social phobia—3% Major depression—24%

HC = healthy controls; NS = not significant; OCD = obsessive-compulsive disorder.

between asthma and panic disorder (65). A bidirectional relationship was observed in which asthma predicted onset of later panic disorder, and panic disorder was antecedent to active asthma. Childhood anxiety, parental smoking and a family history of allergy have been suggested as possible shared etiologic factors in both asthma (65) and panic disorder (89). Environmental factors including low socioeconomic status, exposure to pollutants, environmental stressors and childhood adversity may predispose youth to both asthma and anxiety and depressive disorders (78). Potential factors that could play a role in causal mechanisms for the relationship between asthma and panic disorder include increased levels of anxiety associated with fear of the next asthma attack, the anxiogenic properties of asthma medications, hyperventilation associated with panic attacks, and poor adherence to asthma treatment in patients with psychiatric diagnoses (65, 78).

Treatment. Data demonstrating the relationship between asthma and anxiety disorders suggest that psychopharmacological and/or psychosocial interventions might improve asthma control. Yet, there is a remarkable paucity of studies that address this issue. One recently published report from the Cochrane Collaboration reviewed the effectiveness of psychological treatment for adults with asthma (90). A total of 14 randomized, controlled studies of 617 subjects were reviewed. Most studies were small, and methodologies varied widely. However, data pooling suggests future avenues of research. Relaxation therapy reduced the need for rescue bronchodilators in two studies, and CBT improved quality of life in two other studies. Spirometry measures improved following bio-feedback in two studies, but not with relaxation therapy in four studies. Overall, the authors concluded that it is not possible to assess the role of psychotherapeutic interventions in patients with asthma because of the lack of an adequate database (90). Larger, more rigorously controlled trials in patients with comorbid asthma and anxiety, including trials of pharmacotherapy, are needed before the role of mental health interventions in the treatment of asthma can be determined.

CARDIOVASCULAR DISEASE

Epidemiology. Cardiovascular disease (CVD) has been the leading cause of mortality in the USA for over 100 years, with one in three American adults now dying from one or more types of CVD, accounting for one out of every 2.8 deaths in 2004 and more deaths each year than cancer, chronic lung disease, accidents and diabetes mellitus combined. The estimated total cost of CVD in the USA for the year 2007 was US$431.8 billion (91). Hypertension, diabetes mellitus, hypercholesterolemia, elevated body mass index, unhealthy diet, sedentary lifestyle and smoking are key modifiable risk factors for CVD (91). Chronic stress, depression and anxiety also increase the risk of developing CVD and complicate recovery following acute cardiac events (92). Much attention has been paid to depression as both a risk factor for incident CVD and a predictor of poor outcome in cardiac patients. Depression is strongly associated with increased rates of serious cardiac events, all-cause mortality and cardiac mortality following myocardial infarction (MI), unstable angina and coronary artery bypass surgery (7, 93).

Although it is less well studied than depression, emerging data suggest that anxiety is also an important risk factor for both incidence and progression of CVD. Indeed, one comprehensive literature review concluded that there is considerable covariation between depression, anxiety and anger/hostility as risk factors for CVD (94). Denollet et al. (95) found that anxiety symptoms are core features of post-MI depression and concluded that screening for anxiety may be useful in identifying patients at risk for depression following MI. Studies in several cohorts suggest that the general distress shared across depression, anxiety and anger/hostility is a significant risk factor for incident CVD (96–98). However, additional analyses in one study also showed that anxiety symptoms were associated with increased cardiac risk beyond effects of general distress, suggesting the utility of considering anxiety separately from depression and other psychosocial risk factors (96). Depression and anxiety are also as strongly associated with cardiac symptoms and functional impairment in patients with CVD as are physiological measures of cardiac impairment (i.e., number of vessels with $\geq$50% occlusion or decreased ejection fraction) (4, 99).

The findings of community-based population studies demonstrate that anxiety symptoms (e.g., worry, tension, feeling restless, difficulty making decisions) and anxiety disorders are associated with increased risk for incident CVD, such as MI, sudden cardiac death, angina pectoris, and hypertension (100–105). A recent overview of the literature summarizing findings from 11 prospective studies examining the association between chronic anxiety and incident CVD reported consistently elevated risk associated with anxiety with relative risks ranging from 1.5 to 8 (106). Especially strong data exist for phobic anxiety (100, 107). One study also recently reported increased risk of developing CVD associated with higher levels of PTSD symptoms (108).

Anxiety disorders are also associated with adverse cardiac outcomes. In a recent study of 3369 generally healthy community-dwelling postmenopausal women, a history of recent panic attacks was associated with both coronary heart disease [HR: 4.20 (1.76–9.99)] and the combined end point of coronary heart disease or stroke [HR: 3.08 (1.60–5.94)] after controlling for multiple potential confounders (109). General measures of anxiety and psychological distress were associated with increased rates of 5-year cardiac-related mortality in patients with MI (110). Anxiety in post-MI patients was associated with adverse cardiac events, cardiovascular death (111–113) and increased rates of cardiac rehospitalization and outpatient visits to cardiologists (113). Interestingly, one study of 318 male survivors of a first MI showed that anxiety (HR: 3.01; $P = .019$) was more strongly associated with subsequent cardiac events than depression (HR: 2.32; $P = .039$) or hostility (HR: 1.03; $P = .950$) (113). Studies on cardiac outcomes in patient populations find a particularly strong effect associated with panic disorder (114, 115). Other work has suggested that the trauma of having an MI may cause PTSD, which then adversely impacts survival (116). For example, PTSD was considered in a small study of post-MI patients and found to be associated with cardiac rehospitalization and poor adherence to aspirin prophylaxis regimens (117).

Pathophysiology. Rozanski and Kubzansky (118) proposed a number of pathways by which anxiety may influence CVD. Effects of anxiety may accumulate over time leading to cardiovascular damage, setting the stage for atherosclerosis and coronary artery disease (93, 119). Thus, similar to chronic stress and other negative emotions, anxiety may lead to excess activation of the HPA axis and sympathetic nervous system. Increases in sympathetic nervous system activity and release of plasma catecholamines may damage the vascular endothelium and also lead to the release of fatty acids above levels needed for metabolic requirements. Excess HPA activation may lead to increased inflammation (120). Anxiety is also hypothesized to increase cardiovascular reactivity to stress leading to greater strain on the heart as a result of increased resting heart rate, baroreflex dysfunction and variability in ventricular repolarization (111, 114, 118, 121). Moreover, anxiety has been linked to altered cardiovascular autonomic control with studies demonstrating reduced heart rate variability among individuals with high levels of anxiety (122). Taken together, the effects of sympathetic nervous system and HPA axis hyperactivity along with altered sympathovagal control of the heart increase the risk of incident CVD and lower the threshold for cardiac ischemia, arrhythmias and sudden cardiac death (93). Anxiety may also influence CVD indirectly, as anxiety is associated with poor health-related behaviors including smoking and excess alcohol consumption, which in turn increase the risk of CVD (122). Acute effects of anxiety are also possible. There is some evidence to suggest that extreme emotional states, like an acute anxiety episode, may actually trigger an MI (123, 124).

Treatment. Despite the strong association between depression and CVD, many studies designed to assess the effect of psychosocial interventions or antidepressant medications on depression and CVD outcomes failed to show a significant difference between active treatment and placebo on CVD outcomes (7, 92, 125). Given that many patients have had long-term exposure to depressive symptoms and most interventions occur after disease processes are initiated (126), it may be that these interventions have not been administered during the appropriate etiologic window (107). There are very few studies of anxiety treatment in cardiac patients, although issues of exposure duration and appropriate timeframes for interventions are also likely to be relevant for treating anxiety. In a cohort of patients with PTSD who were recovering from an MI, the combination of trauma-focused CBT and education about treatment adherence resulted in improved PTSD symptoms and adherence to aspirin therapy (127). Fluoxetine treatment in patients with mild depression following their first MI resulted in significant improvements in measures of hostility (128). Case-control studies also suggest that the use of SSRIs may be associated with decreased rates of mortality in patients with depression and CVD (129). Clearly, knowledge about the effects of anxiety treatment on CVD risk and outcome is in its infancy and further studies are needed.

CANCER

Epidemiology. Cancer is a common and frequently deadly diagnosis despite remarkable advances in the past 40 years. During 2006, 1.4 million new cases were diagnosed in the USA, and more than 560,000 Americans died from cancer. However, continued improvements in the prevention, diagnosis and treatment of cancer are at work to improve survival. The 5-year survival rates for all cancers increased from 50% in the 1970s to 65% between 1995 and 2001, and deaths from colon, rectum, stomach, prostate, breast and lung (men only) cancers are declining. As of 2002, there were 10.1 million Americans who had survived cancer or who were undergoing treatment (130).

Conventional wisdom and clinical experience dictate that cancer is a source of situational anxiety, causing psychological distress, fear, dread and sadness. However, apart from these normative emotional responses, cancer is associated with high rates of anxiety and depressive disorders (Table 2), though the latter have been much more extensively studied. Prevalence rates for anxiety and depressive disorders are generally in the range of 10% to 30%, with rates of various anxiety disorders equivalent to or greater than those of depression in many cases. However, rates vary depending on the type and stage of cancer, treatment regimens, time since diagnosis, gender and methods used to diagnose psychiatric illness. Specific phobias, panic disorder with or without agoraphobia, and GAD are commonly reported anxiety disorders in this population, as are adjustment disorder with anxious mood or depressed/anxious mood and PTSD.

Pathophysiology. Factors that influence distress include endocrine or metabolic changes associated with cancer or its treatment, cancer prognosis, individual coping style and social support systems. Some medications commonly used in the treatment of cancer are associated with symptoms of anxiety (e.g., glucocorticoids) or depression (e.g., interferon, glucocorticoids) (140). Variables independently associated with anxiety disorders in one set of patients with advanced cancer who were receiving palliative care were global health status, emotional/cognitive/social functioning, fatigue, nausea and vomiting (136). In another study of patients with mixed types of cancer, anxiety disorders correlated with female sex and poor social support systems (131). Dahl et al. (137) studied 1408 long-term survivors of testicular cancer and found that anxiety disorders correlated with young age at follow-up, relapse anxiety, psychiatric treatment, peripheral neuropathy, alcohol abuse, economic problems and sexual dysfunction. Anxiety and depression among women with a first recurrence of breast cancer correlated with current toxic chemotherapy treatment (i.e., doxorubicin/cyclophosphamide), history of major depression, and feelings of helplessness or hopelessness (133).

Treatment. Even though psychiatric illness in the context of cancer can increase somatic symptom burden and impair functioning and quality of life, negatively affect adherence to cancer treatment regimens and result in poor outcomes (131, 137, 139, 141), they should not be considered untreatable. Attention to patients' mental health status is an essential part of cancer treatment. However, anxiety and mood disorders in patients with cancer are often untreated or inadequately treated because of time or training constraints or because oncologists do not ask about psychological distress or endorse its importance. Patients contribute to under-treatment by trivializing symptoms of fear, anxious preoccupation, or helplessness/hopelessness, or because they feel that these symptoms are an expected part of their diagnosis and treatment (142, 143). Many physicians prescribe short-term benzodiazepines to help patients cope with the situational anxiety associated with surgery, chemotherapy or radiation (144). There are relatively few placebo-controlled drug trials in patients with depression and cancer (12, 145–151) and virtually none focusing on anxiety disorders. Nonetheless, the traditional antidepressants [e.g., TCAs, SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs)] possess anxiolytic properties, and some studies demonstrated improvement in anxiety symptoms in patients with a primary diagnosis of depression (144, 148). This provides some degree of support for their use in patients with cancer and comorbid anxiety disorders (144, 152).

In contrast, a large body of literature, as summarized in several reviews (153–156), evaluates the use of psychological interventions in patients with cancer. Cognitively based psychotherapy alone or in conjunction with skills training and relaxation therapy has been shown in some controlled trials to improve quality of life, coping skills, symptoms of anxiety, and general distress (141, 156, 157). One rigorously conducted systematic review of 329 intervention trials concluded that extant data are insufficient to support strong recommendations for the use of psychological interventions for anxiety in patients with cancer. Few of these trials examined patients with specific anxiety disorders, such as panic disorder or GAD. The overwhelming number of trials examined patients with adjustment disorders, where placebo response rates are likely very high. However, CBT, therapist-delivered interventions, self-practice techniques, communication/expression training and guided imagery/visualization strategies warrant further study (154). Psychosocial interventions lasting 3 months or longer may be more effective than short-term treatment strategies (156, 157), and the combination of different behavioral treatments may be useful in relieving symptoms of anxiety (155). However, findings of recent studies show that psychological treatments do not actually affect survival time in cancer patients (158, 159).

CHRONIC PAIN

Epidemiology. Contemporary models describe pain as a complex perceptual experience that is determined by sensory as well as psychological (i.e.,

Table 2. Anxiety Disorders Diagnosed Using Structured or Semistructured Interviews or Standardized Self-Report Instruments in Patients With Cancer

Reference	Clinical population	Diagnostic instrument	Findings
Stark et al, 2002 (131)	178 adults with lymphoma, renal cell carcinoma, malignant melanoma or plasma cell dyscrasia	SCAN and HAD-A	Current prevalence: Any anxiety disorder—18% Phobia—14% Panic disorder—9% GAD—8% Adjustment disorder w/anxious mood—0.6% Depression—15%
Härter et al, 2001 (132)	200 adults with cancer	CIDI	12-month prevalence: Specific phobia—12% Panic disorder/agoraphobia—6% Social phobia—2% PTSD—2% GAD—1% MDD—5%
Okamura et al, 2005 (133)	50 women with first breast cancer recurrence	SCID	Current prevalence: Adjustment disorder w/anxious mood—2% Adjustment disorder w/depressed mood—8% Adjustment disorder w/mixed mood—10% PTSD—2% MDD—2%
Kissane et al, 2004 (134)	Breast cancer: 303 early-stage 200 advanced	MILP	Current prevalence—early stage vs advanced: Mood disorders—37% vs 31% Anxiety disorders—9% vs 6% Adjustment disorder w/depressed mood—25% vs 23% Adjustment disorder w/anxious mood—4% vs 4%
Kangas et al, 2005 (135)	82 adults with head/neck or lung cancer	SCID; CAPS	Current prevalence 6 months post-diagnosis: Anxiety disorder—33% MDD—22% PTSD—22%
Smith et al, 2003 (136)	68 adults with advanced cancer	HADS	Current prevalence: Anxiety disorder—25% MDD—22%
Dahl et al, 2005 (137)	1408 long-term testicular cancer survivors	HADS	Current prevalence vs HC: Anxiety disorders—19% vs. 14% ($P < .001$) MDD—10% vs. 10% (NS)
Roth et al, 2006 (138)	367 men with prostate cancer	MAX-PC; GAD-Q	Current prevalence: High degree of anxiety—11% GAD—13%
Tagay et al, 2005 (139)	130 patients with thyroid cancer hospitalized for radioiodine therapy	HADS	Current prevalence: Anxiety disorder—22% MDD—9%

SCAN = Schedules for Clinical Assessment in Neuropsychiatry; HAD-A = Hospital Anxiety and Depression Scale for Anxiety; MDD = major depressive disorder; CIDI = Composite International Diagnostic Interview; SCID = Structured Clinical Interview for DSM-III-R; MILP = Monash Interview for Liaison Psychiatry; CAPS = Clinician Administered PTSD Scale; MAX-PC = Memorial Anxiety Scale for Prostate Cancer; GAD-Q = Generalized Anxiety Disorder Questionnaire.

cognition, emotion, behavior) and social influences. Pain is an essential adaptive process that enables one to curtail further physical harm and permit recuperation. However, for some persons pain becomes chronic, losing its adaptive qualities. The National Comorbidity Survey Part II estimates that approximately 7% of the general population in the USA has experienced chronic pain in the past 12 months (160), at an annual cost of about US $100 billion (161). However, because rates of chronic pain vary depending on the population, definition of chronicity (e.g., pain lasting ≥3 months vs. ≥6 months) and type of pain studied, rates upwards of 20% to 30% have been reported in recently published community-based population studies (162–165). Chronic pain is associated with disability, physical deconditioning, excessive utilization of healthcare resources and emotional distress (163–166). The spectrum of distress seen in chronic pain includes depression, anger, guilt, social withdrawal, fear and anxiety (160, 167, 168).

Depression is strongly and consistently associated with chronic pain in both clinical and community-based samples (160, 162, 169). Fear and anxiety are also significant contributors to the experience of chronic pain, but until relatively recently the anxiety component of psychiatric morbidity in chronic pain received little attention. Means-Christensen et al. (170) found that primary care patients with somatic pain-related complaints (e.g., headache, stomach pain, muscle pain) had high rates not only of depressive symptoms, but also of anxiety symptoms (notably, panic and GAD symptoms). High rates of anxiety disorders have been observed in patients with different pain syndromes, including chronic spinal pain (11% to 27%) (165, 167), rheumatoid arthritis (25% to 35%) (160, 171), fibromyalgia (60%) (171) and migraine (172). In patients seeking treatment for chronic pain (Table 3), the most prevalent past 12-month anxiety disorders are phobic disorders (9% to 13%), GAD (0% to 13.4%) and panic disorder (2.1% to 7.2%). Particularly high rates of panic disorder and phobias are found in patients with chest pain and negative cardiac workups (178, 179). The most prevalent past 12-month anxiety disorders reported in community samples with chronic pain (Table 3) are specific phobia (12.5% to 15.7%), social anxiety disorder (8.3 to 11.8%) and PTSD (7.3 to 10.7%). These rates are higher than 12-month prevalence rates in the general US population (180). Pooled data from a recent survey of 85,088 community-dwelling adults from 17 countries indicate that persons with back or neck pain are two to three times more likely to have had past 12-month panic disorder/agoraphobia, social anxiety disorder, GAD or PTSD compared to those without (181).

Data from the NCS (160) and the Midlife Development in the United States (MIDUS) survey (173) demonstrated that compared with the general population, rates of depression and anxiety disorders were significantly higher in persons with chronic pain. Somewhat surprisingly, they also found that the association with chronic pain was stronger for anxiety disorders than for depression. For example, among persons with chronic pain in the NCS, the 12-month prevalence of any anxiety disorder was 35.1% compared to 21.7% for any mood disorder (160). When chronic pain in persons with rheumatoid arthritis, migraine or back pain was assessed in MIDUS, the strength of association was consistently larger for panic attacks (OR: 2.09–3.58) and GAD (OR: 2.17–3.86) than for depression (OR: 1.48–2.84) (173).

There is some evidence to suggest that anxiety disorders precede the onset of pain. In a sample of 146 injured workers with chronic musculoskeletal pain, Asmundson et al. (174) found that, in all but one case, the anxiety disorder preceded the pain complaint. Likewise, Kinney et al. (176) found that among 90 patients with chronic low back pain, 23% had a preexisting anxiety disorder. Additional research on temporal sequence and course of anxiety disorders in chronic pain is needed.

Pathophysiology. Pain and anxiety are both associated with physiological arousal. Bodily changes stemming from arousal (see Sections on IBS and CVD) serve a protective function by promoting escape and withdrawal. However, if prolonged, arousal can have detrimental physical effects. Physical injury and stressful or uncontrollable experiences also initiate other complex neural and hormonal processes (e.g., release of cytokines, β-endorphin, 5-HT-moduline) that, while designed to promote tissue healing and reinstate homeostasis, can be destructive to various body systems (e.g., muscle, bone, neural tissue) when prolonged (182, 183). Illustrating these effects, Sareen et al. (24) found strong associations between anxiety disorders, particularly PTSD, and medical illnesses characterized by pain (e.g., multiple sclerosis, ulcer, hernia, arthritis, rheumatism).

Persons with anxiety sensitivity (i.e., fear of anxiety symptoms based on the belief they may have harmful consequences) or injury/illness sensitivity or who have preexisting anxiety disorders may respond to chronic pain with catastrophic misinterpretation of the meaning of the pain, physiologic arousal, fear of recurrent pain, fear of movement or re-injury, avoidance of pain, and hyper-vigilance (184). Such maladaptive responses may lead to a

Table 3. Twelve-Month Prevalence of Anxiety Disorders in Persons With Pain in Community and Treatment-Seeking Samples[a]

Reference	Clinical population	Diagnostic instrument	Findings
McWilliams et al, 2003 (160)	5877 adults (NCS)	DSM-III-R	Chronic pain (arthritis: $n = 382$) Any anxiety disorder—35.1% PD—6.5% AWHPD—8.4% SP—11.8% SiP—15.7% PTSD—10.7% GAD—7.3%
McWilliams et al, 2004 (173)	3032 adults (MIDUS)	DSM-III-R	Arthritis ($n = 588$) Panic attacks—11.2% GAD—5.6% Migraine ($n = 340$) Panic attacks—17.4% GAD—9.1% Back pain ($n = 614$) Panic attacks—13.0% GAD—6.2%
Von Korff et al, 2005 (165)	5692 adults (NCS-R)	DSM-IV	Chronic spinal pain ($n = 2397$) Any anxiety disorder—26.5% PD—4.8% AWHPD—1.3% SP—8.3% SiP—12.5% PTSD—7.3% GAD—6.4%
Asmundson et al, 1996 (174)	200 treatment-seeking patients with chronic musculoskeletal pain	DSM-IV	Any anxiety disorder—17.0% PD—2.1% SP—11.0% SiP—2.7% OCD—0% PTSD—2.1% GAD—0%
Polatin et al, 1993 (175)	200 treatment-seeking patients with chronic low back pain	DSM-III-R	Any anxiety disorder—17.0% PD—3.0% Phobic disorders—9.0% OCD—2.0% PTSD—1.0% GAD—2.0%
Kinney et al, 1993 (176)	90 treatment-seeking patients with chronic back pain	DSM-III-R	Any anxiety disorder—25.0% PD—3.0% Phobic disorders—13.0% OCD—3.0% PTSD—2.0% GAD—4.0%
Atkinson et al, 1991 (177)	97 treatment-seeking patients with chronic low back pain	DSM-III	Any anxiety disorder—28.8% GAD—13.4% PD—7.2% OCD—8.2%

NCS = National Comorbidity Survey Part II; PD = Panic Disorder; AWHPD = Agoraphobia Without History of Panic Disorder; SP = Social Phobia (also called social anxiety disorder); SiP = Simple Phobia.
[a] Not all studies evaluated all anxiety disorders.

self-perpetuating cycle that promotes and maintains activity limitations, disability, pain, and additional fear and anxiety (168, 185–187).

Treatment. There is a relatively large literature suggesting that CBT in patients with chronic pain may improve pain levels, coping skills and functional abilities (188–190). Consideration of chronic pain and anxiety in the context of a cognitive-behavioral fear-avoidance phenomenon has implications for the design of therapeutic interventions. Graded exposure in vivo is one cognitive-behavioral technique that has been shown in single case-controlled (191, 192) and randomized controlled (193) studies to reduce fear and pain intensity and improve physical activity in patients with chronic pain. These treatments are promising for those with co-occurring chronic pain and anxiety disorders, although it remains to be determined what specific effect they will have on the anxiety disorder symptoms. There is also a large literature suggesting that antidepressants have beneficial effects in treating chronic pain, even in patients without comorbid depression. The TCAs and SNRIs appear to be more effective than the SSRIs in treating neuropathic pain (194).

CRITICAL SUMMARY

The studies reviewed here have numerous methodologic limitations. Some epidemiological studies failed to use structured interviews or standardized rating scales, others did not account for medication effects and some used too narrow a sampling frame. Despite these limitations, each of which would presumably weaken any anxiety-medical condition association, the wealth of evidence clearly shows that anxiety is associated with an increased prevalence of these five broad categories of medical conditions. The extant data cannot tell us at this point the magnitude of these associations, nor how this association compares with depression, though the NCS-R data suggest that the association of anxiety with a number of medical illnesses is likely to be comparable to that of depression. Our understanding of pathophysiological substrates accounting for associations with these five medical conditions is largely inferential and mostly based on preclinical data or knowledge of human pathophysiology. Although more specific understanding is limited by the small number of available human studies, neuroimaging studies are providing a useful window into CNS substrates that may mediate links between anxiety and medical illness. Understanding of pathophysiology is much more advanced for the association between anxiety and some medical conditions (e.g., IBS, CVD) and poorly developed for others (e.g., cancer). Treatment studies with either an anxiety or depressive intervention have focused much more on some medical conditions (e.g., CVD, IBS) than on others (e.g., asthma, cancer), and the majority of treatment studies have targeted depression, with few if any treating anxiety. However, for some conditions (e.g., CVD), treatment may have an impact on behavioral and pathophysiological processes, as well as on some clinically important outcomes of the medical condition such as quality of life. Thus, it is not clear whether anxiety treatments can have an impact on the underlying medical condition, and if so, to what degree.

RESEARCH PRIORITIES

Conference participants outlined research needs to advance understanding of anxiety disorders and comorbid medical illness and improve patient care. No attempt was made at the conference to rank order these priorities, but all were felt to be of substantial importance to the field.

EPIDEMIOLOGY

- Include anxiety indicators, especially those fulfilling *DSM-IV* diagnostic criteria, in large population-based health surveys.
- Collect data on the economic impact of anxiety disorders in medically ill patients that are important to both the medical/scientific community and policy makers.
- Evaluate temporal onset in the relationship between anxiety disorders and medical illness by longitudinally following a cohort of children at risk of developing a chronic medical condition, such as asthma, and documenting which comes first.
- Conduct observational studies to identify the medical or psychiatric comorbidities that are most strongly associated with quality of life (critical new work in this area has recently been published (195)) and medical prognosis. The findings would aid primary care physicians to focus on baseline symptoms that most urgently require attention.

PATHOPHYSIOLOGY

- Conduct studies that further examine the vicious cycle of central activation-somatization by identifying brain regions, neural circuits and neurotransmitter systems involved in the visceral hyperalgesia, hypervigilance and in-

creased smooth muscle tone associated with anxiety disorders.
- Examine potential biological mechanisms of the association between anxiety disorders and medical conditions, while also adjusting for and examining the role of potential confounding/mediating factors.

TREATMENT

- Develop generalized CBT interventions for primary care patients and measure the effect of improving fear, avoidance, somatization and other elements of negative affect on function, clinical outcomes of medical illness, and utilization patterns.
- Assess the utility of novel delivery methods for broad-based (i.e., targeting anxiety, depressive and related somatic symptoms) CBT, such as telephone- and web-based CBT or stepped collaborative-care approaches to treatment delivery.
- Study the effectiveness of CBT approaches in the top 10% of healthcare utilizers in a given healthcare system using a collaborative care model.
- Identify medically ill patients needing treatment by stratifying patients with *DSM-IV* anxiety disorders according to severity of emotional distress and randomizing each group to evidence-based treatment vs. usual care.
- Integrate successful components of collaborative care treatment models, such as brief evidence-based CBT combined with pharmacologic interventions in patients with panic disorder (196, 197), to address symptoms of anxiety and depression and improve functional and medical outcomes in primary care patients.
- Create a demonstration project that measures the clinical and economic outcomes when financial incentives are provided to primary care physicians for screening high utilizers of healthcare resources and using best-practices treatment guidelines.

CONCLUSIONS

The clinical importance of the bidirectional relationship between psychiatric and physical illness is beginning to be appreciated by the medical, clinical and research communities. Extant studies primarily focus on comorbid depression. However, emerging evidence suggests that anxiety and the anxiety disorders, which have received relatively less attention, may be as important as depression. In addition, many patients have comorbid anxiety and depressive symptoms, which are associated with increased severity of psychiatric illness, additive functional impairment and medical costs. Much like depression, anxiety disorders and subsyndromal anxiety amplify symptoms of some medical illnesses and appear to worsen clinical outcomes. The considerable overlap of anxiety, depression and chronic stress states suggests that clinicians should broaden their search for mental health problems beyond depressive symptoms in their patients with chronic medical illnesses to include symptoms of anxiety.

Increased funding for research programs that address basic science issues, epidemiology, treatment and healthcare delivery systems is needed. Development of effective messages about the role of anxiety and anxiety disorders in common medical illnesses will facilitate educational approaches designed to increase awareness among patients, physicians, healthcare systems and policy makers. Inclusion of data about the role of mental disorders in comorbid medical illnesses into medical school, residency and continuing medical education curricula will improve awareness in the medical community. Primary care physicians who frequently see patients with chronic medical illness are in an excellent position to assess patients' mental state and begin appropriate interventions. However, there is a remarkable lack of data from rigorously designed clinical trials to guide treatment decisions in this population. In addition, stigma about mental health issues can color patients' acceptance of a psychiatric diagnosis. Patients who understand that a medical illness may be the result of a variety of risk factors that include mental health issues and brain function and who are engaged participants in their care are likely to have better clinical outcomes. Although much work remains to be done, the stage has been set to explore the relationship between anxiety disorders and medical illness with the aim of developing and subsequently promoting evidence-based treatment strategies to improve prognosis and quality of life in patients with chronic medical illnesses.

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