Generalized Anxiety Disorder and Medical Illness

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Patients with generalized anxiety disorder (GAD) often have multiple medical comorbidities. The adrenal system and genetic and environmental factors are intermediaries between anxiety and medical illnesses such as chronic pain conditions and gastrointestinal, cardiovascular, endocrine, and respiratory disorders. Medical disorders associated with anxiety include migraine, rheumatoid arthritis, peptic ulcer disease, irritable bowel syndrome, coronary heart disease, hyperthyroidism, diabetes, asthma, and chronic obstructive pulmonary disorder. Compared to people with pain conditions without GAD, individuals with pain conditions and GAD experience and register pain differently; they also have increased awareness of symptoms. Comorbid medical illnesses may influence treatment choice for GAD. Treatment of anxiety in young patients with GAD needs to be long-term to decrease vulnerability to medical conditions. *(J Clin Psychiatry 2009;70[suppl 2]:20–24)*

Patients with generalized anxiety disorder (GAD) often have medical comorbidities. After controlling for sex, comorbid substance abuse or dependence, and depression, Härter and colleagues[1] found that subjects with lifetime GAD or panic disorder had higher rates of medical illness than individuals without anxiety. Rates of migraine, gastrointestinal problems, cardiac disorders, and respiratory disorders were especially high among those with anxiety. Genetic and environmental factors, as well as the adrenal system, are thought to intermediate between anxiety and medical illnesses.

INTERMEDIARIES BETWEEN ANXIETY AND MEDICAL CONDITIONS

Genetic and Environmental Factors

Both genetic and environmental factors contribute to the development of GAD, as Stein[2] and Simon[3] discuss elsewhere in this supplement. Genetic factors create vulnerability to psychiatric pathology, and these factors interplay with neurodevelopment to result in the phenotype, which is malleable.[4] Adverse experiences or stress may be more traumatic to someone with a genetic vulnerability to pathology, although the development of pathology can be modulated by social support or deprivation. Stress, which is stimulation that is perceived as either excessive or threatening, affects both the mental and the physical states.[5]

The Adrenal System

The chronic stress response that accompanies anxiety disorders can contribute over time to vulnerability to chronic medical conditions.[6] The thalamus, amygdala, hippocampus, hypothalamus, and prefrontal cortex are thought to comprise the primary fear assessment network.[7] This network is hypothesized to work as shown in Figure 1 and is summarized here.[6]

When a sensory or visceral stimulus enters the thalamus, information is relayed to the amygdala and other brain structures that are associated with the anxiety response.[7] The amygdala mediates arousal and fear and has reciprocal connections with the prefrontal cortex, hippocampus, and hypothalamus, through which it activates the hypothalamic-pituitary-adrenal (HPA) axis.

The amygdala assesses the threat[8] by accessing the individual's memories through the hippocampus.[9] When a threat is detected, the hypothalamus initiates neuroendocrine and autonomic responses. Corticotropin-releasing hormone triggers the hypothalamic release of adrenocorticotropic hormone into the bloodstream, which stimulates the adrenal cortex to produce the glucocorticoid, cortisol, and stimulates the adrenal medulla and sympathetic nerves to produce epinephrine and norepinephrine and to activate cytokines.[5,6,10]

As shown in Table 1, the neurologic correlates of the stress response affect a wide variety of body systems, including the cardiovascular, respiratory, renal, and

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FOR CLINICAL USE

- Over time, the stress response to generalized anxiety disorder (GAD) not only stimulates changes that lead to medical disorders but also increases awareness of pain and other symptoms.
- Treatment of GAD needs to be long-term to both control GAD and decrease vulnerability to medical conditions.

endocrine systems.[5,11] Activities that are unnecessary for response to the threat, such as digestion and cognition, are inhibited, and activities that are needed, such as respiration and cardiovascular outflow (see Figure 1), are activated.[6] Cortisol activates many body systems, and cytokine activation of the brain by peripheral body parts triggers the stress response.[6]

Excess amounts of cytokine can be toxic to nerve cells, and cytokine crosstalk between the immune system and the brain may lead to suppression of immune functioning and, thus, increased susceptibility to disease. Activation of the HPA axis and of the sympathetic nervous system can lead to chronic cardiovascular and metabolic alterations. Therefore, chronic activation of the stress response may play a prominent role in the vulnerability to chronic medical illnesses in individuals with GAD.[5,11]

GAD AND MEDICAL DISORDERS

Pain Conditions

An analysis[12] of data from a nationally representative sample of 3032 adults aged 25 to 74 years showed that GAD was found in more individuals with arthritis, migraine, or back pain than in those without these pain conditions (Table 2). Individuals with GAD have altered registering and experiencing of pain. The response to pain of patients with anxiety underlies their response to many other chronic medical conditions. A relationship exists among the patient's perception of the environment, alterations in mechanisms of the central nervous system, and consequences of the somatovisceral effects of GAD.[13]

Pain perception can differ depending on whether the person approaches pain with anxiety or fear because the central processing of these 2 emotions is not the same. Research[13] suggests that subjects who fear pain approach it with a certainty of the impending painful event, and this fearful approach leads to reduced pain sensitivity, or hypoalgesia. In contrast, individuals who have high levels of anxiety, such as those with GAD, approach pain perception from a perspective of uncertainty, unpredictability, and uncontrollability. With an anxious approach, individuals experience hyperalgesia and become more sensitive to pain and more alert for pain sensations. This pattern of response appears to be linked to changes in activity in the cortical and limbic areas in the brain.[13]

Gastrointestinal Illness

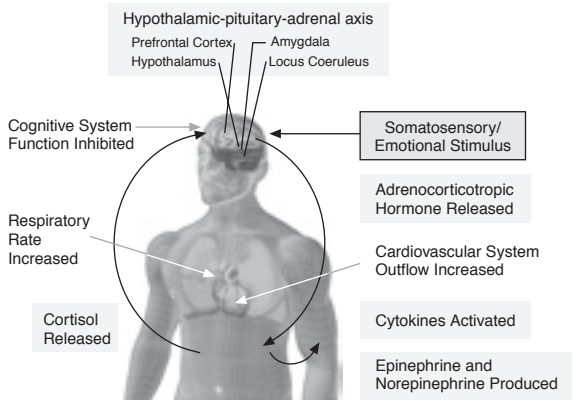
In patients with persistent anxiety, the effects of cortisol and alterations in the sympathetic nervous system have a complex relationship with peptic ulcer disease. The risk of gastric ulcers may be associated with alterations in the mucous lining that protects against ulcers and with changes in the stimulation of acid secretion that causes ulcers. In a study[14] of data from the National Comorbidity Survey of adults in the United States, individuals with GAD, in comparison with those without GAD, were over 4 times more likely to report peptic ulcer disease (OR = 4.5, 95% CI = 2.5 to 7.9, $P < .05$); after adjusting for sociodemographic characteristics, physical morbidity, and comorbid psychiatric disorders, the prevalence of peptic ulcer disease among those with GAD was 2.8 times greater than that of people without GAD (CI = 1.4 to 5.7, $P = .0002$). Irritable bowel syndrome is another gastrointestinal disorder associated with greater frequency among patients with GAD.[15]

Cardiovascular Conditions

Cardiovascular disorders have been associated with GAD.[16] One study[17] found that GAD was associated with increased risk of coronary heart disease independent of major depression (Figure 2). Härter and colleagues[1] found that 20% of male cardiac patients had GAD, and, in 62% of all cases, GAD preceded the onset of the cardiac disorder.

Cardiovascular patients can exemplify the interrelationship between medical symptoms, anxiety, altered perception, and exacerbated symptoms. A patient with GAD may believe that he or she has a weak heart or is vulnerable to heart problems. His or her anxiety may lead to increased awareness of and scanning for cardiac-related symptoms. The individual may be more likely to notice nuances in cardiac activity, focusing on the heartbeat particularly when at rest or when attempting to go to sleep. Normal physiologic variability is interpreted catastrophically, leading to symptoms of fight-or-flight, such as racing heart. Then the patient becomes fearful of these sensations based on mistaken beliefs about their dangerousness. Because physical activity can lead to palpitations, the anxious patient may avoid exercise because of perceived vulnerability. In such cases, anxiety sensitivity leads to altered sensation and altered behaviors, which,

Figure 1. Effects of Anxiety on the Brain and the Body[a]



[a]Based on Sternberg and Gold.[6]

Table 1. Medical Consequences of Prolonged Exposure to Stress Response in Untreated GAD[a]

Stress Response	Medical Consequences
Sustained hypothalamic-pituitary-adrenal (HPA) activation	Hypercortisolemia Hypocortisolemia Glucocorticoid signaling disruption either way Loss of ability to shut off HPA axis
Uncontrolled cytokine-mediated inflammatory activity and norepinephrine release	Hippocampal and prefrontal cortex neurodegeneration Hypertension Coronary artery disease Obesity Type II diabetes Hyperlipidemia/hypercholesterolemia Immune dysfunction

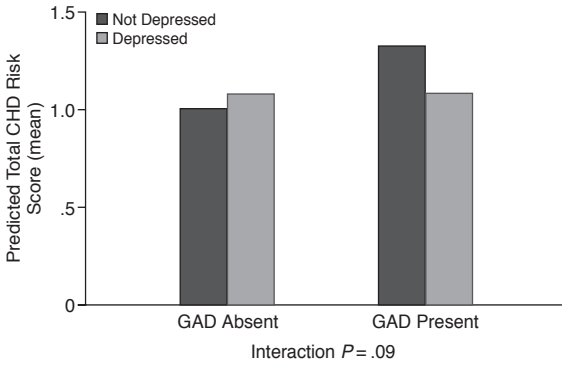
[a]Data from Habib et al[5] and McEwen.[11]

Table 2. Prevalence of Psychiatric Disorders in Adults With or Without 3 Pain Conditions[a]

Psychiatric Disorder	Pain Condition		
	No arthritis, %	Arthritis, %	Odds ratio (95% CI)
Depression	13.1	18.2	1.48 (1.16 to 1.88)
Panic attacks	5.8	11.2	2.09 (1.54 to 2.83)
GAD	2.7	5.6	2.17 (1.42 to 3.33)
	No migraine, %	Migraine, %	Odds ratio (95% CI)
Depression	12.3	28.5	2.84 (2.19 to 3.70)
Panic attacks	5.5	17.4	3.58 (2.59 to 4.97)
GAD	2.5	9.1	3.86 (2.48 to 6.00)
	No back pain, %	Back pain, %	Odds ratio (95% CI)
Depression	12.4	21.0	1.87 (1.49 to 2.36)
Panic attacks	5.3	13.0	2.69 (2.00 to 3.62)
GAD	2.5	6.2	2.54 (1.67 to 3.85)

[a]Adapted with permission from McWilliams et al.[12] Diagnoses were made using the Composite International Diagnostic Interview-Short Form scales. All findings were significant at $P < .001$.
Abbreviation: GAD = generalized anxiety disorder.

Figure 2. Predicted Total Coronary Heart Disease (CHD) Risk in 3032 Individuals With or Without GAD and MDD[a]



[a]Adapted with permission from Barger and Sydeman.[17] Predictions are adjusted for age, gender, ethnicity, education, marital status, medical visits over the last 12 months, and first-order effects of GAD and MDD.
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder.

over time, may increase susceptibility to cardiac conditions and lead to increased emergency room or physician visits.

Endocrine Conditions

Generalized anxiety disorder often occurs in patients with endocrine disorders. Among patients with current or past endocrine disorders, 29% were found to have GAD.[18] Grave's disease is an endocrine disorder with elevated rates of GAD; symptoms of GAD often develop before Grave's disease, but the mechanisms of this association have not been elucidated.[16]

Simon et al[19] found a history of thyroid disease in 10% of patients with GAD. The investigators recommended a thyroid screen for patients with GAD who have not had prior testing.

Patients with diabetes have a 14% current and 21% lifetime prevalence rate of GAD.[20] Several mechanisms have been suggested for this association, but little original research has been carried out.[16,20] The psychological stress related to self-management of diabetes may play into the initiation and perpetuation of GAD, as may fear of hypoglycemia and the medical complications of diabetes. As diabetes develops at an earlier and earlier age, the relationship between GAD and diabetes becomes more prominent in younger populations. The development of hypothalamic, neurohormonal, and neurotransmitter abnormalities in GAD may influence diabetes control and vice versa.

Few trials have examined the impact of treating GAD in patients with diabetes or of treating diabetes in patients with GAD. One small randomized controlled trial[21] found that, compared with placebo, the benzodiazepine alprazolam had little impact on GAD symptoms among individuals with diabetes, although alprazolam did have a

beneficial effect on glycemic symptoms. Another small trial[22] found that fludiazepam led to some improvement in both anxiety and high-density lipoprotein cholesterol level in patients with diabetes. These data suggest complex relationships between GAD and diabetes and that the treatment of either disorder may influence the other.

Respiratory Conditions

Patients with anxiety disorders have higher rates of both asthma[23–26] and chronic obstructive pulmonary disease (COPD)[16] than individuals without anxiety.

In patients with COPD, the lifetime prevalence of GAD was found to be about 10% to 16%.[27] Anxiety is a component of the experience of COPD, and hypoxia, which is inherent in COPD, often stimulates anxiety. Conversely, individuals who experience anxiety symptoms related to other life events often become sensitized to their breathing and respiratory status, which in turn worsens their anxiety. A quality of life impaired beyond that expected for the individual's respiratory state can result, and visits to the emergency department and hospital admission may be precipitated.

In treatment of anxiety in patients with COPD, the influence of medication on the respiratory drive is a concern. Traditionally, benzodiazepines have been considered to be contraindicated in patients with respiratory conditions because of their potential to suppress respiratory drive. Other treatments, including buspirone and nortriptyline, have been evaluated in small studies[27] of patients with COPD and have demonstrated benefit. Cognitive and behavioral approaches such as progressive muscle relaxation and cognitive-behavioral therapy can also reframe cognitive misperceptions regarding COPD and may ameliorate the impact of respiratory symptoms and anxiety symptoms.[27]

Addressing anxiety should be considered a component of long-term pulmonary rehabilitative therapy. Typically, pulmonary rehabilitation in patients with COPD involves a gradual increase in exercise. Increased exercise tolerance may function as a type of exposure therapy and raise the patient's tolerance of the physical symptoms of exercise that can induce anxiety (eg, breathlessness). Stress management techniques may also allow the patient to control anxiety symptomatology that otherwise would be limiting.

TREATMENT CONSIDERATIONS AND CONCLUSION

When treating patients with GAD and comorbid medical conditions, GAD should be addressed as an independent problem that has a pronounced influence on the course of the medical condition and on the functional resilience of the patient. Through treating GAD, clinicians can improve patients' functioning, even with the limitations superimposed on them by their medical illnesses. Medical conditions associated with GAD are often chronic; similarly, as Weisberg[28] describes in this supplement, GAD has a chronic course and requires long-term treatment. As Davidson notes elsewhere in this supplement,[29] if GAD treatment is stopped, many patients are likely to relapse. For example, Rickels and Schweizer[30] found that, after stopping treatment, 60% to 80% of patients treated with an anxiolytic relapsed within a year.

Collaboration between psychiatric and general medical providers is important in establishing and maintaining control of GAD. Controlling GAD may not only improve the patient's quality of life and functionality related to generalized anxiety but may also improve the patient's physical health through decreased vulnerability to chronic physiologic stressors that are mediated by the sympathetic nervous system and cortisol mechanisms.

Drug names: alprazolam (Xanax, Niravam, and others), buspirone (BuSpar and others), nortriptyline (Pamelor and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, nortriptyline is not approved by the US Food and Drug Administration for the treatment of generalized anxiety disorder.

REFERENCES

1. Härter MC, Conway KP, Merikangas KR. Associations between anxiety disorders and physical illness. *Eur Arch Psychiatry Clin Neurosci*. 2003; 253:313–320.
2. Stein MB. Neurobiology of generalized anxiety disorder. *J Clin Psychiatry*. 2009;70(suppl 2):15–19.
3. Simon NM. Generalized anxiety disorder and psychiatric comorbidities such as depression, bipolar disorder, and substance abuse. *J Clin Psychiatry*. 2009;70(suppl 2):10–14.
4. Plotsky PM, Owens MJ, Nemeroff CB. Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. *Psychiatr Clin North Am*. 1998;21(2):293–307.
5. Habib KE, Gold PW, Chrousos GP. Neuroendocrinology of stress. *Endocrinol Metab Clin North Am*. 2001;30(3):695–728;vii–viii.
6. Sternberg EM, Gold PW. The hidden mind: the mind-body interaction in disease. *Sci Am (Special Edition)*. 2002;12(1):82–89.
7. Kent JM, Rauch SL. Neuroimaging studies of anxiety disorders. In: Charney DS, Nestler EJ, eds. *Neurobiology of Mental Illness*. 2nd ed. New York, NY: Oxford University Press; 2005.
8. Bremner JD. Brain imaging in anxiety disorders. *Expert Rev Neurother*. 2004;4(2):275–284.
9. Gorman JM, Kent JM, Sullivan GM, et al. Neuroanatomical hypothesis of panic disorder, revised. *Am J Psychiatry*. 2000;157(4):493–505.
10. Charney DS. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am J Psychiatry*. 2004;161(2):195–216.
11. McEwen BS. Mood disorders and allostatic load. *Biol Psychiatry*. 2003; 54(3):200–207.
12. McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: results from a nationally representative sample. *Pain*. 2004;111(1–2):77–83.
13. Mayer EA, Naliboff BD, Chang L, et al. V. Stress and irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol*. 2001;280(4): G519–G524.
14. Goodwin RD, Stein MB. Generalized anxiety disorder and peptic ulcer disease among adults in the United States. *Psychosom Med*. 2002;64(6):862–866.
15. Gros DF, Antony MM, McCabe RE, et al. Frequency and severity of the symptoms of irritable bowel syndrome across the anxiety disorders and depression [published online ahead of print Aug 27, 2008]. *J Anxiety Disord*.

16. Muller JE, Koen L, Stein DJ. Anxiety and medical disorders. *Curr Psychiatry Rep*. 2005;7(4):245–251.
17. Barger SD, Sydeman SJ. Does generalized anxiety disorder predict coronary heart disease risk factors independently of major depressive disorder? *J Affect Disord*. 2005;88(1):87–91.
18. Sonino N, Navarrini C, Ruini C, et al. Persistent psychological distress in patients treated for endocrine disease. *Psychother Psychosom*. 2004; 73(2):78–83.
19. Simon NM, Blacker D, Korbly NB, et al. Hypothyroidism and hyperthyroidism in anxiety disorders revisited: new data and literature review. *J Affect Disord*. 2002;69(1–3):209–217.
20. Grigsby AB, Anderson RJ, Freedland KE, et al. Prevalence of anxiety in adults with diabetes: a systematic review. *J Psychosom Res*. 2002; 53(6):1053–1060.
21. Lustman PJ, Griffith LS, Clouse RE, et al. Effects of alprazolam on glucose regulation in diabetes: results of double-blind, placebo-controlled trial. *Diabetes Care*. 1995;18(8):1133–1139.
22. Okada S, Ichiki K, Tanokuchi S, et al. Effect of an anxiolytic on lipid profile in non-insulin-dependent diabetes mellitus. *J Int Med Res*. 1994;22(6):338–342.
23. Goodwin RD. Asthma and anxiety disorders. *Adv Psychosom Med*. 2003; 24:51–71.
24. Katon WJ, Richardson L, Lozano P, et al. The relationship of asthma and anxiety disorders. *Psychosom Med*. 2004;66(3):349–355.
25. Deshmukh VM, Toelle BG, Usherwood T, et al. Anxiety, panic and adult asthma: a cognitive-behavioral perspective. *Respir Med*. 2007;101(2): 194–202.
26. Cooper CL, Parry GD, Saul C, et al. Anxiety and panic fear in adults with asthma: prevalence in primary care. *BMC Fam Pract*. 2007;8(62):1–7.
27. Brenes GA. Anxiety and chronic obstructive pulmonary disease: prevalence, impact, and treatment. *Psychosom Med*. 2003;65:963–970.
28. Weisberg RB. Overview of generalized anxiety disorder: epidemiology, presentation, and course. *J Clin Psychiatry*. 2009;70(suppl 2):4–9.
29. Davidson JRT. First-line pharmacotherapy approaches for generalized anxiety disorder. *J Clin Psychiatry*. 2009;70(suppl 2):25–31.
30. Rickels K, Schweizer E. The clinical course and long-term management of generalized anxiety disorder. *J Clin Psychopharmacol*. 1990; 10(suppl 3):101S–110S.