Generalized Anxiety Disorder in Primary Care: The Precursor/Modifier Pathway to Increased Health Care Utilization

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Generalized anxiety disorder (GAD) is commonly seen in the primary care setting and is associated with disability, medically unexplained symptoms, and over utilization of health care resources. The authors review the rare occurrence of GAD uncomplicated by other psychiatric illness and the important relationship between GAD and depression. They suggest that GAD may exert its major effect on health care utilization not by a direct path, but by acting as a precursor or concurrent modifier of other psychiatric disorders that more directly affect health care costs.
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A previous paper has reviewed preliminary evidence that generalized anxiety disorder (GAD) and mixed anxiety-depression are commonly seen in primary care settings and are associated with disability, medically unexplained physical symptoms, and overutilization of health care services and resources.[1] There continues to be considerable debate about whether GAD is a freestanding primary disorder, a prodromal or residual phase of other disorders, a personality trait, or a comorbid condition that modifies the course, treatment response, and outcome of other disorders.[2,3] Although this question has not yet been resolved, the related disorder, mixed anxiety-depressive disorder, has now been introduced into the DSM-IV appendix with similar questions regarding whether it is primary/independent or prodromal/residual.[4]

This paper will focus on the important role that GAD plays in many patients as either a precursor to or concurrent modifier of other psychiatric disorders, especially major depression, and the possibility that its major effect on health care utilization is via this kind of pathway. This premise will be supported by evidence that (1) GAD rarely occurs in the absence of either current or lifetime psychiatric comorbidity, and major depression is among the most common of its comorbid disorders; (2) GAD and major depression share a common genetic diathesis that appears distinct from other "affective spectrum" disorders such as panic, phobia, and bulimia; (3) GAD co-occurs in primary care patients with major depression at a much higher rate than other anxiety disorders; (4) comorbid GAD and major depression is more distressing, disabling, and difficult to treat than pure major depression, and primary care GAD patients with current psychiatric comorbidity have higher health care costs than "pure" GAD patients; and (5) in the life history of individual patients, anxiety disorders in general—and GAD in particular—commonly precede the development of major depression. This paper will conclude with a review of preliminary evidence that treatment of major depression in primary care (although loosely defined and possibly inadequate) may not be associated with reduced health care costs and a proposal that GAD might be the third factor that contributes to both depression and health care utilization and continues to drive utilization even after depression resolves.

GAD: HIGH RATE OF CURRENT AND LIFETIME COMORBIDITIES

The recently completed National Comorbidity Survey[5] provided data on the current (1.6%), 1-year (3.1%), and lifetime (5.1%) rates for GAD on a more representative sample of the U.S. population (compared with the earlier five-site Epidemiologic Catchment Area [ECA] study) using DSM-III-R criteria, which required a longer duration for GAD along with definite symptoms of worry and rumination. More importantly, this survey found that two thirds of individuals with current GAD had an additional current psychiatric diagnosis and that 90% of those with lifetime GAD had another lifetime psychiatric diagnosis. A general inference then is that a minority (10%) of GAD patients have GAD alone and that, in a larger number, GAD may

exist as either a prodromal/residual phase (30%) or a modifier (60%) of other psychiatric disorders. Interestingly, almost two thirds of the GAD patients with a lifetime psychiatric history had suffered from major depression, and 39% of them had suffered from dysthymia. In individuals with current GAD, 39% also had current depression and 22% had current dysthymia. These figures reinforce GAD's important relation to depression.
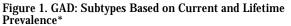
Data on GAD from primary psychiatric settings are scarce, but figures[6,7] suggest that 80% to 90% of GAD patients have an additional, current psychiatric diagnosis and that almost 98% have a lifetime history of another diagnosis. A more detailed analysis of data from one of these studies[6] showed that 63% of GAD patients had a current panic disorder diagnosis, while 54% had either major depression or dysthymia.[8]
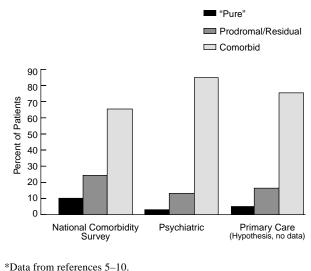
Data from the more important primary care setting are even more scarce. While a number of studies[9,10] now provide prevalence estimates for current or 12-month GAD that vary between 2% and 12% depending on the diagnostic criteria (DSM-III or DSM-III-R), duration required (1 or 6 months), and technique used (full structured interview or abridged version), figures for current and lifetime psychiatric comorbidity in primary care patients selected for GAD have not been published. It might be expected that figures in this setting would lie somewhere between those found in the general population and those found in psychiatric settings. Thus, between 66% and 85% of primary care GAD patients would have current comorbidity, and between 90% and 98% of them would have lifetime comorbidity. Figure 1 illustrates this notion.

GENETIC EPIDEMIOLOGY

The relationship between anxiety and depression, whether conceptualized as symptoms, syndromes, or DSM disorders, has been extensively debated over the years. Although most studies and analyses have indicated that anxiety and depression are distinct and unique at the level of certain DSM disorders, there is also substantial overlap in terms of shared symptoms, comorbid syndromes, familial psychiatric history, neurobiology, and treatment responsivity.[11]

Methods of multivariate genetic analysis have recently been applied by Kendler et al.[12] to large numbers of twin pairs to examine self-reported symptoms of anxiety and depression. These analyses showed that genes act nonspecifically to increase the level or intensity of symptoms, irrespective of symptom type (e.g., anxiety or depression). In contrast, evidence could be found for specific environmental effects that uniquely contributed to depression or anxiety (i.e., specific "depressogenic" and "anxiogenic" environments). This finding suggests that differences between anxiety and depression are more likely due to environmental factors and is concordant with findings

Figure 1. GAD: Subtypes Based on Current and Lifetime Prevalence*
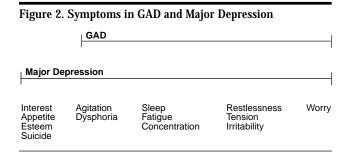

*Data from references 5–10.

from life event studies that implicate distinct kinds of events in the precipitation of these respective syndromes ("threat" for anxiety and "loss" for depression).[13]

The initial analysis, suggesting that clusters of anxious and depressive symptoms may be derived from a common, singular, genetic vulnerability, was followed up by an elegant analysis of over 1000 female twin pairs, using lifetime psychiatric diagnosis generated by personal structured interview and similar multivariate twin analyses.[14] This analysis concluded that genetic influences were best explained by two factors: one for phobia, panic, and bulimia and the other for GAD and major depression. This surprising result suggests, in particular, that the anxiety disorders, from a genetic perspective, are not etiologically homogeneous and supports previous studies suggesting that panic/phobia and GAD are distinct in terms of not just phenomenology, but neurobiology and treatment response. However, this study also suggests that there is a close relationship between GAD and depression and that GAD may be more similar to major depression than to panic disorder. Because this notion conflicts with the high rate of panic disorder comorbidity in GAD patients previously cited,[8] it may be fairer to say that GAD is probably as closely related to major depression as it is to panic. Figure 2 illustrates the substantial overlap in the type of symptoms of the two disorders (GAD and major depression).

GAD IN PRIMARY CARE: IMPORTANT COMORBIDITIES

Prevalence figures for GAD in primary care have previously been reviewed and may be on the order of 5%. However, three studies[15–17] have shown that between 35% and

Figure 2. Symptoms in GAD and Major Depression

GAD				
Major Depression				
Interest	Agitation	Sleep	Restlessness	Worry
Appetite	Dysphoria	Fatigue	Tension	
Esteem		Concentration	Irritability	
Suicide				

50% of patients with a current diagnosis of major depression have a diagnosis of GAD. This is much higher than comorbidity rates for panic (9%) and phobia (22%) in one of the studies[15] and is similar to the comorbidity rate for panic in another.[17] More importantly, it argues that GAD may be a crucial factor in modifying the presentation, course, and outcome of major depression in the primary care setting.

Although there are no data comparing anxious and non-anxious depressions in primary care, there are considerable data from psychiatric settings suggesting that the presence of anxiety increases the severity of depression in several ways. More specifically, compared with pure depressives, anxious depressives have increased risk of suicide,[18] more severe symptoms,[19] poorer outcome and treatment response,[20,21] and higher numbers of medically unexplained symptoms and greater functional disability.[22] Interestingly, a role for comorbid GAD states in promoting excess utilization of health care services has been suggested by a recent study[23] of 1042 patients with GAD. In this study, health care costs were estimated, and utilization was found to be highest in GAD patients with other comorbid diagnoses compared to those with "pure" GAD. In particular, costs of hospitalization, laboratory tests, medications, and absenteeism from work were higher in the comorbid group.

Although previous reports have focused on GAD's possible role in promoting somatization, which then accounts for unnecessary utilization of health care services, GAD's relatively high prevalence in patients with chronic medical illness (far higher than rates of other anxiety disorders in one study[15]) could also promote increased costs in this group, although this possibility has not been systematically explored.

ANXIETY PRECEDES DEPRESSION

Psychoanalytic theories of attachment and loss have long emphasized that the observable human response to separation, studied carefully in children, can be described as a two-stage process.[24] Initially, the infant becomes agitated and anxious and "protests" fiercely. After a time, the infant becomes resigned to the fact of the separation and enters a phase of "despair" that is quite similar to depression. In this process, an initial reaction of anxiety about the uncontrollability of the world (but a retained hope that somehow the situation might favorably resolve due to others' efforts) is followed by depression and despair as the infant becomes certain nothing will reverse the loss. Interestingly, this two-stage process was more recently conceptualized in neurobiological terms by Paul,[25] who explained that perturbations in GABA-benzodiazepine neuronal systems thought to underlie anxiety can, by themselves, lead to perturbations in monoamine neurotransmitter systems (e.g., noradrenergic) thought to underlie depression.

Actual data support this sequential process in which anxiety leads to depression. In one early study[26] that followed the longitudinal course of patients initially presenting with either an anxiety or depressive disorder, 24% of the anxious patients subsequently developed depression, whereas only 2% of the depressed patients subsequently developed an anxiety disorder. In another study,[27] prospective follow-up showed that 50% of patients with initial anxiety had developed a pure or comorbid depressive disorder 5 years later, while only 33% of depressed patients developed a pure or comorbid anxiety disorder. If comorbid "mixed" anxiety and depressive disorder is eliminated, 62% of patients with "pure" anxiety develop "pure" depression, while only 18% of patients with "pure" depression develop "pure" anxiety. Finally, in the previously cited GAD study,[8] 47% of 149 GAD patients with lifetime comorbidity reported that GAD had preceded other diagnoses, while 13% reported simultaneous onset of multiple diagnoses. Within episodes themselves, there is also evidence that anxiety symptoms often herald the development of depressive symptoms.

These earlier studies have been extended by an elegant, large scale epidemiologic analysis by Breslau and colleagues.[28] Over 1000 individuals were interviewed on two occasions 3.5 years apart, and a prior history of anxiety greatly increased the risk for development of major depression. Gender differences in prior anxiety disorders also accounted for much of the gender difference in development of depression (female preponderance). The odds ratio that any anxiety disorder would increase the risk of depression was 7.9 and 5.6 for males and females. For GAD, the figures were 9.2 and 7.5. Only panic and OCD had higher odds ratios. Again, this risk phenomenon operated in both males and females.

WHAT, THEN, IS GAD?

The extensive current and lifetime prevalence of other anxiety and mood disorders in GAD needs to be considered in light of the chronicity of GAD symptoms. The previously cited study[8] of 166 GAD patients reported a mean duration of GAD of more than 20 years and a likelihood of GAD symptom remission of only 15% and 25% at 1 and 2

years, respectively. This chronicity is consistent with a previous study of a large group of anxiety disorder patients with different diagnoses[29] which reported that GAD patients were symptomatic for 56% of their lives after onset compared with much lower proportions in anxiety disorders traditionally thought to be more severe[1] (16% for panic and 29% for agoraphobia with panic).

This raises the possibility that GAD is sometimes a trait-like "platform" that sets the stage and confers the vulnerability for the development of major depression and panic. This is consistent with carefully designed, prospective studies by George Brown and colleagues[30] showing that patients with anxious symptoms at baseline are most likely to develop major depression when exposed to stressful life events. After remission of major disorders, symptoms of GAD will often remain. In fact in one study, the best predictor of persistence of depression in primary care[17] was degree of "neuroticism," a construct that overlaps to a significant degree with GAD. This notion of GAD as an underlying "core," as opposed to an independent entity, may provide the key (as shown in the next section) to understanding how depression (and possibly panic) may increase health care utilization.

DOES PSYCHIATRIC TREATMENT DECREASE HEALTH CARE COSTS?

Numerous reports have examined the supposed "cost-offset" effect of psychiatric interventions in medical patients and settings.[31] Although there is some supportive evidence for this phenomenon, few studies have been prospectively designed to address this issue, and the existence and extent of this supposed effect are still being debated. Most studies have focused on inpatient medical settings so that the possibility of this effect in outpatient primary care settings has been relatively neglected.

One recent study[32] in a large Health Maintenance Organization (HMO) examined a carefully selected sample of 373 primary care patients. Health care costs were highest in those with depressive or anxiety disorders (N = 66), next highest in those with subthreshold diagnoses (N = 56), and lowest in those with no symptoms over 2 months. Most symptomatic subjects showed improvement in their symptoms, and a majority no longer met criteria for either their disorder or a subthreshold diagnosis at the time of follow-up. Despite this fact, changes in health care costs were not significantly greater in patients who improved symptomatically compared with those who did not (i.e., improvement in anxiety or depression does not automatically produce cost swings).

There are a number of flaws with this study. The HMO setting with intrinsically tighter cost controls may have obscured a potential effect. The follow-up period may have been too short to observe changes in utilization patterns. Finally, these findings do not necessarily reflect the effects

of treatment. Most patients did not receive specific mental health treatment and those who did were most severely ill and perhaps less likely to readily improve. Randomized studies or more intensive treatment would be required to test the possibility of a true cost-offset effect.

This study was followed up by a much larger study[33] that examined health care costs in 5595 patients with depression before and after initiation of treatment. This study found that greater costs in depressed patients persisted for the next 9 months after treatment initiation. Because automated pharmacy prescription records were used to estimate treatment, adequacy and effectiveness of treatment could not be determined. This is a major problem, since primary care studies have shown that few primary care patients receive adequate dosage and duration of antidepressant treatment based on Agency for Health Care Policy and Research (AHCPR) guidelines.[34] Again, these findings may also be due to an inadequate period of observation (i.e., perhaps changes in utilization take longer to occur than changes in depression). Alternatively, high utilization may reflect other factors associated with depression that might also increase utilization. For example, there may be a third factor that increases both vulnerability to depression/anxiety and propensity to seek health care.

Such a factor might well be the presence of underlying "neurotic" traits or personality disorder. This is particularly intriguing with respect to GAD, since I have previously suggested that GAD is especially related to these traits and since there was debate during the development of DSM-IV as to whether GAD should be conceptualized as an Axis II disorder.[35] For example, in a recent study[36] of high utilizers, a quarter to a third had only GAD at the time of the interview, despite an astonishingly high rate of lifetime major depression. Is this GAD, then, the prodrome for the next major depression and yet perhaps also the driving force for utilization? This would be consistent with one study[37] showing that the majority of depressed patients in primary care do not fully remit, but rather retain subthreshold symptomatology that is often consistent with GAD. GAD may then continue to produce unexplained physical symptoms and high costs.

In conclusion, GAD may have an important role not just as a cross-sectional condition itself, but as a persisting vulnerability state that increases the risk of other disorders, increases their severity when they co-occur, and may be the longitudinal factor that is most important in determining health care utilization. Prospective studies of primary care populations that carefully measure DSM-IV anxiety and depressive disorders and health utilization, over a period of several years, are needed to test this hypothesis.

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