Generalized Anxiety Disorder and Psychiatric Comorbidities Such as Depression, Bipolar Disorder, and Substance Abuse

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Generalized anxiety disorder (GAD) has a high rate of comorbidity with other psychiatric disorders, including major depressive disorder (MDD), bipolar disorder, other anxiety disorders, and substance use disorders. The similarities between GAD and MDD have led some to suggest that GAD should be reclassified as a mood disorder. The concurrence of GAD with another disorder heightens a patient's risk for impairment, disability, and suicidality. Clinical trials for GAD and disorders that are most likely to occur with GAD have generally not taken comorbidity into account, and there is a paucity of data guiding how comorbidity should inform treatment selection. Research into the biology and psychopathology underlying the high rate of comorbidity of GAD and into efficacious interventions for GAD with comorbidity is needed. *(J Clin Psychiatry 2009;70[suppl 2]:10–14)*

Generalized anxiety disorder (GAD) is one of the most common anxiety disorders[1] and is frequently comorbid with several other psychiatric disorders, each of which may complicate the diagnosis, treatment, and outcome for the patient. Anxiety disorders and comorbid disorders can be difficult to detect when evaluating patients if the diagnostic process does not include a clinical interview specifically structured to detect anxiety disorders. One study[2] supporting this notion found that a substantially higher percentage of individuals with major depressive disorder (MDD) who were assessed with a semistructured diagnostic interview were diagnosed with GAD, whereas a smaller percentage assessed with an unstructured interview were diagnosed with GAD.

GAD COMORBIDITIES

Individuals with lifetime GAD have an extremely high rate of lifetime mood disorders. Epidemiologic data from the National Comorbidity Survey suggest that 67% of individuals with GAD have a lifetime unipolar depressive disorder, 17% have bipolar disorder, and only 16% have no lifetime mood disorder.[3] Wittchen et al[4] similarly reported that individuals with GAD have a 90% likelihood of at least 1 comorbid psychiatric diagnosis in their lifetime. Highest among these comorbidities were MDD and dysthymia, while alcohol abuse and dependence, simple phobia, and social anxiety disorder were also common (Figure 1).

GAD and MDD

Anxiety disorders tend to develop relatively early in life, and, therefore, as many studies suggest, they frequently occur before the first episode of MDD.[5] GAD may be a prodrome to MDD in the individuals who later develop this comorbidity. In fact, after an individual has a new onset of GAD, he or she has an increased likelihood of developing a major depressive episode within the year than someone without an anxiety disorder.[5]

Conversely, some longitudinal prospective data of children and young adults suggest that order of onset may be more varied, with about one third of individuals with GAD having anxiety onset prior to the onset of MDD, about one third having the disorders onset concurrently, and about one third having onset of MDD first.[6] Of note, one study that followed individuals until age 32 years found that 72% of cases of lifetime GAD also had lifetime MDD. Even GAD defined more loosely, with only a 1-month requirement for symptom duration, has a substantial comorbidity with mood and anxiety disorders, although increased severity of GAD is associated with greater likelihood of prediction of subsequent depression.[7]

Impairment and disability. A primary care study[8] that defined impairment as an inability to work on at least 1 day within the past month found that 67% of patients with

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FOR CLINICAL USE

- Generalized anxiety disorder (GAD) can be difficult to detect as a comorbid condition. Clinicians should use structured evaluations designed to detect the presence of anxiety and other comorbid disorders.
- The comorbidity of GAD and other psychiatric disorders puts patients at risk for increased impairment and disability. Although comorbidity treatment data are limited, clinicians can consider each concurrent disorder when selecting treatment to minimize these risks.
- The onset of secondary MDD in GAD may be preventable with appropriate intervention, although additional research is needed.

pure GAD and 68% of patients with pure MDD were impaired, but those with comorbid GAD and MDD had an 81% rate of impairment. The impairment rate was 17% if neither GAD nor MDD were present.

In general, additive psychiatric comorbidity has been associated with greater disability; one study[9] found an increase in the level of disability as the number of comorbid psychiatric disorders increased. A meta-analysis by Hoffman et al[10] analyzed the impact of both pure GAD and GAD comorbid with depression or other disorders on functioning and quality of life. While GAD alone is clearly associated with disability and impaired quality of life, patients with comorbidity increased impairment overall. This finding highlights the importance of not only diagnosing the first disorder but also testing for the presence of comorbid conditions.

Biologic and environmental risks. There is a paucity of data examining the biology underlying the presence of comorbidity in GAD, and more attention to this is needed in pathophysiology studies of GAD in general. One hypothesis is that the onset of the anxiety disorder may serve as a stressor triggering an underlying neurobiologic vulnerability to MDD, perhaps mediated by serotonergic dysregulation. Similarly, the overlapping risk may be related to hypothalamic-pituitary-adrenal axis dysfunction. More research examining the underlying neurobiology of GAD and MDD comorbidity is needed, with attention to comorbidity in ongoing studies of GAD.

One contributing factor to the high comorbidity rate of GAD and MDD may be overlapping genetic factors. In a study of identical and nonidentical female twin pairs, Kendler[11] found the same genetic risk factors for GAD and MDD. Another possibility is that environmental stressors interact with underlying genetic risks to produce anxiety and depressive disorders. Researchers have hypothesized that the environmental risk factors that predispose an individual to GAD might be distinct from those that increase the risk for MDD. Thus, the development of one disorder instead of the other may be due to a difference in the patterns of life stress. In other words, someone may have an underlying biologic risk, but whether it becomes expressed as GAD or MDD could be determined by environmental factors such as stressful life events.

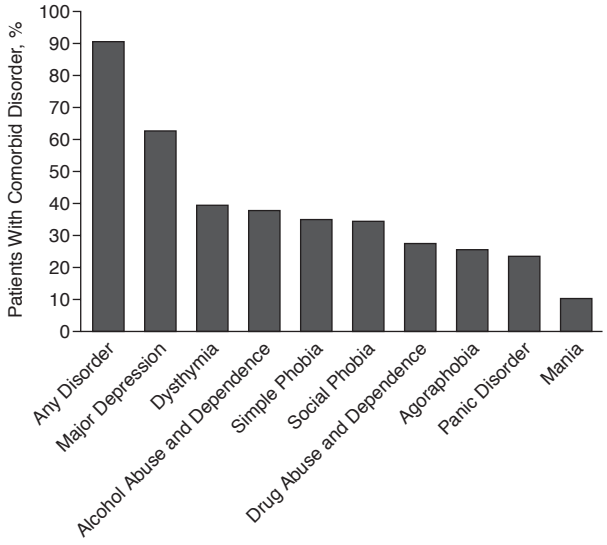
Pursuing this hypothesis, Kendler et al[12] classified stressful life events into categories of loss, humiliation, danger, and entrapment and examined how subjects with GAD, MDD, or both described their stressful experiences within 1 month of onset. Of the 4 categories, loss and danger were associated with the most risk for GAD, while loss and humiliation were associated with the most risk for MDD and comorbid GAD and MDD. Entrapment was associated only with comorbid GAD and MDD.

Debate is ongoing about whether genetics will ultimately better explain mood-related and anxiety-related traits such as neuroticism rather than specific DSM mood and anxiety diagnoses.[13] Neuroticism has been found to be a risk factor for both GAD and MDD.[14] Kendler et al[15] demonstrated that, if one has a high level of neuroticism, a less severe stressful life event is more likely to trigger the onset of a major depressive episode than if an individual has a low level of neuroticism. This finding may be true for anxiety disorders as well; data suggest that underlying vulnerability and life stressors have additive risk for the development of anxiety in late life.[16]

Another possibility for individuals with GAD is that the negative psychological impact of work and social dysfunction due to GAD itself may result in depression and demoralization about the anxiety disorder and associated impairment which, in some cases, may trigger MDD. This pathway would support the possibility that early intervention for GAD could reduce the prevalence of later MDD.

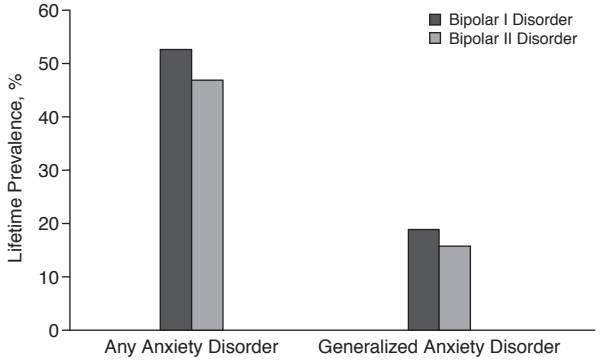
Questions concerning classification. Some overlap in the diagnostic criteria for GAD and MDD exists in DSM-IV, and contemporary researchers continue to question whether GAD and depression should be classified as distinct disorders in the upcoming DSM-V.[17–20] Because of the symptom overlap (i.e., irritability, insomnia, and trouble with concentration), high rate of lifetime comorbidity, overlapping antidepressant response, shared trait risk factor of neuroticism, and shared genetic risks between GAD and MDD, some in the field have questioned whether GAD should be reclassified as a mood disorder instead of as an anxiety disorder. Slade and Watson[21] have

Figure 1. Lifetime Prevalence of Comorbid Disorders in Patients With GAD[a]



[a]Data from Wittchen et al.[4]

Figure 2. Lifetime Anxiety Comorbidity in 475 Patients With Bipolar Disorder[a]



[a]Data from Simon et al.[24]

suggested that GAD and MDD should both be classified as distress-based internalizing disorders along with posttraumatic stress disorder and dysthymic disorder, as opposed to fear-based internalizing disorders such as panic, social anxiety, and obsessive-compulsive disorders and agoraphobia.

Despite the commonalities between GAD and MDD, the syndromes do have distinguishing factors. For instance, as already noted, the environmental triggers appear to differ. Additionally, neuropsychological studies[22,23] have shown that the attentional bias differs between individuals with depression, who focus on negative affect, and individuals with GAD, who focus on threat. Finally, benzodiazepines are not effective treatment for depression, as they are for GAD, suggesting that some differences in the underlying biology of GAD and MDD are likely.

Given the available data, it is probably premature to make a judgment concerning the reclassification of GAD. The issue will be a topic of discussion for DSM-V evaluation groups.

GAD and Bipolar Disorder

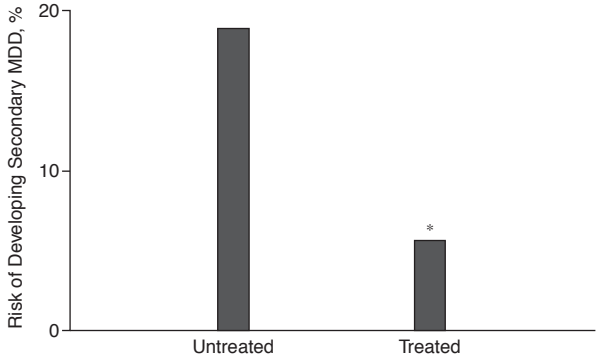
Until recently, the frequent comorbidity of GAD and bipolar disorder has been underappreciated in the clinical setting. Baseline data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)[24] showed that approximately 18% of subjects with bipolar disorder had a lifetime occurrence of GAD, with rates being somewhat higher for bipolar I than for bipolar II disorder; fully 51% of bipolar disorder patients overall had at least 1 type of lifetime anxiety disorder (Figure 2).

As with MDD, comorbid anxiety can worsen the course of bipolar disorder. Anxiety disorders concurrent with bipolar disorder are associated with a younger age at bipolar onset, poorer role functioning and decreased quality of life, substantially less time spent euthymic, lower likelihood of recovery, greater risk of comorbid substance use disorder (SUD), and a greater lifetime risk of suicide attempts.[24] The mean duration of the longest euthymic period during the prior 2 years for patients entering the STEP-BD study with current GAD was less than half that of those who had bipolar disorder only. Further, a prospective follow-up[25] of patients with bipolar disorder in the STEP-BD study documented that those with comorbid GAD lost an estimated 29 days well (defined as relative euthymia) during the 12 months they were followed compared with individuals without an anxiety disorder.

About twice as many patients with bipolar disorder and comorbid GAD appear to have a history of at least 1 suicide attempt compared with those without GAD.[24] Among patients with bipolar disorder and current GAD, 62% reported having attempted suicide, and, among patients with bipolar disorder and lifetime GAD, the rate was about 53% compared to 22% of those without a lifetime anxiety disorder.[24]

Impulsivity is a core feature of bipolar disorder, and the presence of a comorbid anxiety disorder has been theorized to reduce the likelihood of impulsiveness. However, Taylor and colleagues[26] demonstrated that individuals with bipolar disorder and a current anxiety disorder have a significantly higher level of impulsivity, as measured by the Barratt Impulsiveness Scale, than those without an anxiety disorder ($P = .002$). Higher impulsivity was predicted at 9-month follow-up by higher levels of baseline panic attack frequency, phobic avoidance, anxiety sensitivity, fear of negative evaluation, and worry. The association of anxiety symptoms with increased impulsivity was present

Figure 3. Risk of Developing MDD in Untreated GAD[a]



[a]Data from Goodwin and Gorman.[28]
*At least 4 doses of psychotropic medication.
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder.

even after statistical adjustments for age, gender, SUD comorbidity, and current mood episode.

GAD and Substance Use Disorders

Using data from the National Epidemiologic Survey on Alcohol and Related Conditions, Compton and colleagues[27] reported that GAD is associated with significantly increased odds for 12-month SUD. They reported odds ratios of 4.5 for drug use disorders, 2.0 for drug abuse, and 9.5 for drug dependence in the presence of GAD, after adjusting for demographic characteristics. After adjusting for other psychiatric comorbidities as well, the odds ratios were lower, but the risk for drug dependence was still significant (OR = 2.5). The investigators recommended further research on common factors, such as genetic risk, that may underlie both types of disorders.

PHARMACOTHERAPY AND RELATED ISSUES FOR GAD AND COMORBID CONDITIONS

Although comorbidity between GAD and other disorders is common, and patients with GAD and comorbid conditions clearly present for treatment in the clinical setting, few data about how these comorbidities should inform treatment selection are available. Unfortunately, pharmaceutical trials have generally not attended to the issue of comorbidity, with large US Food and Drug Administration randomized controlled trials specifically excluding most comorbid psychiatric disorders.

Limited but intriguing data, however, suggest that treating GAD may serve to limit the onset of secondary MDD. One study[28] compared patients with GAD who had been treated with psychotropics to patients with GAD who were untreated. A higher incidence of secondary MDD was found among the untreated group (Figure 3). These results were acquired using a minimum requirement of 4 known psychotropic doses for the treated group. Targeted, prospective research examining the impact of both pharmacotherapy and psychotherapy interventions for GAD on MDD prevention is needed, but initial results support the hypothesis that treating GAD early may help prevent the onset of later MDD for the subset of patients with GAD but no current depression.

The presence of anxiety comorbidity in patients with primary depression has also been demonstrated to interfere with treatment response. Researchers with the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study evaluated 2,876 adult outpatients who were given first-line pharmacotherapy treatment with citalopram and found that those with anxious depression had significantly lower remission rates—22% versus 33% ($P < .0001$)—according to the 17-item Hamilton Rating Scale for Depression scores and a longer time to remission than those with nonanxious depression.[29] Anxious depression was also associated with a worse side-effect profile and a poorer response in the next treatment stages for citalopram nonresponders in STAR*D.

Examining baseline data from the STEP-BD database, Simon et al[30] evaluated whether comorbid anxiety disorders had any impact on naturalistic pharmacotherapy treatment of bipolar disorder. The presence of anxiety disorders was minimally associated with pharmacotherapy selection. In fact, only 59% of all patients met study criteria for receiving adequate mood stabilizer treatment, suggesting that clinicians do not have optimal, evidence-based pharmacotherapies available for bipolar disorder regardless of the presence of comorbidity. Of patients with current GAD comorbidity, 33% were receiving minimally adequate anxiolytic pharmacotherapy. Likely reasons for inadequate treatment include a lack of data to support appropriate choices in the setting of comorbid anxiety and bipolar disorder, risk of mania and possibly increased cycling with antidepressant use in patients with bipolar disorder, and concerns about using benzodiazepines in patients who have a higher risk of SUD comorbidity. A simple lack of anxiety disorder detection in the bipolar setting, as with MDD, may also contribute to the problem of treatment inadequacy.

SUMMARY

Despite high rates of comorbidity, GAD is commonly underdiagnosed and undertreated in patients with other psychiatric disorders, especially MDD, bipolar disorder, and SUD. Clinicians should evaluate patients with GAD for medical, psychiatric, and substance comorbidities. Patients with GAD and comorbid disorders are at risk for increased impairment, disability, and suicidality, as well as for poorer quality of life and role function. Careful treatment selection must take into consideration each disorder to offer the best outcome.

Drug name: citalopram (Celexa).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, citalopram is not approved by the US Food and Drug Administration for the treatment of anxious depression.

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