Comorbidity in Generalized Anxiety Disorder: Impact and Implications

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Studying comorbidity may be particularly useful in shedding light on the nature, course, and management of generalized anxiety disorder (GAD). This article reviews the common comorbidities in GAD, their impact on functioning and on medical utilization, and their implications for treatment. Comorbidity in this area is complex in that GAD may be primary (predating other illnesses) or secondary (following other conditions). Nevertheless, studies demonstrate the high prevalence of patients with a matrix of anxious-somatic-depressive symptoms and show that GAD comorbidity is associated with both increased disability and increased medical utilization. Clinical implications of this work include the need for rigorous assessment of anxiety, somatic, and depressive symptoms in patients who present with any one of these sets of complaints and the possibility that early treatment of GAD may be critical in preventing subsequent morbidity.

**COMMON COMORBIDITIES IN GAD**

Both the Epidemiologic Catchment Area study and the National Comorbidity Survey (NCS) found that GAD is a common disorder in the general population (with a 1-year prevalence of 3.1%–3.8%), but that “pure” GAD, without comorbid psychiatric disorders, constitutes only about one third of the total prevalence. In the NCS, 90% of those with lifetime GAD had another lifetime psychiatric diagnosis, most commonly major depression and dysthymia, followed by substance abuse, simple phobia, and social phobia. The onset of these comorbid disorders relative to the onset of GAD is illustrated in Figure 1. Similarly, a series of clinical studies have found high rates of comorbidity in GAD patients, with common comorbid diagnoses including major depression, social phobia, and simple phobia. Even in GAD patients without concurrent major depression, social phobia and simple phobia are the most common comorbid diagnoses. Furthermore, such studies invariably report higher comorbidity in GAD than in other anxiety disorders. Similar findings are also seen in children and adolescents, and to some extent in the elderly.

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morbid with other conditions, such as attention-deficit/
chronic medical illness (hypertension, diabetes, and heart
disease).30,41
It has been argued that the extent and severity of somatic
symptoms in patients with anxious-somatic-depressive
symptoms are informed by cultural factors.44 Certainly, the
prevalence of GAD diagnoses (with perhaps an increasing
emphasis on psychic over somatic symptoms) seems lower
in some African and Asian countries than in other parts
of the world.45 On the other hand, a matrix of anxious-
somatic-depressive symptoms does appear to be common
universally.46 Although genetic factors may well be rele-
vant, the role of environmental traumas and other stress-
s should be borne in mind, however, that different definitions
of what is the primary and secondary diagnosis may lead
to different prevalence rates and that diagnostic reliability
may be lower for additional disorders than for principal
disorders.19

It is perhaps worth noting that despite the high comor-
bidity of GAD in many studies, the comparative odds ra-
tios of GAD and major depression with other disorders
may not be consistently larger for GAD.20 Lifetime and episo-
de comorbidities of GAD and major depression are
in fact similar, suggesting that any argument that major
depression is a true independent disorder, in contrast to
GAD, is incorrect.20 Specific aspects of GAD comorbidity
are discussed in greater detail in the following sections.

Depression
In the NCS,21 subjects with current GAD frequently
also had current major depression (39%) or dysthymia
(22%). Similarly, in GAD patients with a lifetime psychi-
atriatric diagnosis, there was often a history of major depres-
sion (62%) or dysthymia (39%). Unipolar disorders were
4 times more common than bipolar disorders.

Similarly, in the Harvard/Brown Anxiety Disorders Re-
search Program (HARP) study22 of primary psychiatry set-
tings, 54% of GAD patients had either current major de-
pression or dysthymia. Conversely, a number of primary
care studies have shown that 35% to 50% of patients with
current major depression have comorbid GAD16; this is of-
ten higher than levels of other comorbid disorders.

Interestingly, long-term follow-up studies have shown
that anxiety is commonly followed by depression (and that
this sequence occurs more commonly than depression fol-
lowed by anxiety).23–28 This may not be the case in the el-
dery, however.15 Similarly, within a particular episode of
depression, anxiety symptoms may begin first.16 Further-
more, in prospective studies, patients with anxious symp-
toms are more likely to develop major depression on expo-
sure to stressful life events.27 Finally, after remission of
depression, GAD symptoms may remain.28

Somatic Symptoms and Medical Disorders
In patients with unexplained somatic complaints, there
is a high prevalence of both GAD and major depres-
sion.29,30 Furthermore, there is some evidence that GAD
may often precede the onset of somatic symptoms.31,32

Conversely, patients with GAD are more likely to have
somatoform disorders than are other anxiety disorder pa-
tients in some studies,33 although not in all.34 There are,
however, no differences in somatic symptoms between pa-
tients with pure GAD and those with comorbid disorders.12

Indeed, GAD appears to be commonly associated with
chest pain,35–38 chronic fatigue syndrome,39 irritable bowel
syndrome,31,32,40 hyperventilation,41 tension headache,42 and
chronic medical illness (hypertension, diabetes, and heart
disease).30,41

Substance Use Disorders
The relationship between anxiety disorders and sub-
stance use disorders has been reviewed extensively else-
where.46 It is generally accepted that there is high cross-
sectional comorbidity of anxiety disorders and alcohol
dependence, and there is evidence both that alcohol is used
to self-medicate anxiety symptoms and that alcohol de-
pendence may lead to anxiety symptoms.50

However, there appears to be a stronger association be-
tween GAD and alcohol-dependent patients undergoing
withdrawal than there is between alcohol use disorders
and GAD. This is consistent with findings that in patients
with comorbidity, GAD onset is later than that of the alco-
hol use disorder.49 In contrast, in social anxiety disorder
and agoraphobia, alcohol appears more likely to represent
self-medication.

Other Disorders
GAD may also be associated with a range of other Axis
I disorders. A particularly common comorbidity is with
other anxiety disorders, including panic disorder51,52 and
posttraumatic stress disorder.48 However, GAD is also co-
morbid with other conditions, such as attention-deficit/
hyperactivity disorder,53 trichotillomania,54 and stereotypic
movement disorder.55
Personality disorders in GAD have been described in a range of studies. In one epidemiologic study, Nestadt et al. found that the odds of having GAD were higher in patients with increased compulsive personality scores, but lower in patients with more severe antisocial personality disorder.

An association has also been described between GAD and traumatic brain injury, stroke, and thyroid disorders.

**IMPACT ON FUNCTIONING**

In the NCS, it was found that when comorbid mood disorders were present in GAD, there was a significant increase in associated disability and dysfunction. Methodological limitations of this work include the possibility that mood disorders distorted perception of role functioning. Nevertheless, it is noteworthy that 28% of respondents with pure GAD reported that symptoms interfered with life activities, in contrast to 51% of respondents with comorbid GAD (Figure 2). Similarly, 30% of the pure GAD group reported significant interpersonal problems, in comparison with 46% of GAD subjects with comorbid major depression (see Figure 2) and 64% of GAD subjects with comorbid bipolar disorders. Conversely, major depression comorbid with GAD is associated with more impairment than major depression without GAD. In another analysis of the NCS data, together with the Midlife Development in the United States Survey, Kessler and colleagues emphasized that comorbid major depression and GAD are associated with more impairment than is pure major depression or pure GAD. Furthermore, the degree of impairment of pure GAD and pure major depression was similar, providing additional support to the argument that GAD is an important independent disorder, irrespective of whether subjects have comorbidity.

Clinical studies have also emphasized the importance of comorbid anxiety in depression; in comparison with patients with depression alone, patients with anxious depression have higher severity of symptoms and higher risk for suicide. A recent study, based on interviews of 209 outpatients, emphasizes the significance of comorbid mood and anxiety disorder in suicidal ideation and behavior. Mean scores for suicidal ideation and hopelessness were greatest for patients with comorbid primary mood disorder and panic disorder. However, the authors noted that the role played by comorbid panic disorder did not differ markedly from that played by other anxiety disorders, including GAD.

In the World Health Organization study on psychological problems in primary care, marked social disability, as assessed by the global Sheehan Disability Scale, was significantly higher in GAD with comorbid psychiatric disorder (46.3%) than in pure GAD (25.0%), which in turn was markedly higher than in subjects with somatic disorders without psychiatric disorder (19.5%) (see Figure 2). Similar findings were apparent even in patients who did not meet the duration criterion for GAD (42.3% in comorbid GAD vs. 24.3% in pure GAD vs. 19.5% in somatic disabilities), and the authors conclude that the diagnostic criteria for GAD are too restrictive in this setting. Other analyses of this study demonstrate similar findings; for example, the mean number of disability days in the past month was 4.4 in pure GAD, but 6.3 in comorbid GAD. Similarly, Sherbourne et al. reported that in patients with chronic medical conditions, those with comorbid anxiety disorder had lower levels of functioning and well-being.

**IMPACT ON MEDICAL UTILIZATION**

Comorbidity may also have an impact on medical utilization. Although GAD is the least common anxiety disorder in mental health care settings, it is the most common anxiety disorder in primary care settings and in patients with chronic medical disorders. As noted earlier, somatization is associated not only with comorbid GAD and depression, but also with elevated disease burden and with negative perception of health.

In the NCS, 48% of respondents with pure GAD sought professional help and 25% took medications for GAD symptoms at some point, versus 68% and 46%, respectively, of respondents with comorbid GAD (Figure 3). About 16% of subjects with pure GAD had sought psychiatric outpatient treatment in the past year, in comparison with 31% of GAD respondents with comorbid major depression and 32% of GAD respondents with comorbid bipolar disorders.

Similarly, in a study of 1042 GAD patients, those with other comorbid diagnoses had higher medical utilization than patients with pure GAD. In patients with comorbidity, there were higher costs of laboratory tests, medication, hospitalization, and absenteeism from work. Hospitalizations and loss of productivity were the 2 major components of costs in patients both with and without comorbidity.
Notably, patients who present to primary care practitioners with somatic complaints appear less likely to have psychiatric conditions recognized than are patients who present with psychosocial problems. Furthermore, anxiety symptoms may be more commonly missed than depressive symptoms. Given the importance of somatic symptoms in GAD, it is possible to speculate that the psychic component of this disorder is often missed.

This lack of recognition might conceivably result in unnecessary medical consultations and diagnostic tests; indeed, annual medical expenditures for anxious patients have been quoted as being up to 10 times higher than for nonanxious patients.

Certainly, GAD, somatization, and depression played a prominent role in a study of distressed high utilizers of health care, and high utilizers who were rated as “frustrating patients” had higher rates of GAD and of somatization.

**IMPACT ON TREATMENT**

Epidemiologic studies have demonstrated the negative implications of comorbidity for course of illness. Thus, Angst and Vollrath found that the best predictors in cases of GAD and panic were severity and duration of symptoms, as well as comorbidity with depression. Similarly, in the HARP study, likelihood for remission for GAD and any other comorbid condition after 1 year was half the annual remission rate for GAD alone.

Again, in the Munich follow-up study of epidemiologic and clinical samples, the outcome for subjects with both anxiety and depressive symptoms tended to be worse than that for those with anxiety alone. Similarly, in comparison with patients with nonanxious depression, those with anxious depression may have a poorer outcome and treatment response. In a prospective study of 157 primary care patients with major depression treated with nortriptyline or interpersonal psychotherapy, it was shown that while both treatments were effective, patients with comorbid GAD had a longer time to recovery. In a psychotherapy study of patients with GAD, Axis I comorbidity predicted worse outcome.

In GAD patients with comorbid disorders such as social and simple phobia, but not major depression or panic, who underwent psychotherapy, there was a significant decrease in comorbidity after treatment, particularly in responders. Conversely, psychotherapy for panic disorder reduced the frequency of additional GAD and other comorbid disorders. While such a finding may be an artifact of overlapping symptoms, it may also reflect a generalization of therapeutic skills.

Developments in pharmacotherapy strategies for GAD arguably offer similar hope. Antidepressants have proved useful in patients with a matrix of anxious-somatic-depressive symptoms in a range of different cultural settings. Furthermore, combinations of antidepressants and short-term anxiolytics appear useful in patients with both depression and anxiety. Unfortunately, patients with comorbid GAD and depression continue to be treated inappropriately with benzodiazepines alone. Although clinical trials tend to select for patients without comorbidity, certain antidepressant agents will, in all likelihood, be useful not only for GAD, but also for comorbid disorders such as major depression and social phobia.

**CONCLUSION**

There are several possible theoretical models for explaining comorbidity between multifactorial disorders, and in the case of GAD and major depression, the data support a number of possibilities. Rather than viewing GAD as a residual diagnosis or marker of severity, or simply, as a basic anxiety disorder or prodrome, it may be useful to see GAD as involving a specific set of psychobiological dysfunctions that manifest as a matrix of anxious-somatic or anxious-somatic-depressive symptoms. In this view, comorbidity in GAD does not weaken the diagnostic validity of the disorder; it simply reflects the course of a common constellation of symptoms, which may be seen the world over. Clinically, it is important to evaluate symptoms of anxiety, somatization, and depression in patients who present with any one of these sets of complaints.

GAD may be either a primary or a secondary disorder. Primary GAD is arguably a risk factor for subsequent depression, and patients with comorbid GAD and depression are particularly likely to demonstrate disability and dysfunction. In contrast, whether or not GAD first occurs before or after another anxiety disorder, it is possibly similar in terms of prevalence, course, and treatment. Importantly for the clinician, patients with GAD who present to medical practitioners with somatic symptoms may not be diagnosed with a psychiatric condition; this lack of recognition may contribute to increased medical utilization.
Although benzodiazepines reduce anxiety symptoms in GAD, patients who suffer from the full matrix of anxious-somatic-depressive symptoms may fail to respond to these older medications. Fortunately, the appropriate use of antidepressants may result in decrease of both anxiety and depression symptoms and may also play a role in preventing comorbid major depression in GAD. Although there is growing research on new agents for GAD, further research on the response of comorbidity to management is crucial. In the interim, clinicians should be aware of the potentially crucial importance of early treatment of anxiety symptoms.

Drug name: nortriptyline (Pamelor and others).

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