

# 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. (*J Clin Psychiatry* 2001;62[suppl 11]:29–34)

Despite recent advances in the conceptualization and treatment of generalized anxiety disorder (GAD), several questions remain. The boundary of GAD with other disorders has been a subject of particular contention,<sup>1</sup> as has the optimal first line of pharmacotherapy. This article focuses on studies of comorbidity in GAD, on the assumption that such work may make a particularly crucial contribution to understanding the nature, course, and treatment of this disorder.

In DSM-III, GAD was a “residual” diagnosis: it was diagnosed only in the absence of other Axis I disorders. Indeed, several authors have argued that GAD should not be diagnosed in the presence of a mood disorder.<sup>2</sup> An opposite approach, however, argues that GAD can be conceived as the “basic” anxiety disorder,<sup>3</sup> with the psychobiological processes involved in GAD serving as vulnerability factors for the development of a range of psychiatric disorders.

This kind of debate about the nature of GAD demands a focus on comorbidity. In this review, the common comorbidities in GAD, their impact on functioning and medical

utilization, and their implications for treatment are discussed. 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.

## COMMON COMORBIDITIES IN GAD

Both the Epidemiologic Catchment Area study<sup>4</sup> and the National Comorbidity Survey<sup>5</sup> (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,<sup>6–11</sup> 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.<sup>12</sup> Furthermore, such studies invariably report higher comorbidity in GAD than in other anxiety disorders.<sup>11,13</sup> Similar findings are also seen in children and adolescents,<sup>14</sup> and to some extent in the elderly.<sup>15</sup>

In primary psychiatric settings, 80% to 90% of patients with current GAD have an additional current psychiatric diagnosis, and they almost invariably have a lifetime history of another psychiatric diagnosis.<sup>16</sup> In primary medical settings, similar figures have been documented.<sup>17,18</sup> It

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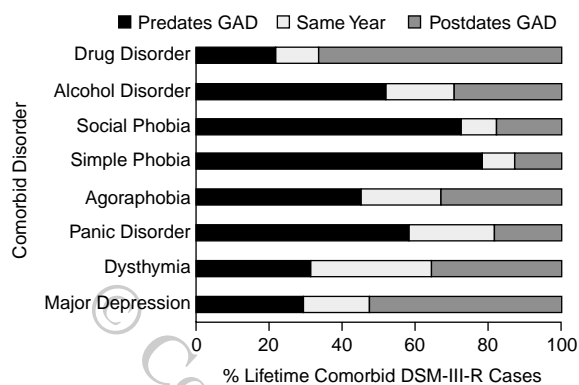
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**Figure 1. Onset of Mood and Anxiety Disorders Comorbid With Generalized Anxiety Disorder (GAD)<sup>a</sup>**



<sup>a</sup>Data from Wittchen et al.<sup>5</sup>

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.<sup>19</sup>

It is perhaps worth noting that despite the high comorbidity of GAD in many studies, the comparative odds ratios of GAD and major depression with other disorders may not be consistently larger for GAD.<sup>20</sup> Lifetime and episode 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.<sup>20</sup> Specific aspects of GAD comorbidity are discussed in greater detail in the following sections.

### Depression

In the NCS,<sup>21</sup> subjects with current GAD frequently also had current major depression (39%) or dysthymia (22%). Similarly, in GAD patients with a lifetime psychiatric diagnosis, there was often a history of major depression (62%) or dysthymia (39%). Unipolar disorders were 4 times more common than bipolar disorders.

Similarly, in the Harvard/Brown Anxiety Disorders Research Program (HARP) study<sup>22</sup> of primary psychiatry settings, 54% of GAD patients had either current major depression or dysthymia. Conversely, a number of primary care studies have shown that 35% to 50% of patients with current major depression have comorbid GAD<sup>16</sup>; this is often 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 followed by anxiety).<sup>23–26</sup> This may not be the case in the elderly, however.<sup>15</sup> Similarly, within a particular episode of depression, anxiety symptoms may begin first.<sup>16</sup> Furthermore, in prospective studies, patients with anxious symptoms are more likely to develop major depression on expo-

sure to stressful life events.<sup>27</sup> Finally, after remission of depression, GAD symptoms may remain.<sup>28</sup>

### Somatic Symptoms and Medical Disorders

In patients with unexplained somatic complaints, there is a high prevalence of both GAD and major depression.<sup>29,30</sup> Furthermore, there is some evidence that GAD may often precede the onset of somatic symptoms.<sup>31,32</sup>

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

Indeed, GAD appears to be commonly associated with chest pain,<sup>35–38</sup> chronic fatigue syndrome,<sup>39</sup> irritable bowel syndrome,<sup>31,32,40</sup> hyperventilation,<sup>41</sup> tension headache,<sup>42</sup> and chronic medical illness (hypertension, diabetes, and heart disease).<sup>30,43</sup>

It has been argued that the extent and severity of somatic symptoms in patients with anxious-somatic-depressive symptoms are informed by cultural factors.<sup>44</sup> 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.<sup>45</sup> On the other hand, a matrix of anxious-somatic-depressive symptoms does appear to be common universally.<sup>46</sup> Although genetic factors may well be relevant,<sup>47</sup> the role of environmental traumas and other stressors should also be borne in mind.<sup>33,48</sup>

### Substance Use Disorders

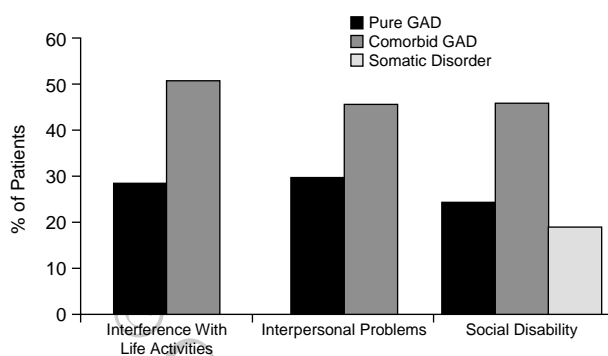
The relationship between anxiety disorders and substance use disorders has been reviewed extensively elsewhere.<sup>49</sup> It is generally accepted that there is high cross-sectional comorbidity of anxiety disorders and alcohol dependence, and there is evidence both that alcohol is used to self-medicate anxiety symptoms and that alcohol dependence may lead to anxiety symptoms.<sup>50</sup>

However, there appears to be a stronger association between 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 alcohol use disorder.<sup>49</sup> 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 disorder<sup>51,52</sup> and posttraumatic stress disorder.<sup>48</sup> However, GAD is also comorbid with other conditions, such as attention-deficit/hyperactivity disorder,<sup>53</sup> trichotillomania,<sup>54</sup> and stereotypic movement disorder.<sup>55</sup>

Figure 2. Impact of Pure and Comorbid Generalized Anxiety Disorder (GAD) on Functioning<sup>a</sup>



<sup>a</sup>Data from Wittchen et al.,<sup>5</sup> Maier et al.,<sup>18</sup> and Judd et al.<sup>21</sup>

Personality disorders in GAD have been described in a range of studies.<sup>56-58</sup> In one epidemiologic study, Nestadt et al.<sup>59</sup> 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,<sup>60</sup> stroke,<sup>61</sup> and thyroid disorders.<sup>9</sup>

### 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.<sup>20</sup> 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<sup>5</sup> (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.<sup>21</sup> Conversely, major depression comorbid with GAD is associated with more impairment than major depression without GAD.<sup>62</sup> In another analysis of the NCS data, together with the Midlife Development in the United States Survey, Kessler and colleagues<sup>20</sup> 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.<sup>20</sup>

Clinical studies have also emphasized the importance of comorbid anxiety in depression; in comparison with patients with depression alone, patients with anxious depres-

sion have higher severity of symptoms and higher risk for suicide.<sup>63,64</sup> A recent study, based on interviews of 209 outpatients, emphasizes the significance of comorbid mood and anxiety disorder in suicidal ideation and behavior.<sup>65</sup> 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,<sup>18</sup> 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.<sup>66</sup> Similarly, Sherbourne et al.<sup>67</sup> reported that in patients with chronic medical conditions, those with comorbid anxiety had lower levels of functioning and well-being.

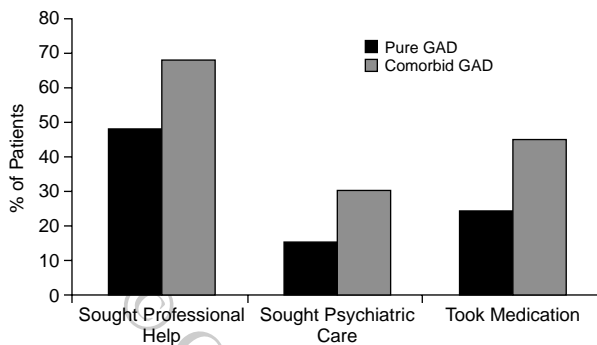
### IMPACT ON MEDICAL UTILIZATION

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<sup>18</sup> and in patients with chronic medical disorders.<sup>67</sup> 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.<sup>46</sup>

In the NCS,<sup>5</sup> 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.<sup>21</sup>

Similarly, in a study of 1042 GAD patients,<sup>68</sup> 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.

Figure 3. Impact of Pure and Comorbid Generalized Anxiety Disorder (GAD) on Health Care Utilization<sup>a</sup>



<sup>a</sup>Data from Wittchen et al.<sup>5</sup>

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.<sup>69</sup> Furthermore, anxiety symptoms may be more commonly missed than depressive symptoms.<sup>70</sup> 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<sup>37</sup>; indeed, annual medical expenditures for anxious patients have been quoted as being up to 10 times higher than for nonanxious patients.<sup>43</sup>

Certainly, GAD, somatization, and depression played a prominent role in a study of distressed high utilizers of health care,<sup>71</sup> and high utilizers who were rated as “frustrating patients” had higher rates of GAD and of somatization.<sup>72</sup>

### IMPACT ON TREATMENT

Epidemiologic studies have demonstrated the negative implications of comorbidity for course of illness. Thus, Angst and Vollrath<sup>24</sup> 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,<sup>73</sup> 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.<sup>25</sup> Similarly, in comparison with patients with nonanxious depression, those with anxious depression may have a poorer outcome and treatment response.<sup>2,74</sup> 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 comor-

bid GAD had a longer time to recovery.<sup>75</sup> In a psychotherapy study of patients with GAD, Axis I comorbidity predicted worse outcome.<sup>76</sup>

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.<sup>77</sup> Conversely, psychotherapy for panic disorder reduced the frequency of additional GAD and other comorbid disorders.<sup>3</sup> 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.<sup>44</sup> Furthermore, combinations of antidepressants and short-term anxiolytics appear useful in patients with both depression<sup>78</sup> and anxiety. Unfortunately, patients with comorbid GAD and depression continue to be treated inappropriately with benzodiazepines alone.<sup>15</sup> 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.<sup>79</sup> 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.<sup>80</sup> 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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