



**FOR CLINICAL USE**

- ◆ The prevalence of GAD appears to be higher among women; adults; whites; people with a low income; and those who are widowed, separated, or divorced.
- ◆ Reduced likelihood of recovery and remission is associated with poor family relationships, comorbid cluster C personality disorders, comorbid Axis I disorders, and female sex.
- ◆ Diagnostic criteria for GAD have been controversial since their introduction in 1980 and still cause confusion and debate.

and older), the prevalence of anxiety disorders except GAD appears to decrease compared with younger ages, but the rate of GAD may actually grow; the current prevalence of GAD in older adults has been estimated to be 4%.<sup>11</sup> However, a study<sup>12</sup> of DSM-IV disorders in older African-American adults (55 years and older) reported the lifetime prevalence of GAD to be 3.09%, somewhat lower than in the general population. In this sample,<sup>12</sup> GAD was found to be less prevalent than social phobia and posttraumatic stress disorder (PTSD) and also less prevalent than MDD and alcohol abuse.

Scant data are available for the prevalence of DSM-IV GAD in children and adolescents, in part due to changes in nomenclature. Prior to DSM-III-R, the diagnosis of GAD did not apply to children and adolescents. Even with the DSM-III-R criteria allowing the GAD diagnosis in younger patients, the symptoms of GAD in children overlapped with those of overanxious disorder. However, available research suggests that strictly defined DSM-IV GAD is uncommon in children and adolescents. Low lifetime rates of DSM-IV GAD in children were found in European studies (0.4 to 2.7%).<sup>9</sup> Further, the 1-year prevalence of DSM-IV GAD was 0.5% in children and adolescents in a US primary care site; this prevalence rate was the lowest of any of the psychiatric disorders measured in the sample.<sup>13</sup>

Generalized anxiety disorder appears to be differentially prevalent across genders and cultural groups. The disorder occurs approximately twice as often in women as it does in men.<sup>4,14</sup> Studies<sup>15,16</sup> in the United States have found that, besides female gender and older age, risk factors for GAD include having a low income and being widowed, separated, or divorced; groups that have a lower risk for GAD are Asian, Latino, and black adults. A greater 12-month prevalence of GAD has been reported in lesbian and bisexual women compared with heterosexual women (14.7% vs 3.8%), but no difference has been found between gay men and heterosexual men.<sup>17</sup>

**COURSE OF GAD**

Generalized anxiety disorder is a long-term illness with a high likelihood of recurrence. The course of GAD can be predicted or exacerbated by several factors.

**Probability of Recovery and Recurrence**

The Epidemiologic Catchment Area (ECA) study,<sup>18</sup> which used DSM-III criteria, reported that GAD persisted for longer than 5 years in 40% of individuals who were diagnosed with the disorder. Most of the available data on the longitudinal course of GAD come from the Harvard-Brown Anxiety Research Project (HARP) study,<sup>19</sup> which used DSM-III-R criteria. The HARP data support the chronic nature of GAD, as reported in the ECA study,<sup>18</sup> even though the GAD criteria changed considerably from DSM-III to DSM-III-R (see Table 1). In HARP,<sup>19</sup> over 12 years, DSM-III-R GAD was found to have a probability of recovery of 0.58, and the probability of recurrence in patients who recovered was 0.45. During the 12 years of the study, the average amount of time that patients with GAD spent ill was 74%.

Utilizing data from the Primary Care Anxiety Project, Rodriguez and colleagues<sup>20</sup> examined the probability of recovery in primary care patients with DSM-IV GAD. In this sample, the probability of recovery was 0.39 over 2 years, which is somewhat higher than that at 2 years in the HARP study.<sup>19</sup> The difference in probability rates between the 2 studies may relate to different population samples or to differences between DSM-IV and DSM-III-R criteria, but most of the methodology for these studies was very similar. Rodriguez and colleagues<sup>20</sup> found that older age at onset and less severe psychosocial impairment were associated with an increased likelihood of recovery.

**Predictors of the Course of GAD**

Predictors of the course of GAD include the status of family relationships, the presence of comorbidity, and gender. Poor relationships with a spouse or relatives and the presence of comorbid cluster C personality disorders have been associated with a reduced likelihood of GAD remission.<sup>21</sup> Comorbid Axis I disorders have also been found to affect the course of GAD; patients with GAD who had comorbid MDD, panic disorder with agoraphobia, or substance use disorders were found to be less likely to recover from GAD than those without these comorbid disorders.<sup>19</sup> Gender also seemed to affect the course of GAD; women were found to be less likely to remit than men, but they also appeared to be less likely to relapse once they had remitted.<sup>22</sup>

Table 1. Evolution of Key Criteria for Generalized Anxiety Disorder in the *Diagnostic and Statistical Manual of Mental Disorders*

DSM-III, 1980 <sup>a</sup>	DSM-III-R, 1987 <sup>b</sup>	DSM-IV, 1994, <sup>c</sup> and DSM-IV-TR, 2000 <sup>d</sup>
Generalized, persistent anxiety of at least 1 month's duration, without symptoms of phobias, panic, or obsessive compulsive disorder; or symptoms due to another mental disorder, such as depressive disorder or schizophrenia	Unrealistic or excessive worry about 2 or more circumstances, more days than not, for 6 months' duration	Anxiety and worry that: Are excessive and difficult to control, occur more days than not for at least 6 months, and are about a number of events or activities
Symptoms from 3 of the following 4 categories: • Motor tension • Autonomic hyperactivity • Apprehensive expectation (including anxiety, worry, fear) and vigilance • Must be at least 18 years old (manifested as "overanxious disorder" in children)	At least 6 symptoms from the following 3 categories: • Motor tension • Autonomic hyperactivity • Vigilance/scanning  Symptoms must not occur exclusively during the course of a mood disorder Diagnosis permissible and identical in children. However, diagnosis of overanxious disorder continued to exist with great overlap in criteria for children	Are associated with 3 or more of the following 6 symptoms: • Restlessness or feeling keyed up or on edge • Being easily fatigued • Difficulty concentrating or mind going blank • Irritability • Muscle tension • Sleep disturbance  Cause significant distress or impairment Do not occur exclusively during a mood disorder, psychotic disorder, pervasive developmental disorder, or posttraumatic stress disorder May occur in children

<sup>a</sup>Based on American Psychiatric Association.<sup>1</sup><sup>b</sup>Based on American Psychiatric Association.<sup>2</sup><sup>c</sup>Based on American Psychiatric Association.<sup>3</sup><sup>d</sup>Based on American Psychiatric Association.<sup>4</sup>

### Impairment and Severity

Impairment and severity of GAD have been examined in several studies. In the NCS-R,<sup>5</sup> 77% of GAD cases were classified as being of moderate or serious severity, which included having impairment in occupational or role function. Similarly, in an Australian survey<sup>23</sup> of current DSM-IV disorders in the general population, 72% of respondents with GAD had moderate or severe disability according to the Medical Outcomes Study 12-Item Short Form; no other anxiety disorder had a rate of moderate or severe disability as high as that of GAD.

Significant impairment in life satisfaction and well-being is also associated with GAD. In a Canadian community sample,<sup>24</sup> after controlling for the effects of MDD, lifetime and current DSM-III-R GAD were both associated with decreased perceived overall well-being. Lifetime GAD was also associated with dissatisfaction with the individual's main activity in life and with family relationships. However, GAD was not independently associated with dissatisfaction with friendships, leisure activities, or income. In other large community surveys (using both DSM-III-R and DSM-IV criteria),<sup>25-27</sup> GAD was associated with impairment that was not only independent of the effects of MDD but also equivalent in magnitude to the impairment caused by MDD.

An association with suicide, in any disorder, is one of the measures of impairment that has the greatest impact, and epidemiologic data show that GAD may be uniquely associated with suicidality. In a prospective population-

based survey<sup>28</sup> of adults in the Netherlands, DSM-III-R GAD was found to be an independent risk factor for suicidal ideation, but not suicide attempts, after adjusting for demographic factors and comorbid Axis I disorders. In a large longitudinal study of young adults (16 to 25 years) in the United States,<sup>29</sup> GAD was associated with a 6-fold increased likelihood of suicidal ideation and a more than 2-fold greater likelihood of attempted suicide, after controlling for other Axis I disorders and stressful life events.

### NOSOLOGY

Nosologic issues and controversies have existed since GAD first appeared in the nomenclature in DSM-III. The diagnostic criteria have been adjusted over time and continue to be debated.

### Past Definitions of GAD

When GAD first appeared in DSM-III, the essential features were generalized persistent anxiety that lasted 1 month or longer and did not contain symptoms of phobia, panic, or obsessive compulsive disorder (see Table 1). These features were substantially changed in the DSM-III-R to worry that was unrealistic or excessive, that was present for more days than not for at least 6 months, and that was about 2 or more circumstances.

The original diagnosis of GAD required symptoms from 3 of 4 categories. Diagnosis in the DSM-III-R

revision, however, required 6 symptoms from 3 categories. Additionally, GAD could not occur exclusively during the course of a mood disorder.

In DSM-III criteria, the individual had to be at least 18 years of age to have GAD. If the individual had similar symptoms and was a child or adolescent, the syndrome was diagnosed as overanxious disorder. In DSM-III-R, a diagnosis of GAD became permissible in children, but the diagnosis of overanxious disorder still existed, leading to a great deal of overlap in the criteria for children.

Poor interrater diagnostic reliability was found for both DSM-III and DSM-III-R.<sup>30-32</sup> High rates of comorbidity associated with GAD caused difficulty with diagnosis and in part sparked the change in the duration criterion from 1 month to 6 months in DSM-III-R; because of the comorbidity, debate surrounded whether GAD was a residual category or a prodrome of other anxiety disorders or MDD.<sup>31,32</sup> Additionally, the 1-month duration had caused challenges in distinguishing GAD from adjustment disorders or situational stress reactions.<sup>32</sup>

### Remaining Nosologic Controversies

Controversies still surround the DSM-IV GAD criteria (Table 1). Current debate relates to the duration and excessive worry criteria, the number of associated symptoms that should exist in order for GAD to be diagnosed, and the relationship between GAD and MDD.

**Duration.** Changing the duration criterion would affect estimates of the prevalence of GAD, but other findings about GAD, such as family history and level of work impairment, may not change. As might be expected, the prevalence of GAD increases as the duration requirement decreases. An analysis<sup>33</sup> of data from the NCS-R found that if the DSM-IV minimum duration criterion was changed from 6 months to between 1 and 12 months, the lifetime prevalence of GAD changed from 6.1% to between 4.2% (12-month minimum duration requirement) and 12.7% (1-month minimum duration requirement). The 1-year prevalence changed from 2.9% to between 2.2% and 5.5% (12-month and 1-month minimum duration requirements, respectively). Angst and colleagues<sup>34</sup> found that nearly half of the patients in a large Swiss prospective study who were treated for generalized anxiety would not have met the 6-month duration requirement in DSM-IV, and so they argued that this duration requirement may exclude some individuals who are significantly impaired and seek treatment.

A duration requirement less than 6 months is generally not associated with less comorbidity than the 6-month criterion. The Swiss prospective study<sup>34</sup> found that GAD with a duration criterion of less than 6 months was associated with similar comorbidity of major depressive episodes, bipolar disorder, and suicide attempts compared with GAD of 6 months' duration. An examination<sup>33</sup> of NCS-R data also found that comorbidity rates were

similar between GAD defined by a 6-month minimum duration and GAD defined by a 1-month minimum duration; among the 16 comorbid disorders measured, only PTSD, panic disorder, major depression, and bipolar I disorder were significantly ( $P < .05$ ) more common after 6 months. The odds of having comorbid dysthymia increased after 12 months. Episode duration appeared to increase social impairment but was unrelated to family or parental history of GAD, age at onset, work impairment, and persistence.<sup>33,34</sup>

**Excessive worry.** The DSM-IV criterion that states that anxiety and worry must be excessive is controversial. One of the changes in the criteria from DSM-III-R to DSM-IV was that the worry no longer needed to be "unrealistic," but the requirement that worry was "excessive" was maintained (see Table 1). Excessive worry is not required by the *International Statistical Classification of Diseases*, 10th Revision,<sup>35</sup> for a diagnosis of GAD.

Ruscio and colleagues<sup>36</sup> argued that the excessive worry criterion poses diagnostic problems because of confusion over operationally defining the term, which leads to inconsistency. The excessive worry criterion was associated with the lowest interrater agreement among GAD diagnoses, and eliminating this criterion was associated with a large increase in interrater reliability.<sup>37</sup> An examination<sup>36</sup> of NCS-R data compared participants who met the full DSM-IV criteria for GAD with those who met the criteria except for excessive worry; this study showed that, when the excessive worry criterion was dropped, the lifetime prevalence of the disorder increased by about 40%.

Differences were found in the presentation of GAD with and without excessive worry.<sup>36</sup> Generalized anxiety disorder with excessive worry was associated with an earlier age at onset, a more persistent course, greater odds of having comorbid Axis I disorders, and greater symptom severity. However, no differences were found in parental history of GAD, functional impairment, and treatment seeking among individuals with or without the excessive worry criterion. Ruscio and colleagues<sup>36</sup> argued that the excessiveness criterion may leave out many individuals who are impaired by subthreshold GAD.

**Number of associated symptoms.** In the DSM-IV, criteria for a GAD diagnosis require that 3 of 6 associated symptoms be present (Table 1); however, whether or not 3 symptoms is the optimal threshold is unclear. Little research has examined this issue, but Brown and colleagues<sup>38</sup> reported that 4 rather than 3 symptoms appear to be optimal with regard to sensitivity and specificity.

Ruscio and colleagues<sup>39</sup> suggested relaxing the criterion for associated symptoms from 3 to 2. Requiring only 2 of the 3 associated symptoms had little effect on GAD prevalence in NCS-R data because fewer than 8% of participants who endorsed any of the symptoms endorsed only 2 of them. In fact, Breslau and Davis<sup>40</sup> reported that

74% of patients with a 1-month or longer duration of GAD reported 6 symptoms.

**Independence from mood disorders.** Current DSM-IV criteria state that GAD may not occur exclusively during the course of a mood disorder. However, data suggest that this exclusion may not be valid. Zimmerman and Chelminski<sup>41</sup> compared 3 groups of patients with MDD; 1 group had only MDD, 1 group had MDD and comorbid DSM-IV GAD, and 1 group had MDD and comorbid GAD that met all criteria except the mood disorder exclusion. The investigators found that the 2 groups of patients with comorbid GAD did not differ; compared with patients with only MDD, those in both GAD groups had poorer social functioning, more suicidal ideation, more anxiety and other disorders, a greater frequency of GAD in family members, and a higher level of pathological worry.

**Simultaneous relaxation of criteria.** Ruscio and colleagues<sup>39</sup> examined the implications of simultaneously broadening the GAD criteria by reducing the 6-month duration to 1 month, including worry that patients do not describe as excessive, and decreasing associated symptoms from 3 to 2. Broadening just the duration and excessiveness criteria more than doubled the GAD lifetime prevalence (12.8%), and relaxing all 3 criteria resulted in a 13.7% lifetime prevalence. As the criteria were increasingly broadened, cases were associated with less Axis I comorbidity and with lower odds for the subsequent onset of other disorders, although most of these differences were not statistically significant. Because the temporal order of the disorders was determined from retrospective data, further prospective longitudinal studies are needed. The methods used by Ruscio and colleagues<sup>39</sup> did not allow for examination of the relaxation of the MDD hierarchy because the investigators dropped all hierarchical exclusions in their analyses.

## CONCLUSION

Generalized anxiety disorder is a relatively newly defined disorder that, as described by DSM-III-R and DSM-IV, appears to be highly prevalent, particularly among women, non-Latino whites, and older adults. The disorder has a fairly chronic course and is associated with significant impairment in functioning, independent of the effects of comorbid disorders, including MDD. Further, GAD is independently associated with increased risk of suicidality. The GAD diagnostic criteria have changed throughout iterations of the DSM, and their validity still remains in question. More research is needed to determine whether proposed further alterations of GAD criteria would dramatically change the course and presentation of the disorder.

**Disclosure of off-label usage:** The author has determined that, to the best of her knowledge, no investigational information

about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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