

# The Long-Term Clinical Course of Generalized Anxiety Disorder

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Although generalized anxiety disorder (GAD) is a common disorder associated with significant levels of morbidity, little is known of its long-term course and outcomes. During the first 5 years, GAD follows a chronic course with low rates of remission and moderate rates of relapse/recurrence following remission. Retrospective studies suggest that this chronic pattern may last up to 20 years. It is hoped that, as with depression, long-term prospective studies in GAD will provide insight into the course, nature, and outcomes of the disorder over time. The studies will also identify any changes in the duration and severity of episodes of GAD over time, enabling treatments to effectively reflect the course of the disorder. Studies of other anxiety disorders and depression suggest that the course and outcome of the disorder may be influenced by certain factors such as stressful life events, anxiety sensitivity/negative affect, gender, subsyndromal symptoms, and comorbid disorders. Currently, studies are underway to determine the effects of these factors on the risk of relapse/recurrence, maintenance of full symptoms, and development of subsyndromal symptoms in GAD. GAD is currently underrecognized and undertreated, but it is hoped that this will change with the ever-increasing awareness of anxiety disorders. As treatment for GAD becomes more common, future prospective studies will identify the effect of therapy on the course and nature of the disorder, leading to increased understanding of GAD and the development of effective treatment strategies tailored for individual patients.

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Anxiety disorders are commonly observed in the general population. Generalized anxiety disorder (GAD) is defined as chronic excessive worry of at least 6 months' duration (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [DSM-IV]).<sup>1</sup> This worry or apprehensive expectation is accompanied by at least 3 somatic or psychological symptoms, including restlessness, fatigue, muscle tension, irritability, difficulty concentrating, and sleep disturbance. There is often marked impairment of daily functioning,<sup>2,3</sup> and patients are also exposed to increased health risks,<sup>4,5</sup> including cardiovascular events<sup>6</sup> and suicide.<sup>7</sup> These factors all

contribute to the significant economic burden of anxiety disorders.<sup>8</sup>

Despite the prevalence of GAD, little is known of its natural course, although retrospective analyses suggest that the duration of illness exceeds that required for its diagnosis (presence of symptoms for at least 6 months).<sup>9-11</sup> However, data obtained from cross-sectional, retrospective, or epidemiologic analyses or randomized clinical studies may be subject to limitations. These could include restriction of analysis to point prevalence or lifetime prevalence and the answering of only specific questions, for example, clinical epidemiology or a response to treatment. In addition, observations may be restricted to limited time periods. For example, the majority of clinical trials assess patients for periods between several weeks and 1 year or, more rarely, for 3 to 5 years. Prospective long-term follow-up of chronic disorder enables insight into the course and outcome over time. This approach to the study of depression (Collaborative Depression Study) has been successful in providing key information on the characteristics and duration of the disorder and the influence of factors on its clinical course. A similar approach to the study of GAD is likely to yield information invaluable to establishing effective treatment algorithms and management programs for patients with GAD.

At present, GAD is poorly recognized and is consequently often undertreated.<sup>12,13</sup> In recent years, there has been an increasing trend toward the use of antidepressants

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for the treatment of anxiety disorders, rather than benzodiazepines. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine may extend the treatment armamentarium available to the physician for the treatment and management of anxiety disorders. For example, venlafaxine has been shown to be effective in patients with GAD both in short-term studies<sup>14,15</sup> and following 6 months' treatment.<sup>16,17</sup> It increases the proportion of patients attaining remission<sup>18</sup> and reduces the relapse rate.<sup>19</sup> Improved understanding of the long-term course, risk factors, and outcome of GAD may help to establish the most effective mode of treatment with antidepressant therapy and optimize the benefits to patients. This understanding will likely be gained from information on the patterns of the clinical course of GAD, the influence of various factors such as treatment, the impact of GAD on psychosocial functioning, and the nosology/phenomenology of GAD. This article will highlight some of the key issues in these areas, where an increased understanding of the lifetime impact of GAD may help to improve the long-term management of patients with the disorder.

## CLINICAL COURSE OF GAD

### Pattern of Remission and Relapse

Little is currently known of the long-term natural course of GAD. Data from retrospective studies have suggested an episodic pattern in which periods of remission and relapse are evident for up to 20 years.<sup>9-11</sup> A remitting course of GAD has been indicated in the 18-month follow-up of a clinical trial, at which half of the participants were without symptoms.<sup>20</sup> However, prospectively obtained data from a naturalistic short-interval follow-up study have indicated that the remission rate is low, the probability being only 0.38 at 5 years.<sup>21</sup> Moreover, relapses are common at 3 years (probability = 0.27) and more likely for patients attaining only partial remission from symptoms.<sup>21</sup>

Mapping of the clinical course of GAD, in terms of remission, recovery, relapse, and recurrence rates, over longer time periods will enable the determination of appropriate treatment and management of these patients through the course of the disorder. This may be achieved by improvements in the design of future randomized clinical studies that prospectively assess the maintenance and continuation phases of therapy and evaluate the outcome of treatments in patients with GAD, as well as effectiveness outcome studies. A similar undertaking in the evaluation of the clinical course of depression has revealed an increased risk of recurrent depression in some patients. Examples include those with frequent or multiple episodes or long duration of individual episodes.<sup>22</sup> This finding has highlighted the need for maintenance therapy to improve treatment outcomes in these patients. In addition, periods of apparent recovery between episodes when patients exhibit

symptoms of their illness may be characterized by symptoms that do not fulfill DSM criteria, but nonetheless impinge on patients' ability to function normally.<sup>23</sup> These periods of subsyndromal symptoms are predictive of relapse in depression.<sup>24</sup> It is therefore important to determine not only the pattern of the clinical course of GAD, but also whether mild anxiety symptoms persist throughout the course, even after patients have a recovery or remission from an episode. Thus, as with depressive disorders, treatment may need to be given on a long-term basis to maximize resolution of symptoms and increase the interval between episodes of illness.

Although valuable information has been obtained on the early course of GAD (e.g., Yonkers et al.<sup>21</sup>), it is not feasible to predict the course of the disorder over a possible 20-year span by extrapolation of these 5-year data. A similar prospective study of depression has indicated that patterns of relapse and remission early in the disease course may not be predictive of the pattern at later times. For example, the probability of recovery from depression in years 1-5 would predict a low level of recovery in later years,<sup>25</sup> but data collected in years 6-10 showed this not to be the case and that a further 38% of patients, who had been continually depressed for 5 years, experienced a recovery from symptoms.<sup>26</sup> Similarly, the continuous recurrence characteristics of depression were only established with data collection from 6 to 10 years<sup>26</sup> and were not predicted by a shorter follow-up of up to 5 years or the findings of retrospective analyses.<sup>27,28</sup> Hence, there is a need for detailed examination of the characteristics and course of GAD by continued prospective, long-term follow-up of patients. Only by understanding the pattern of illness over time will future treatment be most effectively managed.

### Influence of Aging

Cross-sectional epidemiologic studies have suggested that there is no difference in the prevalence of GAD between older and younger patient populations.<sup>29</sup> However, there may be an alteration in chronicity or episodic nature of the disorder with aging. Data from the U.S. National Comorbidity Survey suggested that periods during which patients were fully symptomatic were more persistent in older patients, whereas these episodes were comparatively short in younger patients.<sup>2</sup> Following patients for extended time periods will be necessary to provide a definitive answer to this issue and to evaluate the associated implications for the choice of treatment required for different groups of patients. If increasing age predicts longer or more recurrent episodes of GAD, as has been demonstrated for depression,<sup>22</sup> the elderly may require different approaches to, or duration of, treatment.

### Duration and Severity Over Time

It is presently unclear whether there is a change in duration and/or severity of fully symptomatic episodes of

GAD over time. The low remission rates reported 5 years after the index episode<sup>21</sup> suggest that, in order to observe a sufficient number of sequential episodes to enable evaluation of this possibility, long-term follow-up of patients will be necessary. Early observations in the Harvard/Brown Anxiety Disorders Research Program (HARP) suggest a trend for reduced length and severity of prospectively observed episodes (i.e., the next episode following recovery from the intake episode) (M.B.K., unpublished observations). However, the low number of patients experiencing remission and recurrence over the time period studied prevented the formation of definitive conclusions. To some extent this may reflect an initial bias due to the nature of the index episode. At study entry, patients often tend to be experiencing a particularly severe or long-lasting episode that has prompted the need to seek treatment. This is common in, and is conceptualized as severity-biased and length-biased sampling. In addition, there is retrospective recall of the precise duration of this index episode. These factors could result in reduced length and/or severity of subsequent, prospectively observed episodes. Following patients over longer periods may reduce the impact of this potential initial bias and provide pointers toward the extent of treatment required for symptoms beyond the index episode.

#### **FACTORS INFLUENCING THE COURSE OF GAD**

There are precedents from studies of other anxiety disorders and depression suggesting that a worse course and outcome in GAD could be mediated by the influence of certain variables. These include stressful life events, anxiety sensitivity/negative affect, gender, subsyndromal symptoms, and comorbid disorders, which may increase the risk of relapse/recurrence or limit the extent of improvement in, or recovery from, symptoms. Identification of these risks may enable the development of prevention strategies or appropriate early intervention with therapeutic agents for at-risk patients.

##### **Stressful Life Events**

Retrospective studies have linked the incidence of stressful or negative life events to an increased risk of developing anxiety disorders, including GAD.<sup>30-32</sup> However, there is little information on the timing of the stress in relation to the time of onset of anxiety symptoms. Furthermore, patients with chronic anxiety disorders like GAD would be likely to experience several stressful life events during the course of the illness, but the influence of these on the clinical course of GAD is yet to be established. In addition to potential effects on relapse/recurrence, it will also be of interest to determine whether life stress is important in either maintaining full symptoms of GAD or perpetuating subsyndromal symptoms. Such work is currently underway in the HARP study, and preliminary findings should be available in early 2003.

##### **Anxiety Sensitivity and Negative Affect**

Anxiety sensitivity (heightened sensitivity to normal physiologic response) and negative affect are 2 trait dimensions related to mood and anxiety disorders. Anxiety sensitivity, or autonomic physiologic hyperarousal, is an enhanced sensitivity to the normal response to anxiety or stress, which manifests as increased heart rate, trembling, shortness of breath, and dizziness. Negative affect, associated with both depression and anxiety, is sensitivity to negative stimuli and a tendency to experience a range of negative moods. Research into the impact of these traits on depressive and anxiety disorders is also currently in progress in the HARP study with preliminary findings anticipated for early 2003. There is strong evidence to suggest that negative affect is linked with a vulnerability to chronic depression and that both negative affect and anxiety sensitivity are associated with a poorer outcome in anxiety disorders.<sup>33-35</sup> However, separate anxiety disorders were not distinguished in these analyses, and hence the role of these trait dimensions in predicting or modulating the course of GAD remains to be elucidated.

##### **Gender**

Women are approximately twice as likely to be affected by GAD as men,<sup>2</sup> a ratio consistent with many other anxiety disorders. In addition, evidence indicates that gender may influence the course of some anxiety disorders. For example, the probability of relapse after remission from panic disorder is higher in female patients.<sup>36</sup> However, it is yet unknown whether gender affects the course of other anxiety disorders, including GAD. Determination of any differences between male and female patients in the course of GAD may therefore be important in establishing appropriate intervention.

##### **Subsyndromal Symptoms**

Little information is currently available on the presence and influence of subsyndromal symptoms in GAD. For patients with depression, these symptoms are predictive of relapse and are associated with impaired normal functioning.<sup>23,24</sup> It is therefore essential to understand the potential risks posed by subsyndromal symptoms in GAD and, if necessary, to determine whether sustained treatment to resolve these symptoms offers an improved long-term outcome. Conversely, it is also important to consider the predictive factors associated with patients remaining well for extended periods, in the absence of subsyndromal symptoms. An understanding of the factors promoting a more favorable course in GAD may offer new directions in its effective treatment and management.

##### **Comorbid Disorders**

Patients with GAD experience a high degree of comorbidity, with 91% presenting with at least one additional diagnosis.<sup>37</sup> Investigators from the HARP study reported

that 83% of participants with GAD had another active anxiety disorder, including 36% with concurrent panic disorder.<sup>21,38</sup> It is also common for patients to experience comorbid GAD and depression. Of patients with GAD responding to the National Comorbidity Survey, 39% reported experiencing depression in the previous 30 days, and lifetime prevalence of comorbid GAD and depression was 62%.<sup>2</sup> The presence of comorbid depression, panic disorder, or other Axis I or II disorders has been associated with a poor outcome in GAD, including a reduced likelihood of remission.<sup>20,31,39</sup> Analyses from prospective studies have reported reduced likelihood of remission from GAD in patients with concurrent personality disorders,<sup>38</sup> but no effect of concomitant depression.<sup>21</sup> Further prospective studies to assess the probability of relapse and failure to recover in patients with and without comorbid disorders should shed further light on the impact of comorbidity on the course of GAD and raise awareness of the need for effective treatment. Recent reports suggest that only 27% of patients with comorbid GAD and a mood disorder receive antidepressants (M.B.K., unpublished observations) despite the mortality and morbidity attributed to the presence of both disorders.<sup>3</sup>

### Treatment

Data obtained from the HARP study<sup>21</sup> have demonstrated that GAD has a chronic course with low remission rates and high relapse rates, despite the availability of medication such as SSRIs and venlafaxine. This would suggest that, to date, treatment does not play a defining role in the course of GAD, a conclusion consistent with other reports of the undertreatment of this disorder.<sup>13</sup> A prospective study of depression has indicated that the lowest recurrence of episodes is linked to provision of adequate therapy.<sup>27</sup> If the same is true of GAD, it is perhaps not surprising that undertreatment is associated with a poor long-term outcome. However, there is increasing public and health sector education and awareness of anxiety disorders, and hence a likely increase in the use of new, effective therapeutic agents like venlafaxine, which is indicated for the long-term treatment of GAD.

It has recently been reported that prescribing patterns of pharmacologic and psychosocial treatments for anxiety disorders have changed over the last decade.<sup>40</sup> The use of prescription medications such as antidepressants has increased dramatically from 1988 to 1998.<sup>40</sup> Although there is an increased awareness of the utility of other forms of treatment for anxiety and depressive disorders, the increase in the use of psychosocial therapy (cognitive and behavioral therapy) over the same time period has been less dramatic. Indeed, the use of 2 validated forms of psychosocial therapy was less frequent than dynamic psychosocial therapy that lacks rigorous validation.<sup>40</sup> As the use of pharmacologic and psychosocial treatments becomes more widespread, future prospective follow-up of

patients with GAD may reveal changes in the course of the disorder and in the influence on this course of factors potentially affected by therapeutic intervention, including subsyndromal symptoms and stressful life events. Moreover, data on the effects of adequate medication on these parameters will be invaluable in designing long-term maintenance studies, which may determine the most effective approaches to the management of GAD.

### PSYCHOSOCIAL FUNCTIONING

GAD is associated with considerable impairment of daily functioning.<sup>2,41</sup> There is no definitive information on the relationship between symptom severity and the extent of this impairment, although preliminary observations from the HARP study suggest that more severe symptoms are associated with worse functioning (M.B.K., unpublished observations). Furthermore, it is likely that there is impaired functioning even during apparent symptom-free intervals, perhaps due to the presence of subsyndromal symptoms. Indeed, data from studies of depression have found these symptoms to be associated with significant dysfunction in multiple domains of functioning,<sup>42,43</sup> which persists into periods of sustained recovery.<sup>44</sup> Preliminary data from a prospective study of patients with GAD indicate that an improvement in functioning after remission is only modest and that considerable psychosocial dysfunction persists for at least 18 months. Moreover, even 6 months after attainment of remission from all anxiety disorders, normal functioning is still not restored (M.B.K., unpublished observations). This is consistent with findings in depressive disorders that show that psychosocial disability is associated with symptoms and disability improves when patients are symptomatic.<sup>43</sup> Data from patients with depression indicate that even after 2 years of remission there was still meaningful improvement in functioning.<sup>44</sup> There is therefore a need to map the changes in psychosocial functioning over the course of GAD, both during episodes of full symptoms and during remission. This may indicate a need to develop and establish maintenance treatments to address impairment in functioning over extended time periods.

### NOSOLOGY OF GAD

The high rates of comorbidity and overlap in symptoms of DSM disorders have led to discussion on the validity of GAD as a distinct diagnosis. The tripartite model<sup>45</sup> to explain this overlap has suggested that negative affectivity and anxiety sensitivity are related to anxiety disorder, while low positive affectivity is specific to depression. Further longitudinal prospective studies may help elucidate the role of these traits in the manifestation and course of GAD. For example, study of the stability of

anxiety sensitivity over time, whether it is predictive of course and whether it varies in different anxiety disorders, may help to determine whether this dimension is a cause or consequence of the chronic anxiety of GAD. Similarly, investigation of all 3 traits in patients with GAD, or GAD and depression, may provide further information on the nature of comorbidity and nosology of anxiety disorders. In addition, these trait dimensions may be found to have a prognostic role, which could be of value in determining appropriate and effective treatment of anxiety disorders.

## CONCLUSION

A number of key issues relating to the long-term course, risk factors, and outcome of GAD remain unclear. Careful and detailed long-term prospective follow-up studies are likely to provide answers to many of these questions and enable determination of the most effective modes of treatment. With the advent of new efficacious agents for the long-term therapy of GAD, increased understanding of this disorder will help to maximize treatment benefits to different patient populations.

*Drug name:* venlafaxine (Effexor).

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