

Key Words: anxiety disorders, long-term treatment, Harvard/Brown Anxiety Research Program study, comorbidity, morbidity, suicide

Raising the Expectations of Long-Term Treatment Strategies in Anxiety Disorders

By Martin B. Keller, MD

ABSTRACT ~ This article describes the long-term course of anxiety disorders based on the findings of the Harvard/Brown Anxiety Research Program (HARP) study—a prospective, naturalistic, longitudinal study of patients with anxiety disorders. Data from the HARP study emphasize both the chronicity of anxiety disorders and their frequent psychiatric comorbidity with other anxiety disorders and depression. Social phobia and generalized anxiety disorder are more chronic than panic disorder, although the latter has higher rates of relapse following recovery. Anxiety disorders have a major impact on the everyday lives of sufferers. The detrimental effects on social, psychological, and physical functioning are comparable with other chronic medical and psychiatric conditions, including diabetes, heart disease, and depression. Comorbidity with depression significantly increases the probability of suicide and is associated with poorer outcome. Findings from the HARP study have significant implications for treatment, which currently tends to focus on short-term outcomes. Future studies should emphasize the role of preventive pharmacotherapy to improve the long-term course of anxiety and to reduce its associated suffering, suicide, and occupational and social impairment. *Psychopharmacology Bulletin*. 2002;36(suppl 2):166-174

INTRODUCTION

Anxiety disorders have significant detrimental effects on both social and physical functioning,¹ and are highly prevalent in the general population. In the National Comorbidity Survey² the lifetime prevalence of anxiety disorder was 24.9%, indicating that anxiety disorders are among the most common mental illnesses. Anxiety disorders encompass phobias, panic disorder, generalized anxiety disorder (GAD) and obsessive-compulsive disorder (OCD). In the Epidemiologic Catchment Area program of the National Institute of Mental Health, the lifetime prevalence rate of phobic disorders, GAD, OCD, and panic disorder was 14.6%, 6.0%, 2.5%, and 1.6%, respectively.^{3,4} Of note is the finding that the 1-month prevalence rates (6.2%, 2.6%, 1.3%, and 0.5%, respectively) were

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around one half of the lifetime rates, suggesting that anxiety disorders have a chronic clinical course.

An understanding of the long-term clinical course of anxiety disorders is required for the development of effective treatment strategies. While cross-sectional data obtained in the 1980s alluded to the chronicity of anxiety disorders, there were no prospective data on the long-term course of these disorders. The Harvard/Brown Anxiety Research Program (HARP) was therefore initiated to investigate patterns of recurrence, treatment status, suicide rates, and major psychosocial outcomes of the different anxiety disorders.⁵ It was hoped that the data generated from this study would provide a basis for the development of appropriate treatment strategies. This article describes the characterization of anxiety disorders based on the data obtained from the HARP study, and examines the implications of the data for future treatment studies.

THE LONG-TERM COURSE OF ANXIETY DISORDERS

The Harvard/Brown Anxiety Research Program

The HARP study is a prospective, naturalistic, longitudinal study of patients with anxiety disorders.⁵ A total of 711 patients seeking treatment for anxiety disorders defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition⁶ who were not suicidal, psychotic, or homicidal were recruited from 12 states in the United States. Approximately 50% of the patients had panic disorder with agoraphobia at study entry. GAD was also a common diagnosis, affecting 25% of patients at enrollment. A similar proportion of patients had social phobia. Other diagnoses were OCD (16%), posttraumatic stress disorder (8%), agoraphobia without panic disorder (4%), and anxiety not otherwise specified (8%). A high degree of psychiatric comorbidity, both with other anxiety disorders and with depression, was apparent (and is discussed in a later section).

The length of time that patients had suffered from anxiety symptoms prior to enrollment into the HARP study was disturbingly high. For patients with social phobia, the median duration of the index episode at study entry was 18 years. Patients with GAD had endured symptoms for a median of nearly 16 years, while median duration for panic disorder with agoraphobia and panic disorder alone was 13.9 and 7 years, respectively. It should be stressed that these are median data and many patients had been suffering with their illness for even longer. For example, in a minority of patients with social phobia, their illness had lasted for longer than 29 years.

Recovery Rates

A disease is described as chronic when the patient remains ill for at least 5 years.⁷ Follow-up of patients in the HARP study revealed high rates of chronicity for each of the anxiety disorders, with low cumulative rates of

recovery (defined as an 8-week period of mild symptomatology) over 5 years (Figure 1).⁸⁻¹¹ The rates of recovery were particularly low for social phobia, panic disorder with agoraphobia, and GAD (approximately 30% to 40%). However, even in panic disorder without agoraphobia, the probability of recovery was only 60% at 5 years. The data have been analyzed to identify variables influencing the clinical course of anxiety. In GAD, for example, factors predictive of failure to achieve a remission included poor family and social relationships, and concurrent personality disorders.⁸

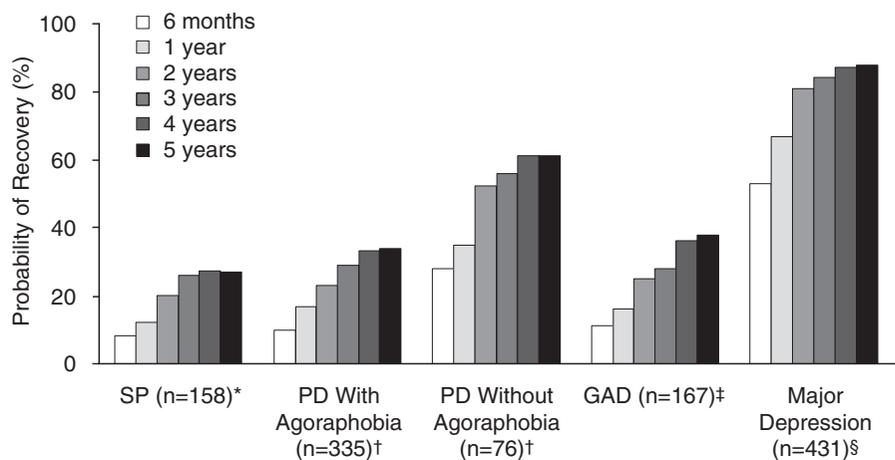
Data obtained after 8 years of follow-up continue to highlight that the clinical path of anxiety disorders has a prolonged course. For example, of the patients with social phobia, only 38% of women and 32% of men had experienced complete remission over the follow-up period.¹¹ Poor baseline functioning and a history of suicide attempts were predictive of more chronic disease, particularly among women.

Relapse Rates

The probability of relapse following recovery from anxiety episodes in participants in the HARP study is shown in Figure 2.⁸⁻¹¹ The data indicate that patients with panic disorder have particularly high relapse rates.^{9,11}

FIGURE 1

RECOVERY FROM EPISODES OF SOCIAL PHOBIA, PANIC DISORDER, GAD, AND DEPRESSION



SP=social phobia; PD=panic disorder; GAD=generalized anxiety disorder.

* Data from: Yonkers KA, Dyck IR, Keller MB. An eight-year longitudinal comparison of clinical course and characteristics of social phobia among men and women. *Psychiatr Serv.* 2001;52:637-643.

† M.B.K., unpublished data, 2001.

‡ Data from: Yonkers KA, Dyck IR, Warshaw M, Keller MB. Factors predicting the clinical course of generalized anxiety disorder. *Br J Psychiatry.* 2000;176:544-549.

§ Data from: Keller MB, Yonkers KA, Warshaw MG, et al. Remission and relapse in subjects with panic disorder and panic with agoraphobia. *J Nerv Ment Dis.* 1994;182:290-296.

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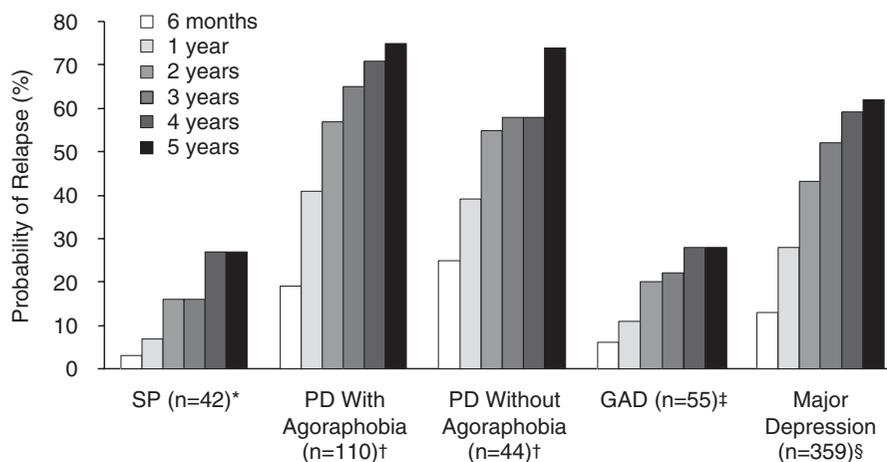
This poor outcome following recovery was apparent irrespective of whether the patient had agoraphobia, despite the difference in recovery rates found between panic disorder with agoraphobia and uncomplicated panic (Figure 1). Patients with social phobia or GAD who had demonstrated the lowest recovery rates, also had low probabilities of relapse (less than 30% at 5 years). Evidently, the different anxiety disorders are distinct in their relative relapse characteristics, with panic disorder behaving differently in its life course compared with social phobia and GAD.

Comorbidity

Patients enrolled in the HARP study had a high degree of psychiatric comorbidity, with respect to both anxiety disorders and mood disorders. This was particularly evident among those with GAD at study entry. Of these patients, over 40% also had panic disorder with agoraphobia, 35% had social phobia, 15% had simple phobia, and 15% also had OCD. Overall, 55% of GAD patients had at least one other anxiety disorder. Furthermore, patients invariably developed other new anxiety disorders during follow-up. For example, after 8 years, all but one of the patients

FIGURE 2

RELAPSE FOLLOWING RECOVERY FROM EPISODES OF SOCIAL PHOBIA, PANIC DISORDER, GAD, AND DEPRESSION



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with GAD had been diagnosed with at least one other anxiety, mood, or substance use disorder (Bruce S, PhD, unpublished data, 2001). These observations suggest that latent cotraits exist among anxiety disorders and that the current classification systems used for this group of illnesses may be inadequate.

At study entry, 58% of patients with GAD, 56% of those with social phobia, and 42% of patients with panic disorder with agoraphobia also had a history of one or more depressive disorders. The most common diagnosis of depressive disorder was major depression, which occurred in 39%, 35%, and 25% of patients, respectively. The rate of dysthymia was also found to be high throughout (up to 23% compared with ~3% in the general population). Nearly 5% of the study population as a whole had double depression (major depression and dysthymia) at study entry. These data on the prevalence of comorbidity of anxiety and depressive disorders are consistent with the findings of many other studies.^{12,13}

Morbidity of Anxiety Disorders

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The HARP study evaluated the extent of morbidity associated with the various anxiety disorders by examining each patient's role in society at study entry. Overall, only ~50% of the patients enrolled in the HARP study were working full time, despite attaining an education status typical of the rest of society. This finding was reasonably consistent across the different disorders; the proportion in full-time employment ranged from 42% for patients with panic disorder with agoraphobia to 52% for those with GAD or uncomplicated panic. Furthermore, over one fourth of the sample required public assistance (unemployment, disability, social security, or welfare). This level of public assistance was four times higher than that observed in the general population. The diagnostic group requiring the highest degree of public assistance was that of patients with GAD (37%).

Impairment of social functioning is another indicator of morbidity, and can be described in terms of the extent to which health interferes with work, housework, schoolwork, and visiting friends or relatives.¹⁴ Social functioning was evaluated in a manner similar to that of Wells and colleagues¹⁴ in their Medical Outcomes Study and it was found that panic disorder with agoraphobia, and particularly social phobia and GAD, had a considerable impact on social functioning (Figure 3).^{15,16} Furthermore, social function was affected to a greater extent in all three diagnostic groups than in patients with depression, diabetes, or coronary heart disease. Patients in the HARP study with comorbid anxiety and depression had a greater disability in most domains of social functioning than those with pure anxiety disorders.¹

The morbidity associated with anxiety disorders imposes a considerable economic burden on society. The estimated annual cost in the

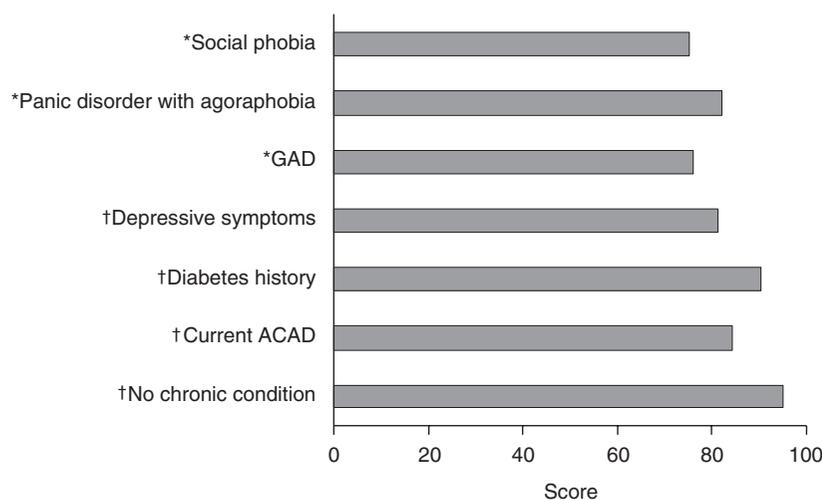
US in 1990, including nonpsychiatric and psychiatric medical treatment, mortality, and workplace costs, was \$42.3 billion.¹⁷ The economic cost of anxiety disorders is comparable to that associated with depression.¹⁸ Greenberg and colleagues¹⁷ suggested that much of the economic burden of anxiety could be avoided with greater recognition and appropriate early intervention.

Risk of Suicide

Cross-sectional studies have previously identified the risk of suicide in patients with anxiety disorders, although such patients make substantially fewer suicide attempts than patients with depressive disorders.¹⁹ In the HARP study, patients with social phobia had a significantly higher risk of attempting suicide than those with other anxiety disorders (17% versus 8%; $P < .0001$). Suicide had been attempted by 8% of patients with panic disorder with agoraphobia and by 13% of those with GAD. Patients were much more likely to attempt suicide if they also had a history of major depression. This tendency was particularly apparent for patients diagnosed with panic attacks with agoraphobia; in this patient subgroup, the risk of suicide attempts in the absence of a history of major depressive disorder was 4%, whereas

FIGURE 3

SOCIAL FUNCTIONING OF SOCIAL PHOBIA, GAD, PANIC DISORDER, DEPRESSION, AND OTHER CHRONIC MEDICAL CONDITIONS



GAD=generalized anxiety disorder.

ACAD=advanced coronary heart disease.

* M.B.K., unpublished data, 2001.

† Data from: Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *JAMA*. 1989;262:914-919.

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25% of those with a history of major depression had attempted suicide. The increased rate of suicide with comorbid depression was also evident for social phobia (21% versus 10%) and GAD (15% versus 7%). These data on the impact of comorbid depression on suicide risk are in accordance with the findings of the Epidemiologic Catchment Area study in patients with panic disorder²⁰ and the National Comorbidity Survey of patients with social phobia.²¹

IMPLICATIONS FOR TREATMENT

The findings of the HARP study have clear implications for the design of future clinical studies of drug treatment. Anxiety disorders, particularly social phobia and GAD, are chronic illnesses associated with considerable morbidity. A comparison of the findings of HARP with those of the Collaborative Study of the Psychobiology of Depression⁷ demonstrates that anxiety disorders have an even more chronic course than depression (Figure 1). It has long been recognized that depressive disorders require long-term treatment. Clearly, a similar approach to the management of anxiety disorders is required.

The HARP study also revealed that comorbidity frequently complicates the course of patients with anxiety disorders. As documented elsewhere in the literature, patients in the HARP study who had comorbid anxiety and depression had a poorer outcome in every domain of functioning than those with pure anxiety disorders, and were at greater risk of attempting suicide. It is also recognized that patients with both anxiety and depressive disorders have a significantly poorer long-term prognosis, greater chronicity, and a more severe clinical presentation of both disorders.^{13,22} Treatment strategies for anxiety must therefore take account of the frequent comorbidity of anxiety with depression. To date, few studies have specifically addressed treatment efficacy in patients with anxiety and concomitant depression.

RAISING EXPECTATIONS OF TREATMENT

The high morbidity and increased suicide risk associated with anxiety disorders, with or without comorbid depression, emphasize the need for effective treatment. The expectation should be of a rapid and sustained response of the anxiety symptoms, as well as of symptoms of depression, if present.

Clinical trials have typically evaluated new therapeutic agents for anxiety in terms of the change from baseline in one or more rating scales (eg, the Hamilton Rating Scale for Anxiety). Generally, a 50% improvement is regarded as a response, irrespective of the baseline score. However, the aim should be to get patients into remission—ie,

the resolution of clinical symptoms—so that the patient can function at a level indistinguishable from an individual without the disorder.

The attainment of remission in anxiety disorders requires long-term treatment with an effective therapy that is maintained for a period sufficient to maximize the possibility of a good treatment outcome. There is now considerable evidence supporting the use of antidepressants in the treatment of anxiety disorders.²³ Furthermore, antidepressants appear to be more effective than anxiolytics in the acute treatment of anxiety disorders.²⁴ Since an antidepressant will also alleviate the symptoms of depression, these drugs represent the most appropriate pharmacologic treatment strategy for patients with anxiety disorders.

Evolving data suggest that abnormalities of the serotonin and norepinephrine systems are involved in the neurobiology of anxiety and depressive disorders.²⁵ In this respect, a dual-action agent, such as a serotonin and norepinephrine reuptake inhibitor, may be more effective in treating anxiety disorders than a single-action, selective serotonin reuptake inhibitor, although no head-to-head comparisons of these different therapeutic agents have so far been undertaken in anxiety disorders.

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CONCLUSION

Anxiety disorders are chronic illnesses that cause psychological and physical impairment comparable to other medical illnesses. Differences in the long-term course of anxiety disorders are apparent. Social phobia and GAD are more chronic than panic disorder, but panic disorder has a high rate of relapse. Anxiety disorders are currently inadequately treated, and there is a compelling need for future clinical studies to focus on the long-term outcomes in order to reduce the disability and suicidality associated with these common disorders. However, only an agent that achieves a high rate of remission can be expected to result in an enduring symptom-free state, thereby providing patients with a better quality outcome. ♣

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