Key Words: generalized anxiety disorder, benzodiazepines, antidepressants, venlafaxine

Generalized Anxiety Disorder: Raising the Expectations of Treatment

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ABSTRACT *~ Anxiety disorders are prevalent and associated with an increase in morbidity and mortality, particularly when present with additional psychiatric disorders. They represent a public health and economic burden, yet they are commonly underrecognized and undertreated. Benzodiazepines are effective anxiolytics, but they primarily treat the somatic symptoms of generalized anxiety disorder (GAD), and are not effective in treating the depressive symptoms that are often comorbid in chronic anxiety disorders like GAD. Some antidepressants may therefore offer the best choice of therapy. Their benefit in the treatment of GAD has been demonstrated using the tricyclic antidepressant, imipramine, and some selective serotonin reuptake inhibitors. The serotonin and norepinephrine reuptake inhibitor venlafaxine extended release (XR), has been indicated for GAD and has proven to be effective in both the short- and long-term treatment of patients with this disorder. Many patients treated with venlafaxine XR achieve and sustain remission from the symptoms of GAD, which is the goal of treatment.* Psychopharmacology Bulletin. *2002;36(Suppl 2):68-78*

Introduction

Anxiety disorders are associated with increased mortality, morbidity, and economic burden.[1] Nevertheless, these disorders, particularly chronic generalized anxiety disorder (GAD), remain under-recognized and undertreated. Patients with GAD often receive inadequate or inappropriate medication, leading to a poor treatment outcome. The availability of the newer medications for the treatment of anxiety and depression has improved the options for treating GAD. This article will discuss the efficacy of these medications including the first Food and Drug Administration-approved antidepressant, venlafaxine extended release (XR), in the treatment of GAD. Because of the superior efficacy of these medications it is reasonable to raise expectations that treatment for this disorder can now attain an improved outcome, both in symptom control and improved functioning.

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The Burden of Anxiety Disorders

Anxiety is prevalent in developed societies, with approximately 10% of men and 20% of women reporting symptoms of worry, anguish, or anxiety in a Swedish survey of the general population (N=37,000).[2] Data indicate that approximately 11% of the people in the United States (US) suffer from diagnosable anxiety disorders.[1] Anxiety disorders are associated with considerable economic costs, estimated at $42.3 billion in the US in 1990.[1] A sizeable proportion of these costs (approximately 10%) is attributable to workplace costs due to lost productivity of those employees with anxiety disorders. This likely reflects the impairment of daily functioning associated with disorders like GAD.[3,4] Furthermore, anxiety disorders are associated with an approximately six times greater risk of suicide.[5] Chronic worry (a key component of GAD) is associated with a 2.4 times increased risk of a myocardial infarction.[6] In addition, there is a high incidence of comorbid disorders in patients with a primary diagnosis of anxiety: 5% of the population are likely to suffer from GAD during their lifetime, 62% of whom will be expected to experience comorbid major depression.[3] The morbidity risks associated with GAD are greatly increased in patients with comorbid GAD and major depression.[4] Therefore, anxiety disorders represent a public health hazard and the recognition and effective treatment of these disorders, particularly chronic disorders like GAD, is likely to have a beneficial impact on health and cost of illness.

Diagnosis and Characteristics of GAD

The *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition[7] (*DSM-III*), replaced the previous category of neurotic disorders with five categories: affective disorders, anxiety disorders, somatoform disorders, dissociate disorders, and psychosexual disorders. For the first time, GAD was included as a residual category defined by persistent anxiety of at least 1 month's duration. This was manifested in symptom clusters of autonomic hyperactivity, muscle tension, apprehensive expectation, and vigilance and scanning. A subsequent revision of these *DSM* criteria (*DSM-III-R*)[8] included GAD as a distinct disorder, characterized by chronic worry lasting at least 6 months. It is both excessive worry about minor issues[9] and apprehensive expectation[10] that distinguish GAD as a separate anxiety disorder. Apprehensive expectation is a mood state characterized by negative affect, chronic hyperarousal, a sense of being out of control, and threat-oriented attention. Determining the focus of this worry and identifying it as worry about multiple life circumstances distinguishes GAD from the anticipatory anxiety of other anxiety disorders.[10] "Intolerance of uncertainty" captures the cognitive dysfunction that is typical for this condition.[11]

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition[12] (*DSM-IV*) criteria defines GAD as a diagnosis for patients with chronic worry of at least 6 months' duration that is excessive, pervasive, and uncontrollable. Additional symptoms include restlessness, irritability, muscle tension, fatigue, sleep disturbance, and concentration difficulties. The somatic symptoms of GAD may be associated with altered autonomic responsiveness in these patients. For example, there is blunting of stress-induced changes in skin conductance, a reduction in blood pressure on standing, and reduced heart rate variability compared with healthy individuals.[13-15] The symptoms of GAD also lead to a chronic impairment of patients' daily and social functioning, and a perception of poor health.[3,4,16]

Although GAD has emerged as a distinct disorder, there is a high comorbidity rate. Indeed, one study reported that 91% of patients with GAD had at least one additional diagnosis.[9] The heritability of GAD and major depression is suggested to involve similar genes and hence there may be a common neurochemical abnormality in these two disorders (Gorman, pages 49-67).[17] Comorbidity is found to increase the mortality risks associated with GAD,[4] which therefore requires effective long-term treatment. The potential benefit of such treatment is illustrated by the 25% reduction in the number of suicide cases observed in Sweden between 1992 and 1997, a period coinciding with the introduction of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs).[18] Similar trends are now being observed in other countries. It seems likely that the effective anxiolytic and antidepressant medications that are available can be of substantial benefit to public health.

Treatment of Generalized Anxiety Disorder

Although GAD and subthreshold symptoms of GAD are associated with marked social disability,[1] the disorder is poorly recognized by primary care physicians; GAD is diagnosed in only 52% of affected individuals in the community.[16] Although the likelihood of treatment increases with the severity of symptoms and the extent of disability and comorbid depression, treatment rates remain low; 15% of patients with GAD are treated with anxiolytics (eg, benzodiazepines) and 8.5% are treated with antidepressants (eg, SSRIs, SNRIs, TCAs). In a general population interview survey, only 8% of patients diagnosed with GAD received treatment of any kind.[19] There is also a risk that patients are misdiagnosed with an anxiety disorder when they are actually depressed, such that they are treated with anxiolytics rather than antidepressants, leading to only partial symptom relief.[20] This may be reflected in a longitudinal study, where GAD was shown to have a worse outcome than depression (Allgulander, pages 79-92). It is therefore important to increase both the likelihood and effec-

tiveness of treatment for patients with GAD. The treatment options available for patients with GAD include psychotherapy and pharmacotherapy.

Psychotherapy

Cognitive behavior therapy (CBT) and applied relaxation, which target the chronic muscle tension, psychic tension, and excessive worry that are core symptoms of GAD, have shown some benefit in the treatment of this disorder. "Recovery rates" (score of 1 or 2 on the Clinical Global Impressions [CGI] scale, more generally defined as response in clinical studies) 6 months after treatment were 51% and 60% in patients receiving CBT or applied relaxation, respectively.[21] In contrast, analytical psychotherapy was poorly effective in the treatment of GAD, with a recovery rate of 4%.[21] CBT may therefore benefit some patients with GAD.

Pharmacotherapy

Historically, pharmacotherapy of GAD has involved the use of benzodiazepines, buspirone, and first generation antidepressants. Benzodiazepines primarily treat the somatic symptoms of GAD. Antidepressants may offer the best course of therapy since, in addition to addressing any coexisting or subsequent depressive symptoms, they appear to be more effective than benzodiazepines in the treatment of the psychic symptoms of GAD (eg, inner tension, worry, hostile feelings, and anxious mood). In addition, antidepressants are effective in GAD even in the absence of depressive symptoms. One study found that administration of imipramine, trazodone, or diazepam for 8 weeks in 230 patients with GAD but without major depression or panic disorder, was associated with a reduction in Hamilton Rating Scale for Anxiety (HAM-A) total scores compared with placebo.[22] Imipramine was associated with the greatest proportion of patients reporting an improvement in symptoms (Figure 1), and a significantly greater improvement than diazepam on the psychic symptoms of anxious mood, tension, apprehension, and worry.[22] Although there was a numeric difference, this did not reach statistical significance on psychic anxiety (worry and anxious mood) or somatic anxiety scores.[22] In addition to these data, assessment of patients with GAD after 4–6 months of treatment with an SSRI or venlafaxine showed that scores on the Temperament and Character Inventory for harm avoidance were markedly reduced, and patients became more self-confident, responsible, and cooperative.[23]

Paroxetine in the Treatment of GAD

Evidence accumulated during the 1980s to support a role for the use of antidepressants in treating patients with GAD. Recently, the efficacy of paroxetine in outpatients with GAD was evaluated in a short-term, placebo-controlled study.[24] Patients meeting the *DSM-IV* criteria for GAD (as

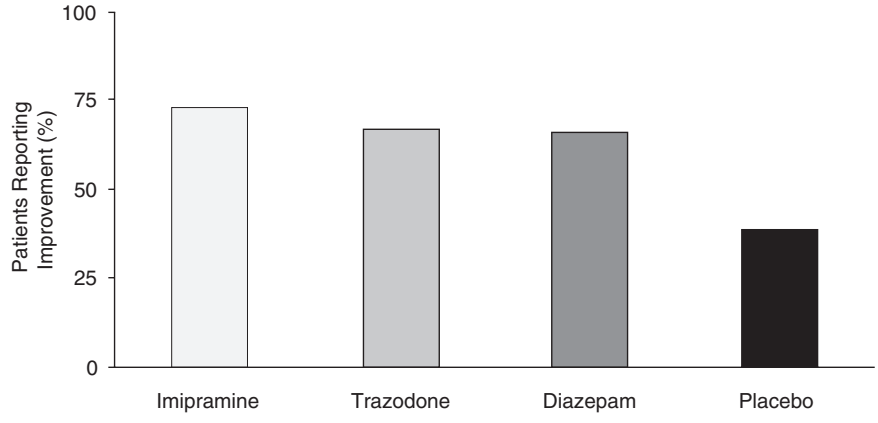
determined with the aid of the Mini-International Neuropsychiatric Interview) were included if they had a baseline HAM-A total score of ≥20 and a score of ≥2 on HAM-A items 1 (anxious mood) and 2 (tension). Patients were randomized to receive either paroxetine (20-50 mg/day; n=161) or placebo (n=163) for 8 weeks. At the last observation carried forward (LOCF), a significantly (P<.007) greater proportion of patients (62%) receiving paroxetine were responders (defined as "very much improved" or "much improved" on the CGI scale), compared with 47% of those receiving placebo. In the computer analysis, response rates were 72% for patients receiving paroxetine and 56% for those in the placebo group.

In the above study, remission was defined as a HAM-A total score of ≤7. In the LOCF analysis, a significantly (P<.006) higher proportion of patients in the paroxetine group was considered to be in remission (36%), compared with those in the placebo group (23%). The proportion of patients completing the study period and considered to be in remission was also notably higher in the paroxetine group compared with the placebo group (42% versus 26%, respectively; P<.006). Significant (P<.05) improvements were also observed on the anxious mood items and tension.

The results of this study also indicate that the impairment in social functioning observed in patients with GAD improved following 8 weeks of treatment with paroxetine, compared with those receiving placebo.

FIGURE 1

The Percentage of Patients With GAD (Without Depression) Reporting Moderate or Marked Improvement in Anxiety Symptoms Following 8 Weeks of Treatment With Imipramine, Trazodone, Diazepam, or Placebo



Adapted from: Rickels K, Downing R, Schweizer E, Hassman H. Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry*. 1993;50:884-895.

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Significant improvements were also seen on the work disability and family life disability items of the Sheehan Disability Scale.

Although the clinical efficacy of paroxetine has been demonstrated in the short-term treatment of GAD, confirmatory long-term studies are warranted, since the chronic course of GAD may require long-term therapy to produce remission.

Venlafaxine in the Treatment of GAD

The evidence available with the SNRI, venlafaxine XR, further supports the advantage offered by antidepressants in the treatment of GAD. The safety and efficacy of venlafaxine XR were evaluated in five placebo-controlled studies of patients meeting *DSM-IV* criteria for GAD, with baseline HAM-A total scores of >18 (anxious mood and tension items ≥2), and without concurrent symptoms of depression (Table 1). Pooling the data from these studies showed that the effects of venlafaxine XR were assessed in a total of 1,381 patients, in comparison with 555 patients receiving placebo. These comparisons involved patients of similar mean age (42–43 years), similar numbers of women and men (60% to 62%), and also assessed patients >60 years of age.

These five studies showed that administration of venlafaxine XR is associated with a significant reduction in HAM-A total scores, with statistical benefit over placebo becoming evident as early as 1 week after commencing treatment (Figure 2). A sustained clinical benefit was evident from weeks 3 to 4, for up to 6 months.[25-27] Effect sizes for venlafaxine XR at 8 weeks and 6 months were greatest on the anxious mood and worry items, and the tension and behavior at interview items of the HAM-A (>1),

TABLE 1

Summary of Placebo-Controlled Studies of the Efficacy of Venlafaxine XR in the Treatment of Generalized Anxiety Disorder

Three short-term studies

- Buspirone (30 mg/day) versus venlafaxine XR (75 or 150 mg/day)
- Flexible dose of venlafaxine XR
- Diazepam (15mg/day) versus venlafaxine XR (75 or 150 mg/day)

Two long-term studies

- Flexible dose of venlafaxine XR (75-225 mg/day)
- Fixed dose of venlafaxine XR (37.5, 75 or 150 mg/day)

One relapse-prevention study

- Responders to venlafaxine XR at 8 weeks re-randomized to venlafaxine XR or placebo for 4 months

XR=extended release.

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which are the key psychological aspects of GAD. Furthermore, the same HAM-A items resulted in the largest effect sizes for venlafaxine XR minus those for placebo (>0.3).[28]

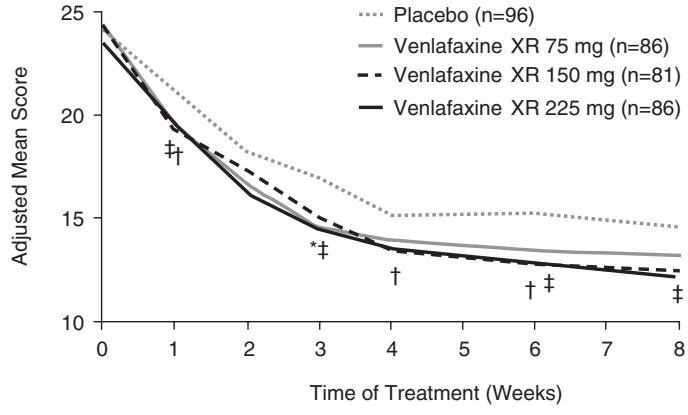
Assessment of subscale HAM-A items indicates that the anxiolytic effect of venlafaxine XR was associated with significant benefit in reducing scores in the items "psychic anxiety"[27] (Figure 3) and "anxious mood" (Figure 4).[25] The beneficial effect of venlafaxine XR (150 mg/day) on the anxious mood item of the HAM-A scale which includes worry, a key characteristic of GAD, was statistically superior to that obtained with the active control, buspirone (Figure 4).

The two most common adverse events were nausea and dizziness (lightheadedness), although the incidence of nausea during venlafaxine XR therapy declined progressively over the first 3–4 weeks from approximately 25% to 5% of patients affected. The dizziness reported by approximately 25% of those receiving buspirone was evident throughout the 8-week study period.[25]

In one study comparing fixed doses of venlafaxine XR, response rate increased dose-dependently.[27] Although this was not clearly reflected in the HAM-A total scores (Figure 2), this effect was apparent when all the separate outcome measures are considered in aggregate. Thus, of eight outcome measures, statistically significant benefit was observed in one,

FIGURE 2

HAM-A Total Scores (Adjusted Mean) at Baseline and During 8 Weeks of Treatment With Placebo or Venlafaxine XR, 75, 150, or 225 mg/day



*$P \leq .05$ venlafaxine XR 75 mg/day versus placebo.
†$P \leq .05$ venlafaxine XR 150 mg/day versus placebo.
‡$P \leq .05$ venlafaxine XR 225 mg/day versus placebo.
HAM-A=Hamilton Rating Scale for Anxiety; XR=extended release.

Adapted from: Rickels K, Pollack MH, Sheehan DV, Haskins JT. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. *Am J Psychiatry*. 2000;157:968-974.

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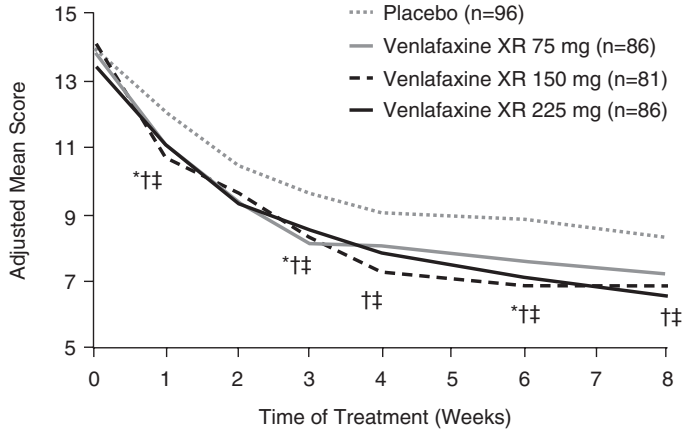
FIGURE 3

HAM-A Psychic Anxiety Factor Scores (Adjusted Mean) at Baseline and During 8 Weeks of Treatment With Placebo or Venlafaxine XR 75, 150, or 225 mg/day



* *P*≤.05 venlafaxine XR 75 mg/day versus placebo.
† *P*≤.05 venlafaxine XR 150 mg/day versus placebo.
‡ *P*≤.05 venlafaxine XR 225 mg/day versus placebo.
HAM-A=Hamilton Rating Scale for Anxiety; XR=extended release.

Adapted from: Rickels K, Pollack MH, Sheehan DV, Haskins JT. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. *Am J Psychiatry.* 2000;157:968-974.

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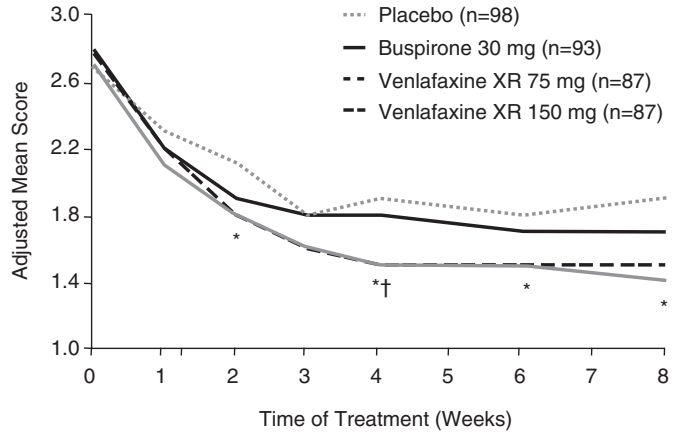
FIGURE 4

HAM-A Anxious Mood/Worry Item Scores (Adjusted Mean) at Baseline and During 8 Weeks of Treatment With Placebo, Buspirone 30 mg/day, or Venlafaxine XR, 75 or 150 mg/day



* *P*<.05 venlafaxine XR 75 mg and 150mg/day versus placebo.
† *P*<.05 venlafaxine XR 150 mg/day versus buspirone.
HAM-A=Hamilton Rating Scale for Anxiety; XR=extended release.

Source: Davidson JR, DuPont RL, Hedges D, Haskins JT. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. *J Clin Psychiatry*. 1999;60:528-535. Reprinted with permission from Physician's Postgraduate Press.

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two, and six of these measures following administration of 75, 150, or 225 mg/day venlafaxine XR, respectively (Table 2).[27]

A separate study administered fixed doses of venlafaxine XR (37.5, 75, and 150 mg/day) for 6 months to patients with GAD. A dose-dependent anxiolytic response, determined as a reduction in the mean HAM-A total score that was significantly greater than placebo, was observed.[29] The onset of anxiolytic effect was observed at weeks 1 and 2 with venlafaxine XR 150 mg, and weeks 2 and 3 with venlafaxine XR 37.5 mg and 75 mg. All doses of venlafaxine XR demonstrated significantly higher treatment response rates versus placebo as early as week 2. The anxiolytic effect of venlafaxine XR was sustained and remained greater than placebo for the 6-month duration of the study. Furthermore, there was evidence of continued improvement in symptoms over time in patients receiving venlafaxine XR, particularly at the higher doses.[29]

In a study of patients with major depression, venlafaxine XR was shown to be effective in reducing anxious symptoms.[30] In two studies, administration of venlafaxine XR for 8 and 12 weeks was associated with a significant reduction in HAM-D anxiety-psychic item scores, in addition to a reduction in Montgomery-Asberg Depression Rating Scale (MADRS) total scores compared with placebo.[30]

TABLE 2

Overview of Dose-Finding Study Results for Venlafaxine in the Treatment of Generalized Anxiety Disorder: *P* Values Versus Placebo, Final-on Therapy

	Venlafaxine XR		
Outcome Measures	*75 mg (n=86)*	*150 mg (n=81)*	*225 mg (n=86)*
HAM-A (total)	.20	.07	.03
HAM-A (psychic)	.10	.03	.01
CGI (improvement)	.15	.15	.02
CGI (severity)	.13	.06	.01
HAM-A (somatic)	.60	.29	.12
HAD (anxiety)	.02	.01	<.001
Covi (anxiety)	.21	.07	.03
Scales Showing Benefit	**1**	**2**	**6**

XR=extended release; HAM-A=Hamilton Rating Scale for Anxiety; CGI=Clinical Global Impressions Scale; HAD=Hospital Anxiety and Depression Scale; Covi=Covi Anxiety Scale.

Adapted from: Rickels K, Pollack MH, Sheehan DV, Haskins JT. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. *Am J Psychiatry*. 2000;157:968-974.

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Anxiolytic efficacy has also been demonstrated in elderly patients with GAD. In these studies, a pooled analysis was undertaken in a subgroup of patients ≥60 years of age. In this population, venlafaxine XR was significantly better than placebo with respect to reductions in HAM-A total (change from baseline: -9.9 versus -12.0 points, respectively), HAM-A psychic anxiety factor (change from baseline: -5.1 versus -6.9 points, respectively), and the Hospital Anxiety and Depression (HAD) scale (change from baseline: -4.0 versus -5.5, respectively).[31]

In summary, studies using venlafaxine XR have demonstrated that this agent is an effective anxiolytic in the treatment of GAD and anxiety symptoms in depressed outpatients. Unlike other agents, the effects of venlafaxine XR show dose-dependency over a range of doses.[27] This offers an advantage in controlling symptoms of GAD by enabling the adjustment of dose, starting from a recommended 75 mg once daily.

Conclusion

GAD is a chronic and common disorder associated with increased mortality and morbidity, which is often complicated by the existence of comorbid disorders. GAD is underdiagnosed, undertreated, and remains an economic and public health burden. Antidepressants, particularly the SSRIs and SNRIs, have a better risk/benefit ratio in the treatment of GAD than benzodiazepines and first-generation antidepressants. To achieve a good anxiolytic effect, particularly on the anxious mood and tension items, patients should be kept on their medication for at least 8 weeks before considering an alternative medication. The expectation of treatment of GAD should be to achieve remission and not just a response, to sustain long-term improvement in symptoms of anxiety, and to target any concurrent depression. The efficacy of the SNRI, venlafaxine XR, has been examined in acute and 6-month treatment studies. The drug's consistent efficacy in these studies represents an improvement over earlier treatments and raises the expectation of better treatment outcomes for patients with GAD. ✤

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