Impact of Gastrointestinal Symptom Severity on Response to Venlafaxine Extended-Release in Patients With Generalized Anxiety Disorder

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Background: This retrospective analysis evaluated the prevalence and severity of pretreatment gastrointestinal (GI) symptoms in patients with generalized anxiety disorder (GAD), the impact of these GI symptoms on the efficacy and tolerability of venlafaxine extended-release (XR), and the effect of treatment on prestudy GI symptoms.

Method: Data from 1932 nondepressed GAD patients were pooled from 5 randomized, double-blind, placebo-controlled studies of venlafaxine XR clinically conducted between May 1995 and December 1997. The GI symptom severity at baseline was estimated from item 11 on the Hamilton Rating Scale for Anxiety (HAM-A). Patients with a GI symptom severity score ≤ 2 (moderate or less) and those with a GI symptom severity score > 2 (severe/very severe) were compared for baseline characteristics and short-term (8-week) and long-term (24-week) outcomes.

Results: At baseline, for all randomized patients with a HAM-A item 11 score, GI symptoms were rated moderate or lower in 82.8% of patients (GI-low) and severe/very severe in 17.2% (GI-high). The GI-high subgroup was statistically significantly ($p < .05$) younger, had a longer duration of GAD, and had higher mean HAM-A total scores than the GI-low subgroup. Compared with placebo, venlafaxine XR significantly reduced HAM-A total and psychic anxiety factor scores, regardless of baseline GI symptom severity. The incidence of adverse events, particularly nausea, was higher for the GI-high versus GI-low subgroup.

Conclusion: Baseline severity of GI symptoms correlated with overall severity of GAD but had no impact on treatment outcome with venlafaxine XR. These data do not support the hypothesis that high baseline GI symptom severity has a negative effect on treatment with venlafaxine XR in GAD patients.

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Generalized anxiety disorder (GAD) is characterized by excessive or unrealistic anxiety or worry about daily activities.[1–3] The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[4] definition of GAD requires that the excessive worry must cause clinically significant distress, impairment in normal functioning, or both. Population-based and naturalistic follow-up studies indicate that GAD is a chronic condition that is unlikely to remit over time and that sufferers often have symptoms for decades prior to diagnosis.[3,5]

One of the reasons that patients with GAD are infrequently recognized is that they are more likely to report somatic symptoms than anxiety.[6] Patients with GAD often have gastrointestinal (GI) symptoms. One of the most common functional GI disorders is irritable bowel syndrome (IBS), which occurs in 8% to 17% of the general population, and up to two-thirds of those individuals have anxiety disorders.[7] In a recent report, GAD was found to be the most prevalent anxiety disorder in a sample of IBS sufferers. The prevalence of GAD in IBS patient samples has been reported to range from 15% to 55%.[8] In the Epidemiologic Catchment Area study, patients with 2 or more unexplained GI symptoms were more likely to have a psychiatric diagnosis than those patients with only 1 GI symptom or those patients without GI symptoms.[9]

The efficacy of venlafaxine extended-release (XR), a serotonin and norepinephrine reuptake inhibitor, has

been demonstrated in the treatment of GAD in short- and long-term studies.[10–14] Some GAD treatments, including venlafaxine XR, are known to have GI side effects. There is no information in the literature as to whether severe baseline GI symptoms in GAD patients may affect treatment tolerability and outcome. The purposes of this analysis were (1) to determine the baseline rate of GI symptoms in carefully assessed nondepressed patients with GAD, (2) to determine the effects of treatment with venlafaxine XR on these GI symptoms, (3) to determine whether the presence of severe GI symptoms at baseline has a negative effect on treatment outcome in GAD, and (4) to investigate the tolerability of venlafaxine XR according to the baseline GI symptom severity.

METHOD

Efficacy and safety data from 5 prospective, randomized, double-blind, placebo-controlled trials of venlafaxine XR (37.5–225 mg/day) for the treatment of GAD, clinically conducted between May 1995 and December 1997, were pooled to provide a large sample for analysis. All 5 studies employed a similar design during the first 8 weeks of treatment (short-term dataset). In 2 of the studies, the efficacy and safety of venlafaxine XR were investigated over 6 months (long-term dataset). All studies were conducted in accordance with the Declaration of Helsinki and used good clinical practices. All patients provided written informed consent prior to participation.

Patient Population

Patients were eligible for inclusion in the studies if they met the following criteria: satisfied DSM-IV criteria for GAD, were at least 18 years of age and in good health, had a Hamilton Rating Scale for Anxiety (HAM-A)[15] total score ≥ 18 (3 studies) or ≥ 20 (2 studies), had a score ≥ 2 on the HAM-A anxious mood and tension items, had a Raskin Depression Scale[16] score ≤ 9, and had a Covi Anxiety Scale[17] score higher than the Raskin Depression Scale score.

Patients were excluded if they had a lifetime history of psychosis, bipolar disorder, obsessive-compulsive disorder, eating disorder, or organic mental disorder. Also excluded were patients who had experienced more than 2 panic attacks within the past month, had received either neuroleptics or fluoxetine within the previous 30 days, had taken any other antidepressant within the previous 14 days, had taken hypnotic drugs within the previous 7 days, or had taken benzodiazepines on a daily or near-daily basis. Individuals diagnosed with major depressive disorder, those who had met DSM-IV criteria for alcohol or substance abuse within 6 months of screening or any other current Axis I disorder that was clinically predominant, and those with a Raskin Depression Scale subscore > 3 on "verbal report" or "behavior" or a subscore > 4 on "secondary symptoms of depression" were also excluded.

Study Assessments

For this analysis, the total scores and the scores from specific HAM-A items were examined. The HAM-A, administered at weeks 1, 2, 3, 4, 6, and 8 in the short-term dataset and additionally at weeks 12, 16, 20, and 24 in the long-term dataset, was the primary efficacy variable. The HAM-A includes 14 items that assess symptoms associated with somatic and psychic anxiety. The scale includes 1 item (item 11) that rates the severity of GI symptoms such as difficulty swallowing, nausea, vomiting, constipation, weight loss, abdominal fullness, dyspepsia, and others. Patients were divided according to their item 11 scores to create 2 subgroups consisting of those with a baseline GI severity of no to moderate symptoms (HAM-A item 11 score ≤ 2) or severe or greater symptoms (score > 2). These subgroups will be referred to as GI-low and GI-high, respectively. Other HAM-A items investigated included anxious mood (item 1), cardiovascular symptoms (item 9), respiratory symptoms (item 10), and the psychic and somatic anxiety factor scores. The anxiety subscale of the self-administered Hospital Anxiety and Depression Scale (HAD)[18] was examined as a subjective measure of anxiety.

Statistical Analyses

For these post hoc analyses, comparisons between the GI-low and GI-high subgroups were conducted. For determining clinical outcome, patients exhibiting at least a 50% decrease from baseline in the HAM-A total score were considered responders, and those with a HAM-A total score of ≤ 7 were considered remitters.

Efficacy evaluations were based on an intent-to-treat analysis, which included all randomized patients with a baseline evaluation and at least 1 evaluation of at least 1 primary efficacy variable during the double-blind treatment phase or within 3 days of terminating treatment with the study drug. Data were analyzed with the last observation carried forward method, where data from patients who discontinued treatment before the end of the study were carried forward to all subsequent time points. For efficacy analyses, scheduled mean changes in scores from baseline to endpoint were compared using analysis of covariance including factors for treatment, subgroup, study, site within study, and treatment-by-subgroup interaction. The baseline score was used as a covariate in the model. A secondary analysis was performed including the treatment-by-study and study-by-subgroup interactions in the above model to test for the validity of pooling the data. A logistic regression model including treatment, subgroup, and treatment-by-subgroup interaction was used to analyze the percentage of responders and remitters, discontinuation rates, and adverse event rates (at

Table 1. Baseline Demographic and Clinical Characteristics of GAD Patient Subgroups

	Short-Term Dataset			Long-Term Dataset[a]		
Characteristic	GI-Low (N = 1515)	GI-High (N = 317)	p Value	GI-Low (N = 622)	GI-High (N = 142)	p Value
Female, %	60	65	.049	58	69	.005
Age, mean, y	42.6	40.6	.009	43.7	40.7	.008
Body weight, kg	74.0	71.1	.009	73.9	69.7	.002
Duration of GAD episode, wk	361.5	561.0	< .001	435.0	705.8	< .001
HAM-A scores						
Total	25.1	29.1	< .001	25.2	29.7	< .001
Psychic anxiety factor	14.3	15.1	< .001	14.2	15.3	< .001
Somatic anxiety factor	10.8	14.0	< .001	11.0	14.4	< .001
Anxious mood (item 1)	2.8	3.0	< .001	2.8	3.0	< .001
GI symptom severity (item 11)	1.4	3.1	< .001	1.4	3.2	< .014
HAD anxiety subscale score	13.0	13.6	.056	13.3	14.2	.001

[a]These patients represent a subset of the short-term treatment dataset.
Abbreviations: GAD = generalized anxiety disorder, GI = gastrointestinal, HAD = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety.

baseline or treatment-emergent). These analyses were run on all patients combined and by treatment group and severity subgroup. Results of the statistical analyses were considered significant when the p value was ≤ .05.

RESULTS

Patient Characteristics

Overall, 1932 patients were randomized, and 1839 of those patients were included in the intent-to-treat analyses. Seven of the 1839 patients had a missing HAM-A item 11 score at baseline and could not be assigned to a subgroup. The short-term treatment dataset included 1832 patients, which provided data up to 8 weeks. Of those 1832 patients, 764 entered into long-term treatment and were included in the long-term treatment dataset, which provided data up to 6 months. Significant differences were observed for several baseline characteristics between the GI-low and GI-high patient subgroups (Table 1). Patients in the GI-high subgroups had significantly longer episode duration of GAD, were younger, and were more likely to be female than those in the GI-low subgroups. In both the short-term and long-term datasets, the GI-high subgroups had significantly ($p < .001$) higher mean HAM-A total, anxious mood, psychic anxiety, and somatic anxiety factor scores on all rating tests, as well as on the HAM-A respiratory (item 9) and cardiovascular items (item 10) (data not shown). On the self-rated HAD, the anxiety subscale score was significantly higher for the GI-high subgroup in the long-term dataset.

Efficacy

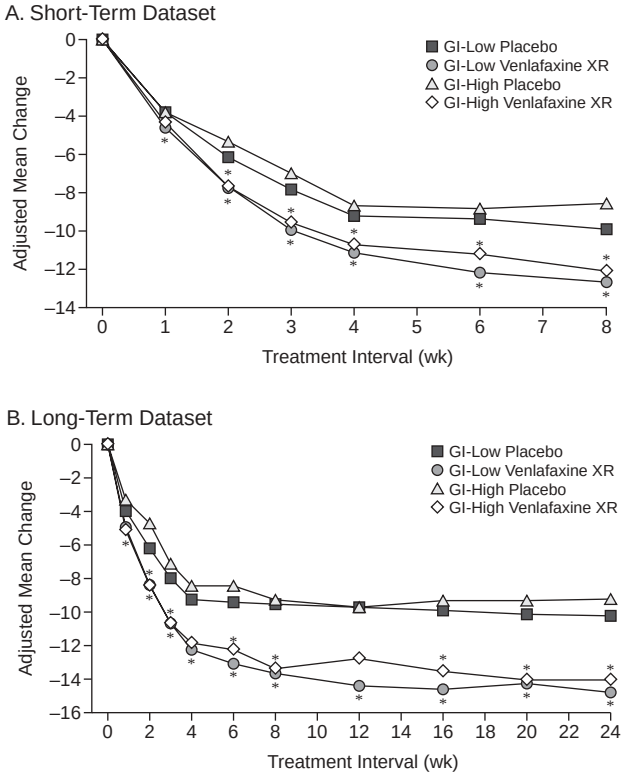
Covariance analysis showed significant treatment differences for venlafaxine XR versus placebo on all efficacy parameters. The mean change in HAM-A total score was significantly greater with venlafaxine XR than with placebo treatment at all assessment times for patients in the GI-low subgroup and at all times except week 1 in the short-term dataset and weeks 1, 4, and 12 in the long-term dataset for the GI-high subgroup (Figure 1). No significant differences were noted for the mean change in HAM-A total score between GI-low and GI-high subgroups for both placebo and venlafaxine XR in either the short- or long-term datasets.

The mean changes in HAM-A anxious mood item scores were significantly ($p < .05$) greater with venlafaxine XR than with placebo regardless of baseline severity of GI symptoms. Again, no significant differences in scores were noted between GI-low and GI-high subgroups. The pattern of anxious mood improvement was similar to that observed for the HAM-A total score.

In the short-term dataset, there were no differences in the mean change in item 11 scores between the GI-low and GI-high subgroups (Figure 2). At week 1 and only in the GI-low subgroup, the decrease in item 11 score was significantly higher ($p < .05$) for placebo-treated patients. In the long-term dataset, no difference was observed between venlafaxine XR and placebo on change in item 11 in the GI-low subgroup. In the GI-high subgroup, significant differences were found between venlafaxine XR and placebo starting from week 2 of treatment, with patients treated with placebo having a lower mean change in item 11 scores.

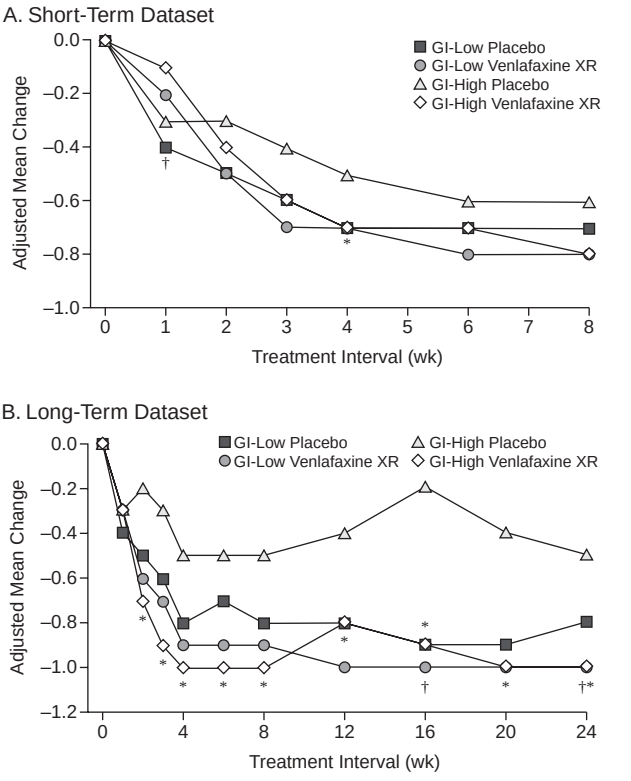
A comparison of HAM-A response rates in the GI-low and GI-high subgroups revealed no significant subgroup effect. HAM-A response rate was significantly higher with venlafaxine XR than with placebo, regardless of baseline GI symptom severity (57% vs. 40%, respectively, in GI-low and 53% vs. 34%, respectively, in GI-high at week 8). For the HAM-A remission rate, venlafaxine XR was significantly more effective than placebo starting from week 2 in the GI-low subgroup and from week 8 in the GI-high subgroup (Figure 3). Moreover, a significant subgroup effect was observed in patients treated with venlafaxine XR; the remission rate of patients in the GI-high subgroup was lower than that in

Figure 1. Mean Change in HAM-A Total Score in Venlafaxine XR and Placebo Subgroups According to Baseline GI Symptom Severity



*p < .05 venlafaxine XR vs. placebo.
Abbreviations: GI = gastrointestinal, HAM-A = Hamilton Rating Scale for Anxiety, XR = extended-release.

Figure 2. HAM-A Item 11 Scores for Venlafaxine XR and Placebo Subgroups According to Baseline GI Symptom Severity



*p < .05 venlafaxine XR vs. placebo in the GI-high subgroup.
†p < .05 venlafaxine XR vs. placebo in the GI-low subgroup.
Abbreviations: GI = gastrointestinal, HAM-A = Hamilton Rating Scale for Anxiety, XR = extended-release.

the GI-low subgroup between weeks 4 and 12 but not beyond.

To assess whether the subgroups chosen for this analysis were appropriate, we further divided the patients into 3 additional subgroups: patients with no or mild GI symptoms (HAM-A item 11 score of 0 or 1), patients with moderate GI symptoms (item 11 score = 2), and the GI-high subgroup (item 11 scores of 3 or 4). The demographic characteristics of the no-to-mild and moderate GI symptoms subgroups were comparable, while the differences between each of these subgroups and the GI-high subgroup difference remained present. Patients in the subgroup with item 11 scores of 0 or 1 symptoms had fewer adverse events at baseline than those patients with an item 11 score of 2, but both subgroups had fewer adverse events at baseline than the GI-high subgroup. There were no differences in efficacy results between the subgroup with baseline item 11 scores of 0 or 1 versus those patients with moderate (item 11 score = 2) severity ratings at baseline. These additional analyses suggest that the subgroups chosen for this retrospective analysis were appropriate.

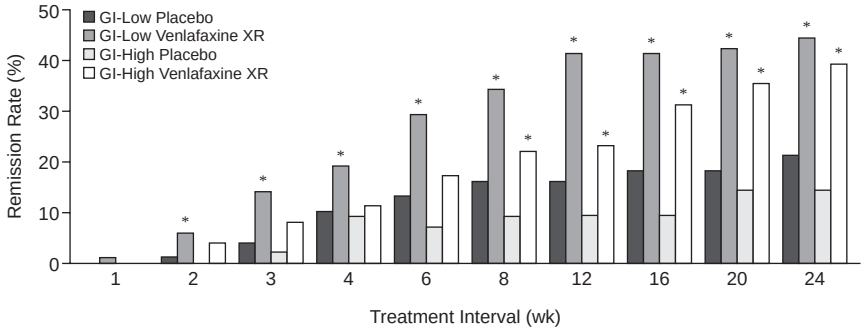
Discontinuation Rates

In the short-term dataset, the overall discontinuation rate was 27% for both placebo and venlafaxine XR in the GI-low subgroups and 33% for placebo and 25% for venlafaxine XR in the GI-high subgroup. In the long-term dataset, the overall discontinuation rate was 55% for placebo and 39% for venlafaxine XR in the GI-low subgroups ($p < .001$) and 51% and 37%, respectively, in the GI-high subgroups. Adverse event discontinuation rates for the GI-low subgroup in the short-term dataset were significantly ($p < .001$) greater with venlafaxine XR than with placebo (16% vs. 8%). However, there were no significant differences in rates of discontinuation for adverse reaction between venlafaxine XR and placebo in the GI-high subgroup.

Tolerability

At baseline, as expected, digestive symptoms reported as adverse events were significantly more common among patients in the GI-high subgroup compared with those in the GI-low subgroup (15.8% vs. 7.0%, $p < .001$ for all digestive symptoms and 5.8% vs. 2.6% for nausea

Figure 3. HAM-A Remission Rates in Venlafaxine XR and Placebo Subgroups According to Baseline GI Symptom Severity (long-term dataset)



*p < .05 venlafaxine XR vs. placebo.
Abbreviations: GI = gastrointestinal, HAM-A = Hamilton Rating Scale for Anxiety, XR = extended-release.

Table 2. Treatment-Emergent Adverse Events by GI Symptom Subgroup and Treatment (short-term dataset)[a]

	GI-Low			GI-High		
Adverse Event	Placebo (N = 463)	Venlafaxine XR (N = 1130)	p Value	Placebo (N = 89)	Venlafaxine XR (N = 241)	p Value
Headache	146 (32)	279 (25)	.006	40 (45)	55 (23)	< .001
Pain	29 (6)	40 (4)	.021	7 (8)	4 (2)	.011
Anorexia	8 (2)	76 (7)	< .001	4 (5)	16 (7)	.460
Constipation	15 (3)	100 (9)	< .001	4 (5)	18 (8)	.320
Dry mouth	28 (6)	159 (14)	< .001	4 (5)	38 (16)	.003
Nausea	48 (10)	341 (30)	< .001	22 (25)	73 (30)	.320
Pharyngitis	44 (10)	59 (5)	.002	9 (10)	22 (9)	.790
Sweating	8 (2)	97 (9)	< .001	4 (5)	18 (8)	.320

[a]Values are shown as N (%).
Abbreviations: GI = gastrointestinal, XR = extended-release.

in the short-term dataset). The most common treatment-emergent adverse events (TEAEs) that were significantly different between treatment groups during double-blind treatment are shown in Table 2. TEAEs were defined as adverse events that were not present at baseline and were observed during treatment or adverse events for which the frequency and/or severity changed during treatment.

In the GI-low subgroup, significant differences between the frequency of headache with venlafaxine XR (25%) or placebo (32%) were reported (p = .006). The next most frequently reported TEAE in the GI-low subgroup was nausea, which was reported by 30% of the venlafaxine XR group and 10% of the placebo group (p < .001). The crude incidence of nausea over time showed a higher rate for venlafaxine XR during only the first 2 weeks of treatment (Figure 4).

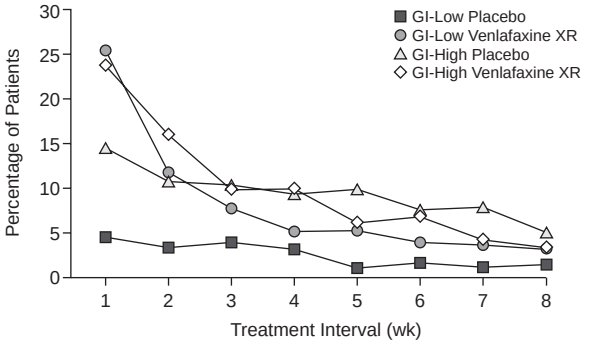
In the GI-high subgroup, again, a significantly higher rate of headache was reported for placebo (45%) compared with venlafaxine XR (23%). Unlike the GI-low subgroup, the incidence of nausea in the GI-high subgroup was not significantly different between placebo and venlafaxine XR (25% and 30%, respectively, p = .320). It is noteworthy that the incidence of treatment-emergent nausea in patients treated with venlafaxine XR was similar between the GI-high and GI-low subgroups, while the incidence of treatment-emergent nausea in the placebo GI-high patients was higher than that for the GI-low placebo patients (Figure 4).

The incidence of TEAEs in the GI-low and GI-high subgroups recorded in the long-term dataset was similar to that for that the short-term dataset during the first 8 weeks of treatment. There was no emergence of additional common TEAEs during long-term treatment.

DISCUSSION

In this large sample of GAD patients, 17.2% had severe or very severe GI symptoms at baseline as assessed by item 11 of the HAM-A. Rates of specific adverse events referable to the digestive tract were also significantly higher in the GI-high subgroup at the beginning of the study. This division of patients into GI-low and GI-high subgroups, based on severity of HAM-A item 11, clearly defined 2 different subpopulations of GAD patients. The GI-high subgroup was significantly younger by a mean of 2 to 3 years, was slightly more likely to be female, and reported a considerably longer duration of episode of GAD (approximately 200 weeks) than those

Figure 4. Incidence of Nausea With Venlafaxine XR or Placebo According to Baseline HAM-A Item 11 Scores (short-term dataset)



Abbreviations: GI = gastrointestinal, HAM-A = Hamilton Rating Scale for Anxiety, XR = extended-release.

with less-severe GI symptoms. Further, the severity of anxiety as rated on the HAM-A was also markedly higher in the GI-high subgroup. This was largely accounted for by an increase in the severity of somatic symptoms as measured by the HAM-A somatic anxiety factor and the HAM-A items for cardiovascular and respiratory symptoms. However, psychic anxiety, as measured by the HAM-A psychic anxiety factor, the HAM-A anxious mood item, and the self-rated HAD anxiety subscale was also rated significantly higher in the GI-high subgroup compared with the GI-low subgroup. These results are in agreement with previous publications that found an association between anxiety symptoms and GI or somatic complaints.[7,19,20] Consistent with higher levels of anxiety, the GI-high subgroup reported a broader range of non-GI somatic complaints at baseline than did the GI-low subgroup.

Despite these baseline and demographic differences, venlafaxine XR treatment when compared with placebo treatment significantly improved somatic and psychic symptoms of anxiety regardless of GI symptom severity. Presenting GI symptoms of severe or very severe intensity do not appear to adversely affect the efficacy of venlafaxine XR in treating anxiety. Moreover, venlafaxine XR was also significantly superior to placebo in improving GI symptom severity (HAM-A item 11 rating), irrespective of the baseline severity. Response rates were unaffected by GI symptom severity, and between-group comparisons showed a significantly higher response with venlafaxine XR in both short- and long-term datasets. There did appear, however, to be some interaction of baseline GI symptom severity on time to remission. The HAM-A remission rate among patients in the severe symptom subgroup was lower than that in the moderate subgroup during the earlier weeks of treatment in both venlafaxine XR and placebo treatment groups. However, by the end of long-term therapy, this difference had disappeared from the venlafaxine XR treatment group, though not from the placebo-treated group. This slower onset of remission in the severe symptom subgroup is most likely a reflection of the higher overall baseline severity of anxiety in this subgroup.

Montgomery et al.[21] reported that there are lower remission rates in patients with severe anxiety than with moderate anxiety until 8 weeks of treatment, but that by 6 months, similar remission rates are achieved regardless of baseline anxiety severity. Therefore, the longer time to remission in the patients with severe GI symptoms is most probably a reflection of their overall anxiety severity. This study[21] suggests that a longer period of treatment may be required for optimal benefit in GAD patients with severe GI (or multiple unexplained somatic) symptoms and underscores the importance of treating for a sufficient period of time in order to maximize the probability of a full remission. Importantly, the higher response and remission rates with venlafaxine XR were not a result of a high discontinuation rate; in fact, the overall discontinuation rate was lower with venlafaxine XR than with placebo.

By rating convention, patients in the GI-high subgroup would be expected to have GI symptoms that interfered significantly with (a rating of severe) or prevented functioning in (a rating of very severe) work, social, or occupational functioning. When patients present in primary care settings with somatic complaints and, more frequently, with unexplained GI disorders,[22,23] they are significantly less likely to be recognized as having GAD than those patients presenting in mental health settings.[24] Among outpatients who account for a significant proportion of health care costs, there is a high prevalence of patients with GAD or other anxiety disorders who have multiple unexplained symptoms and may be referred to as distressed high–health care utilizers.[2,25,26] In our study, the incidence of GI TEAEs, as typified by nausea during both short-term and long-term treatment, was indeed higher in the GI-high subgroup. However, in the GI-high subgroup, there was no difference in the incidence of treatment-emergent nausea or of other specific GI adverse events between venlafaxine XR and placebo. Patients in the GI-low subgroup experienced more nausea with venlafaxine XR treatment than with placebo, but by week 8, the difference was marginal. Patients receiving venlafaxine XR also reported pain less often than patients receiving placebo, with a more pronounced difference between the treatments in patients with severe GI symptoms. Abdominal pain is a common occurrence in patients with GI complaints or IBS and is associated with an increased frequency of anxiety and depression, more often leading patients to seek medical help.[27] Baseline GI symptom severity appeared to have no negative effect on treatment outcome in terms of overall tolerability in patients receiving venlafaxine XR.

Nausea and other adverse effects on the digestive system are well-known side effects of selective serotonin

reuptake inhibitors and have been attributed to the potent 5-HT effects of these agents.[28] The present results are therefore important in that they emphasize the need to correctly diagnose patients who present with somatic symptoms associated with GAD and to treat their symptoms of anxiety fully, even with an agent that may itself be associated with the emergence of GI side effects.

A relationship between the presence of GI symptoms and the central nervous system via involvement of the serotonergic pathway has been suggested.[7,27] A number of 5-HT active compounds, many specific for GI symptoms ($5\text{-}HT_3$/$5\text{-}HT_4$ agonist or antagonist), are under investigation for the treatment of IBS and other GI syndromes.[28,29] Antidepressants may be effective for the treatment of GI symptoms or IBS occurring either with or without comorbid psychiatric illness, although results are mostly from uncontrolled studies.[7]

There are limitations to this study that should be acknowledged. Item 11 on the HAM-A was not meant to be used as a diagnostic tool and provided only general information on the presence and severity of GI symptoms. Item 11 lists several GI symptoms (difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation). By convention, scoring 1 or possibly several symptoms in item 11 that were endorsed as the most bothersome determines the rating score for that item in the HAM-A. Since patients could be troubled by 1 symptom or by several different symptoms, it is difficult to make any more specific inferences about the nature of GI distress experienced in this study.

In conclusion, these results show that the baseline severity score on the HAM-A item 11 discriminates patients according to sex, age, and duration of episode of GAD. There is also a relationship between the severity of GAD and the severity of baseline GI symptoms and a tendency for those with severe GI symptoms to have more somatic complaints in general. However, the effectiveness and tolerability of venlafaxine XR in the treatment of GAD were found to be independent of baseline GI symptom severity. The findings are of clinical relevance since they suggest that venlafaxine XR (and possibly other antidepressants with serotonergic reuptake inhibition) may be effective and relatively well-tolerated for GAD patients with severe GI symptoms.

Drug names: fluoxetine (Prozac and others), venlafaxine (Effexor).

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