Efficacy of Venlafaxine Extended Release in Patients With Major Depressive Disorder and Comorbid Generalized Anxiety Disorder

Peter H. Silverstone, M.D., F.R.C.P.C., and Eliseo Salinas, M.D.

Background: A subset of patients with comorbid major depressive disorder and generalized anxiety disorder (GAD) was examined from a double-blind, placebo-controlled study comparing the efficacy and safety of venlafaxine extended release (XR) and fluoxetine.

Method: From a total of 368 patients, 92 patients meeting DSM-IV criteria for major depressive disorder who also had comorbid GAD were identified. The comparison group comprised 276 evaluable noncomorbid patients. Patients received venlafaxine XR (75–225 mg/day), fluoxetine (20–60 mg/day), or placebo for 12 weeks. Efficacy evaluations included Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), and Clinical Global Impressions (CGI) scale.

Results: By the final assessment at week 12, comorbid patients in the venlafaxine XR group, but not in the fluoxetine group, showed a significantly greater decrease than those in the placebo group in the primary efficacy variables of mean HAM-D and HAM-A total scores ($p < .05$, pairwise comparison). In comorbid patients, significant pairwise differences were noted between venlafaxine XR and placebo at week 12 for the secondary variables of HAM-D anxiety-somatization and retardation factors, HAM-D depressed mood item, HAM-A psychic anxiety factor, the Hospital Anxiety and Depression scale (HAD) anxiety subscale score, and the Covi Anxiety Scale score. Fluoxetine was significantly different from placebo only on the HAD depression subscale score. Response, defined as ≥ 50% decrease in symptoms score, was achieved in 66% and 59% of the comorbid patients for HAM-D and HAM-A, respectively, in the venlafaxine XR group at week 12. This response was higher than that seen with fluoxetine (52% and 45%) or placebo (36% and 24%). Onset of efficacy appeared to be slower in comorbid than in noncomorbid patients.

Conclusion: This is the first evidence from a controlled study of the effectiveness of pharmacotherapy in patients with comorbid major depressive disorder and GAD. The delayed improvement in comorbid patients compared with noncomorbid patients suggests that a longer treatment period may be necessary in comorbid patients.

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Received Aug. 5, 2000; accepted March 29, 2001. From the Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada (Dr. Silverstone) and the CNS Department, Wyeth-Ayerst Research, Paris, France (Dr. Salinas).

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Reprint requests to: Peter H. Silverstone, M.D., Department of Psychiatry, Psychopharmacology Research Unit, 1E7.13 Mackenzie Centre, University of Alberta, Edmonton, Alberta, Canada, T6G 2B7 (e-mail: peter.silverstone@ualberta.ca).

The majority of patients presenting with major depressive disorder in general practice also have some degree of associated or concomitant anxiety symptoms.[1] Indeed, major depression with acute or subsyndromal anxiety is more common than either condition alone.[2] Generally, the occurrence of depression and anxiety symptoms together is associated with greater severity of symptoms, greater impairment, more chronic course of illness, poorer outcome, and higher incidence of suicide.[3,4] In a significant proportion of these patients, the severity, quality, and chronicity of symptoms of depression and anxiety are sufficient to fulfill diagnostic criteria for major depressive disorder and generalized anxiety disorder (GAD) simultaneously.[5]

The selective serotonin and norepinephrine reuptake inhibitor venlafaxine is an established antidepressant that is effective in the treatment of patients with major depression[6,7] as well as in patients with major depression and associated symptoms of anxiety.[8–10] In addition, venlafaxine is the first of the new antidepressants to demonstrate convincing efficacy in both the short- and long-term treatment of GAD.[11,12] The extended-release (XR) formulation of venlafaxine allows once-daily administration with improved tolerability.[13]

Despite the evidence suggesting that when GAD and major depressive disorder are comorbid conditions, the symptom severity and, thus, response to treatment may be different, there have been no placebo-controlled studies examining the effectiveness of drugs in the treatment of this population. Therefore, the aim of this study was to examine the efficacy of venlafaxine XR and fluoxetine compared with placebo in patients with comorbid major depressive disorder and GAD.

METHOD

Study Design

The present analysis used data from a previously reported prospective, multicenter, double-blind, randomized, placebo-controlled comparative study of the efficacy and tolerability of once-daily venlafaxine XR and fluoxetine in 368 patients with major depressive disorder and concomitant anxiety.[14] In this study, major depressive disorder was diagnosed according to DSM-IV criteria,[15] with the symptomatic severity of concomitant anxiety being assessed using the Covi Anxiety Scale.[16] Psychiatric assessment was comprehensive and involved both interview and completion of rating scales.[14] Any comorbid psychiatric diagnoses that met DSM-IV criteria were also recorded in the case record form. Following completion of the study, a subset of patients who had a recorded comorbid diagnosis of GAD was identified in the dataset. It was considered of interest to further analyze this subset of patients.

All patients were aged 18 years or older and met DSM-IV criteria for major depressive disorder. For inclusion, patients needed a minimum score at baseline of 20 on the first 17 items of the 21-item Hamilton Rating Scale for Depression (HAM-D),[17] with ≤ 20% reduction in HAM-D total score between screening and baseline. The patients also all had a minimum score of 8 on the Covi Anxiety Scale and depressive symptoms for at least 1 month prior to study entry. Concomitant use of other psychotropic medication, other than chloral hydrate and zolpidem (10 mg) at night for sleep, was excluded. Details of other patient inclusion and exclusion criteria have been published previously.[14]

Study Procedure

Patients were assessed at baseline and throughout the 12-week double-blind phase by using the HAM-D, the Hamilton Rating Scale for Anxiety (HAM-A),[18] the Covi Anxiety Scale, the Hospital Anxiety and Depression scale (HAD),[19] and the Clinical Global Impressions (CGI) scale.[20] Patients were randomly assigned to receive a once-daily dose of venlafaxine XR, 75 mg; fluoxetine, 20 mg; or placebo for 12 weeks. At week 2, venlafaxine XR and fluoxetine doses could be increased to 150 mg and 40 mg, respectively, depending on the degree of response, with further adjustment up to a maximum of 225 mg and 60 mg, respectively, at week 4. Adverse events were elicited by questioning, and patients underwent repeated physical and laboratory examinations.

Statistical Analysis

Analyses were carried out on the 2 patient populations, those with and those without comorbid GAD. All tests of hypotheses were 2-sided and made at a 5% level of significance. One-way analysis of variance (ANOVA) was used to test for comparability of treatment groups for continuous variables such as age, weight, clinical characteristics, and baseline scores for the HAM-D total and factors, and HAM-A. Fisher exact test was used to compare nominal variables at baseline, such as sex, concurrent diagnoses, and concomitant medications.

Primary efficacy variables were the 21-item HAM-D score, the HAM-A total score, and the final CGI-Improvement (CGI-I) rating. Secondary variables were response and remission rates measured by HAM-D and HAM-A rating scales, scores on the Covi Anxiety Scale, HAM-D factors, HAD anxiety and depression subscales, and HAM-A psychic and somatic anxiety factors. Response was defined as a reduction in HAM-D or HAM-A total score of ≥ 50% from baseline. Remission was defined as a final score of ≤ 7 on the first 17 items of the HAM-D or the total HAM-A score. On the last day of study medication, efficacy assessments were performed on patients who withdrew before completing the study.

Evaluations of efficacy were performed on an intent-to-treat (ITT) basis. These analyses included all patients who were randomly assigned to double-blind medication and received at least 1 dose and had at least 1 CGI-I evaluation while on therapy, or at least 1 on-therapy evaluation and a baseline evaluation on the HAM-D or HAM-A scale. A last-observation-carried-forward (LOCF) analysis was used throughout.

HAM-D total and factor scores, HAM-A, HAD, CGI, and Covi scores were analyzed at each visit by using a 2-way analysis of covariance (ANCOVA) with treatment, center, and treatment-by-center interaction as factors and the baseline score as a covariate. This was followed by pairwise comparisons between each treatment group. A pairwise comparison was considered significant if its p value was ≤ .05. Response and remission rates were compared using the Fisher exact test, which was also used to compare the percentage of patients who discontinued.

RESULTS

From a total of 368 patients, a subset of 92 patients was identified with comorbid major depressive disorder and GAD at baseline. Ninety patients who had at least 1 baseline evaluation for at least 1 of the primary efficacy parameters and had at least 1 on-therapy evaluation for at least 1 of the primary efficacy parameters formed the ITT population of "comorbid patients." For comparative purposes, 269 of the remaining 276 patients were evaluable for the ITT efficacy population of "noncomorbid patients."

Baseline demographics and clinical characteristics of the ITT comorbid GAD and noncomorbid GAD patient subsets according to treatment groups are outlined in Table 1. Statistically significant differences were noted when comparing baseline demographics across the 2 pa-

Table 1. Patient Demographics and Clinical Characteristics at Baseline for Patients With Major Depressive Disorder and Comorbid GAD and Patients Without Comorbid GAD[a]

	Patients With Major Depressive Disorder and Comorbid GAD				Patients Without Comorbid GAD			
Variable	Placebo (N = 25)	Fluoxetine (N = 33)	Venlafaxine XR (N = 32)	Total (N = 90)	Placebo (N = 93)	Fluoxetine (N = 86)	Venlafaxine XR (N = 90)	Total (N = 269)
No. of patients, N (%)								
Male	5 (20)	13 (39)	10 (31)	28 (31)	45 (48)	35 (41)	34 (38)	114 (42)
Female	20 (80)	20 (61)	22 (69)	62 (69)	48 (52)	51 (59)	56 (62)	155 (58)
Age, y, mean (SD)	44.0 (12.0)	43.5 (10.1)	43.0 (11.7)	43.5 (11.1)	41.0 (10.4)	43.1 (11.2)	40.4 (12.1)	41.5 (11.3)
Weight, kg, mean (SD)	82.35 (16.52)	74.70 (18.02)	76.45 (16.08)	77.45 (17.04)	79.48 (18.86)	77.79 (17.48)	78.62 (18.99)	78.65 (18.42)
No. of depressive episodes, mean (SD)	6.4 (7.0)	3.6 (6.1)	3.5 (6.0)	4.3 (6.4)	1.0 (1.6)	2.0 (6.8)	1.1 (1.6)	1.4 (4.1)
Duration of current episode of depression, wk, mean (SD)	114.5 (153.9)	127.7 (359.8)	73.6 (71.3)	104.8 (235.1)	118.3 (171.5)	126.7 (203.1)	128.0 (215.4)	124.2 (196.5)

[a]Data from Silverstone and Ravindran.[14] Evaluations of efficacy were performed on an intent-to-treat basis. Abbreviations: GAD = generalized anxiety disorder, XR = extended release.

Table 2. Adjusted Mean Scores and Between-Group Comparisons Versus Placebo in Patients With Major Depressive Disorder and Comorbid GAD[a]

		Fluoxetine (N = 33)		Venlafaxine XR (N = 32)	
Scale	Placebo (N = 25)	Adjusted Mean Score	Adjusted Mean Different From Placebo (95% CL)	Adjusted Mean Score	Adjusted Mean Different From Placebo (95% CL)
HAM-D total					
Baseline	27.9	27.9		27.9	
Week 1	22.8	22.8	–0.1 (–2.8, 2.7)	24.2	–1.4 (–4.2, 1.4)
Week 2	21.2	20.4	0.8 (–2.2, 3.8)	21.0	0.3 (–2.8, 3.3)
Week 3	20.5	18.9	1.6 (–1.4, 4.7)	19.0	1.5 (–1.6, 4.6)
Week 4	18.5	16.9	1.7 (–1.6, 5.0)	17.3	1.2 (–2.2, 4.6)
Week 6	16.5	16.8	–0.3 (–3.9, 3.3)	15.9	0.6 (–3.0, 4.3)
Week 8	16.0	15.5	0.5 (–3.4, 4.5)	14.5	1.5 (–2.5, 5.6)
Week 12	16.5	14.0	2.5 (–1.7, 6.6)	11.7*	4.8 (0.6, 9.0)
HAM-A total					
Baseline	25.7	25.7		25.7	
Week 1	22.4	21.8	0.6 (–1.9, 3.1)	23.6	–1.2 (–3.8, 1.3)
Week 2	20.6	20.0	0.5 (–2.5, 3.6)	20.4	0.2 (–2.9, 3.3)
Week 3	20.2	18.6	1.6 (–1.6, 4.8)	19.2	1.0 (–2.2, 4.3)
Week 4	19.4	17.2	2.3 (–1.3, 5.8)	17.0	2.4 (–1.2, 6.1)
Week 6	17.5	17.6	–0.1 (–3.8, 3.6)	15.6	1.9 (–1.8, 5.6)
Week 8	16.1	15.9	0.2 (–4.1, 4.5)	14.4	1.7 (–2.6, 6.0)
Week 12	16.9	14.4	2.5 (–1.7, 6.7)	12.5*	4.5 (0.2, 8.7)

[a]Based on data from Silverstone and Ravindran.[14] Analysis based on last observation carried forward. Abbreviations: CL = confidence limits, GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, XR = extended release.
*Significant difference vs. placebo ($p < .05$).

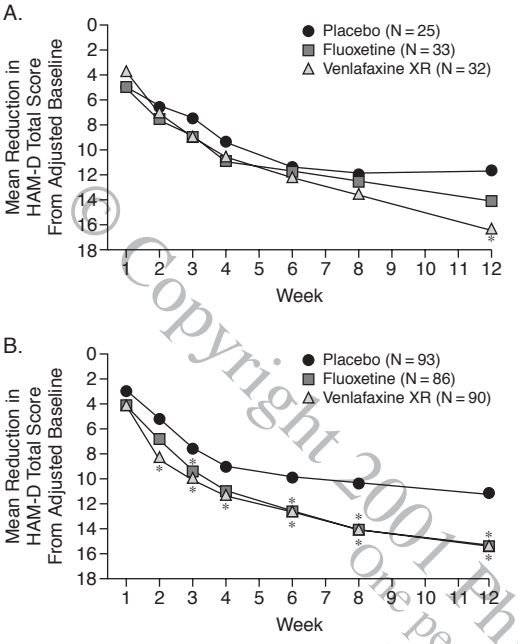
tient subsets. A greater proportion of comorbid patients were female (69%) compared with the noncomorbid population (58%; $p = .036$). Comorbid patients also tended to have a greater number of depressive episodes (mean = 4.3) than noncomorbid patients (mean = 1.4; $p < .001$). The majority of patients in both subsets completed the 12-week study: 63 (70%) of the comorbid and 181 (67%) of the noncomorbid patients, respectively. In patients within the comorbid major depressive disorder and GAD subset, there were some baseline differences between treatment groups for the demographic variables of weight, proportion of females, and number of depressive episodes. However, these differences were within the variability of the available sample size and were not statistically significant.

Efficacy

Overall, there was a steady and progressive reduction in mean HAM-D and mean HAM-A total scores at each timepoint between baseline and week 12 in patients with major depressive disorder and comorbid GAD (Table 2). Venlafaxine XR was associated with a significantly ($p < .05$) greater reduction in symptom severity on both rating scales compared with placebo at week 12 in comorbid patients (Figures 1A and 2A). Changes in CGI scores over the 12-week treatment period also indicated progressive improvement for comorbid patients, although differences between treatment groups did not reach statistical significance. There were no significant pairwise differences between the fluoxetine and placebo groups for any of these endpoints. Patients without comorbid GAD appeared to show an earlier improvement in depressive and anxiety symptoms on active treatments compared with placebo than patients with major depressive disorder and comorbid GAD, according to reductions in HAM-D and HAM-A total scores (Figures 1B and 2B). In the noncomorbid group, venlafaxine XR produced a significantly greater reduction in symptom severity compared with placebo as early as week 2.

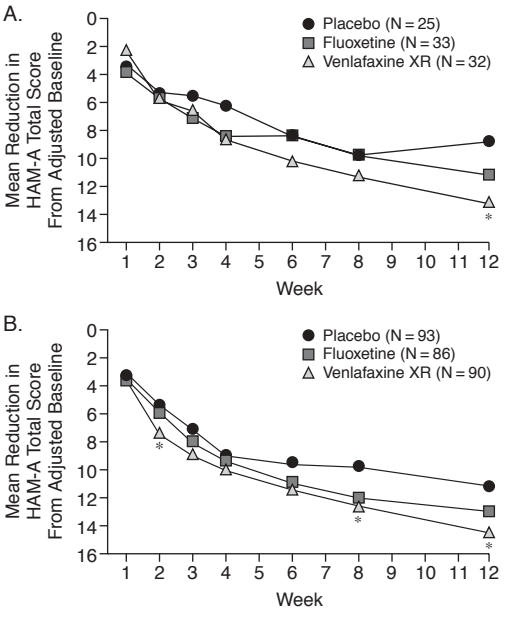
Around one third of patients with major depressive disorder and comorbid GAD treated with venlafaxine XR were rated as responders at week 4 according to HAM-D and HAM-A rating scales (Figure 3A). This proportion

Figure 1. Adjusted Mean Changes From Adjusted Baseline in HAM-D Total Score in (A) Major Depressive Disorder Patients With Comorbid GAD and (B) Patients Without Comorbid GAD[a]



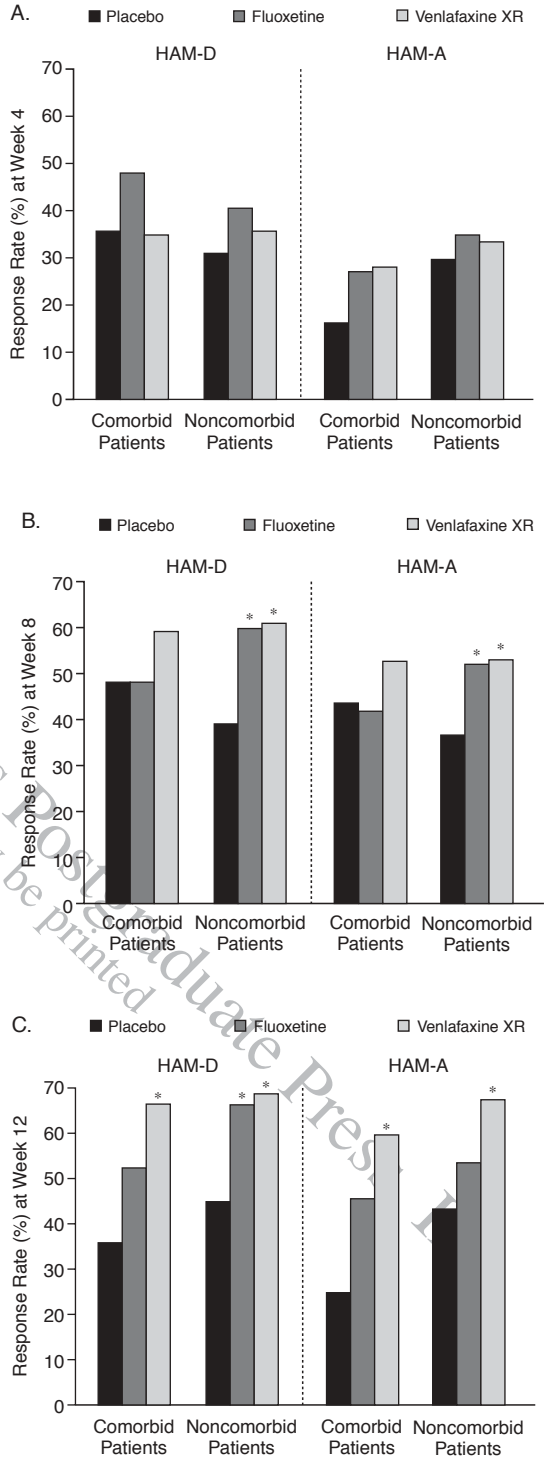
[a]Based on data from Silverstone and Ravindran.[14] Abbreviations: HAM-D = Hamilton Rating Scale for Depression, XR = extended release.
*p < .05 vs. placebo.

Figure 2. Adjusted Mean Changes From Adjusted Baseline in HAM-A Total Score in (A) Major Depressive Disorder Patients With Comorbid GAD and (B) Patients Without Comorbid GAD[a]



[a]Based on data from Silverstone and Ravindran.[14] Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, XR = extended release.
*p < .05 vs. placebo.

Figure 3. Percentage of Patients Responding at (A) Week 4, (B) Week 8, and (C) Week 12 on HAM-D and HAM-A for Major Depressive Disorder Patients With Comorbid GAD and Patients Without Comorbid GAD[a]



[a]Based on data from Silverstone and Ravindran.[14] Response defined as ≥ 50% reduction from baseline in HAM-D or HAM-A total score. Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, XR = extended release.
*p < .05 vs. placebo.

increased to over one half by week 8 (Figure 3B) and to around two thirds by week 12 (66% and 59% of patients on the HAM-D and HAM-A, respectively) (Figure 3C). At week 12, response rates on the HAM-D and HAM-A with venlafaxine XR were higher than those observed with either fluoxetine (52% and 45% of patients) or placebo (36% and 24% of patients). This difference between venlafaxine XR and placebo was statistically significant ($p < .05$) for both HAM-D and HAM-A response rates. Results of completers analyses showed a similar trend to the LOCF results described, however, due to smaller sample sizes available at week 12, there were fewer statistically significant differences between groups. According to the completers analyses, at week 12, 33%, 81%, and 71% of patients in the placebo, venlafaxine XR, and fluoxetine groups, respectively, were HAM-D responders, and 33%, 69%, and 64% of patients, respectively, were HAM-A responders.

Compared with the placebo group, a significantly higher proportion of comorbid patients treated with venlafaxine XR had remission of symptoms at week 12 on the HAM-D rating scale ($p < .05$) (Table 3). Response and remission rates for noncomorbid patients at week 12 followed a similar pattern, with a tendency for slightly higher rates across all treatment groups (Figure 3C, Table 3).

There were a number of between-treatment group differences on secondary parameters over the course of the study period. Comorbid patients treated with venlafaxine XR experienced a significant reduction in mean HAM-D depressed mood item and anxiety somatization and retardation factor scores compared with the placebo group at week 12. The reduction in mean HAM-D sleep disturbance factor score with venlafaxine XR in the comorbid group was significantly greater than that seen in the fluoxetine treatment group. The mean HAM-A psychic anxiety score was significantly reduced compared with placebo at week 4 as well as at week 12 in comorbid patients treated with venlafaxine XR. Venlafaxine XR also showed superior efficacy versus placebo on the HAD anxiety subscale score at week 4 and week 12 and the Covi total score at

Table 3. Remission Rates in Patients With Major Depressive Disorder and Comorbid GAD and Patients Without GAD on HAM-D and HAM-A Rating Scales[a]

	Patients With Major Depressive Disorder and Comorbid GAD						Patients Without Comorbid GAD					
	Placebo (N = 25)		Fluoxetine (N = 33)		Venlafaxine XR (N = 32)		Placebo (N = 93)		Fluoxetine (N = 86)		Venlafaxine XR (N = 90)	
Scale	N	%	N	%	N	%	N	%	N	%	N	%
HAM-D												
Week 4	1	4	4	12	4	13	8	9	12	14	19	21
Week 8	3	12	8	24	10	31	17	18	31	36*	28	31
Week 12	3	12	11	33	13	41*	23	25	41	48*	43	48*
HAM-A												
Week 4	1	4	4	12	1	3	12	13	12	14	20	22
Week 8	3	12	10	30	5	16	18	19	23	27	26	29
Week 12	3	12	12	36	10	31	26	28	28	33	42	47*

[a]Based on data from Silverstone and Ravindran.[14] Remission defined as HAM-D or HAM-A total score ≤ 7. Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, XR = extended release.
*Significant difference vs. placebo ($p < .05$).

Table 4. Primary Reasons for Discontinuation of Treatment in Major Depressive Disorder Patients With or Without Comorbid GAD[a]

	Patients With Major Depressive Disorder and Comorbid GAD						Patients Without Comorbid GAD					
	Placebo (N = 25)		Fluoxetine (N = 33)		Venlafaxine XR (N = 34)		Placebo (N = 94)		Fluoxetine (N = 88)		Venlafaxine XR (N = 94)	
Reason for Discontinuation	N	%	N	%	N	%	N	%	N	%	N	%
Any	7	28	12	36	10	29	41	44*	20	23	27	29
Unsatisfactory response	3	12	2	6	1	3	26	28*	4	5	5	5
Adverse reaction	1	4	2	6	4	12	5	5	6	7	9	10
Other	3	12	8	24	5	15	10	11	10	11	13	14

[a]Based on data from Silverstone and Ravindran.[14] Abbreviations: GAD = generalized anxiety disorder, XR = extended release.
*Significant difference vs. venlafaxine XR and fluoxetine ($p < .001$).

Table 5. Most Common Treatment-Emergent Adverse Events in Major Depressive Disorder Patients With or Without Comorbid GAD[a]

	Patients With Major Depressive Disorder and Comorbid GAD						Patients Without Comorbid GAD					
	Placebo (N = 25)		Fluoxetine (N = 33)		Venlafaxine XR (N = 34)		Placebo (N = 94)		Fluoxetine (N = 88)		Venlafaxine XR (N = 94)	
Event	N	%	N	%	N	%	N	%	N	%	N	%
Headache	14	56	17	52	17	50	45	48	46	52	40	43
Nausea	8	32	9	27	13	38	25	27	30	34	39	41
Dizziness	6	24	4	12	11	32	14	15	18	20	38	40
Insomnia	3	12	3	9	7	21	9	10	27	31	34	36
Sweating	0	0	4	12	4	12	12	13	17	19	32	34
Dry mouth	2	8	3	9	4	12	12	13	19	22	26	28
Dyspepsia	2	8	3	9	1	3	14	15	21	24	12	13
Diarrhea	5	20	7	21	4	12	14	15	16	18	18	19
Nervousness	1	4	2	6	5	15	7	7	12	14	18	19
Constipation	2	8	2	6	4	12	11	12	11	13	18	19
Somnolence	1	4	4	12	4	12	6	6	13	15	13	14

[a]Based on data from Silverstone and Ravindran.[14] Abbreviations: GAD = generalized anxiety disorder, XR = extended release.

week 12. Fluoxetine was significantly different from placebo only on the HAD depression subscale score.

Safety

The proportion of patients with comorbid GAD discontinued from the study for any reason was similar in each of the 3 treatment groups (approximately 30%) (Table 4). In the noncomorbid population, however, a significantly higher proportion of patients who received placebo discontinued compared with patients receiving active treatment ($p < .001$). This difference appeared to be related to the significantly higher proportion of patients that discontinued for unsatisfactory response in the placebo group compared with the active treatment groups. A similar trend was noted for comorbid patients, but the difference was less pronounced and did not reach statistical significance. In both subsets there was a nonsignificant trend for more patients in the active treatment groups than in the placebo group to discontinue because of adverse reactions.

The most common treatment-emergent adverse events in any treatment group in the total population are listed in Table 5. The frequency of these events in comorbid and noncomorbid patients is presented for comparison. There was a tendency for fewer comorbid patients to report such events with active treatment compared with similarly treated noncomorbid patients, although the relative frequency of events between the different treatment groups was broadly similar.

DISCUSSION

Although there is much evidence suggesting that patients with comorbid mood and anxiety disorders have a more chronic course of illness, a poorer outcome, and a higher incidence of relapse and suicide than patients without comorbidity,[3,4] there have been few, if any, evaluations of treatments in this area. This is the first article to present placebo-controlled data on treatment outcomes in patients with comorbid major depressive disorder and GAD. The diagnoses for both conditions in this analysis were made according to DSM-IV diagnostic criteria by the investigator, and these preliminary data from a previously reported double-blind, placebo-controlled trial provide important and clinically relevant information on the efficacy and safety of treatment in this subset of patients, given the current lack of data on this topic.

The results indicate that venlafaxine XR improved symptoms of depression and anxiety in this group of comorbid patients over the 12-week study period. The reduction in mean HAM-D and HAM-A total scores was significantly greater with venlafaxine XR compared with placebo at the study endpoint. Fluoxetine showed a similar trend. However, the reduction in HAM-D and HAM-A scores with fluoxetine failed to differ significantly from the placebo group throughout the study period. Venlafaxine XR demonstrated superiority over placebo on a variety of primary and secondary rating scales as early as week 2 in the original study cohort, but improvements seen with venlafaxine XR in patients with comorbid major depressive disorder and GAD appeared somewhat delayed and more modest.[14] Although the smaller sample sizes in the comorbid patients resulted in loss of power to show statistical differences, there did not appear to be even a trend for a placebo-drug difference until after the eighth week of treatment (Figure 1).

The proportion of comorbid patients responding to treatment with venlafaxine XR (66% on HAM-D and 59% on HAM-A), although lower than that observed in the noncomorbid group or original cohort, was higher than that with fluoxetine in this subset of patients and, in contrast to fluoxetine, significantly superior to placebo at week 12. Significantly more comorbid patients had remission of depressive symptoms with venlafaxine XR than did placebo recipients at week 12. Thus, despite the greater resistance to treatment reported with comorbid major depressive disorder and GAD, around two thirds of patients responded to venlafaxine XR and 30% to 40% achieved remission of anxiety or of depressive symptoms. This finding is in line with several studies demonstrating superior efficacy (both immediate- and extended-release formulations) in patients with major depressive disorder for venlafaxine compared with selective serotonin reuptake inhibitors (SSRIs),[21,22] for example, fluoxetine[23–26] and paroxetine.[27,28] The frequency and nature of adverse events reported in the comorbid subset of patients were substantially similar to those in the original cohort.

These results need to be replicated. This was a post-hoc analysis from a study that was prospectively designed to demonstrate the efficacy of venlafaxine XR in depressed patients with concomitant anxiety, rather than to demonstrate efficacy in patients with comorbid major depressive disorder and GAD. The results, however, strongly suggest that monotherapy with venlafaxine XR is effective and safe in the treatment of patients with comorbid major depression and GAD. Comorbid disorders present a particular challenge for general practitioners and specialists treating psychiatric illness. Findings from the National Comorbidity Survey (NCS) in the United States suggest that the vast majority of psychiatric disorders are comorbid.[5] Overall, around half of NCS participants experienced psychiatric illness during their lifetime, with drug dependence the most common category, followed by anxiety disorders and affective disorders. The most common single psychiatric disorder identified in the NCS was major depression (1-year and lifetime prevalence of 11.3% on HAM-D and 17.1% on HAM-A). Almost one quarter of individuals interviewed in the NCS had an anxiety disorder during their lifetime. GAD had 1-year and

lifetime prevalence of 3.1% and 5.1%, respectively. Similar results are reported in other epidemiologic surveys, with 1-year prevalence rates for GAD of 5.2% in the Zurich epidemiologic survey[29] and 3.8% in the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) Program.[30]

An important finding of the ECA and NCS surveys was the high incidence of comorbidity in psychiatric illness (around 60% of patients had a lifetime history of 2 or more disorders) and that this was associated with a more serious course of illness. Data from the NCS and Early Developmental Stages of Psychopathology Study report a risk of comorbid GAD with major depressive disorder of 15.4% and 17.0%, respectively.[31]

In conclusion, this analysis of data from a double-blind, placebo-controlled study is the first to provide evidence in favor of pharmacotherapy for patients with comorbid major depression and GAD. Once-daily monotherapy with venlafaxine XR significantly improved depressive and anxiety symptoms compared with placebo in this subset of patients and was well tolerated. The apparently later onset of efficacy of venlafaxine XR in comorbid patients compared with noncomorbid patients has clinical implications. From this evidence it appears prudent to assess patients with comorbid major depressive disorder and GAD for a longer period of time than noncomorbid patients before treatment is deemed ineffective and they are either classified as nonresponders or have their treatment altered. This study also adds further evidence to the literature suggesting that in this context, dual-action drugs may be more effective than single-action drugs.

Drug names: fluoxetine (Prozac), paroxetine (Paxil), venlafaxine (Effexor), zolpidem (Ambien).

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