

# Time to Relapse After 6 and 12 Months' Treatment of Generalized Anxiety Disorder With Venlafaxine Extended Release

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**Context:** Generalized anxiety disorder (GAD) is a chronic disorder in need of reliable data to guide long-term treatment.

**Objectives:** To assess the benefits of 6 and 12 months' treatment of GAD with venlafaxine hydrochloride extended release (XR) in patients who improved after 6 months' open-label venlafaxine XR treatment.

**Design:** After 6 months' open-label venlafaxine XR treatment, improved patients were randomized to venlafaxine XR or placebo for 6 months. All venlafaxine XR patients still in the study at 12 months were randomized to receive venlafaxine XR or placebo, and all placebo patients continued taking placebo for another 6 months.

**Setting:** One urban site (5 locations).

**Patients:** Of 268 patients with a diagnosis of GAD entering the open-label venlafaxine XR treatment phase, 158 (59.0%) completed 6 months, and 136 (50.7%) entered relapse phase 2 (6-12 months). Fifty-nine (43.4%) of 136 patients entered phase 3 (12-18 months).

**Intervention:** Six months' open-label treatment with venlafaxine XR, followed by double-blind venlafaxine XR

or placebo for 2 relapse phases, each lasting 6 months.

**Main Outcome Measures:** Time to relapse while receiving venlafaxine XR or placebo after 6 and after 12 months of treatment. Relapse was strictly defined to safeguard against assigning patients with venlafaxine XR discontinuation symptoms or temporary anxiety increase as relapse.

**Results:** For objective 1, relapse rates in phase 2 (months 6-12) were 9.8% on venlafaxine XR and 53.7% on placebo ( $P < .001$ ). For objective 2, relapse rates after 12 months on placebo (32.4%) were lower than after 6 months on venlafaxine XR (53.7%) ( $P < .03$ ).

**Conclusions:** Treatment of GAD with an antidepressant should be continued for at least 12 months. Preliminary data demonstrate that improved patients who relapse while off their antianxiety medication after at least 6 months of treatment will again most likely respond to a second course of treatment with the same medication.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00183274.

*Arch Gen Psychiatry.* 2010;67(12):1274-1281

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GENERALIZED ANXIETY DISORDER (GAD) is a chronic psychiatric disorder that is characterized by excessive and uncontrollable worry, apprehension, and anxiety and by symptoms of irritability, restlessness, fatigue, insomnia, concentration difficulties, and muscle tension. GAD affects approximately 3% to 5% of the general population in the United States and is twice as prevalent among women than among men.<sup>1,2</sup> The disorder typically follows a chronic episodic course<sup>3</sup> and is associated with significant levels of functional disability and with quality-of-life impairment that is similar to major depression.<sup>4-9</sup> GAD is widely recognized as a chronic debilitating disorder with need for long-term treatment.

Short-term efficacy has been established for benzodiazepines,<sup>10,11</sup> buspirone hydrochloride,<sup>12,13</sup> imipramine hydrochloride,<sup>14,15</sup> and selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors.<sup>16-19</sup> However, after short-term treatment, relapse rates at 1-year follow-up remain generally high,<sup>20,21</sup> emphasizing the need for long-term anxiolytic treatment. Few studies have investigated such long-term treatment outcomes systematically in GAD, including 2 studies<sup>22,23</sup> by our research group. Such studies have used various study designs, including randomized double-blind approaches, open-label longitudinal studies, and relapse prevention study designs.

Gelenberg et al<sup>24</sup> showed for first-time long-term efficacy of venlafaxine hydro-

chloride extended release (XR) compared with placebo in a 6-month randomized clinical trial. Because of high attrition rates in the placebo group and potential ethical concerns about withholding effective treatment for patients in the placebo arm for prolonged periods, this study design has become obsolete. Open-label longitudinal studies using various drugs have been performed for many years; however, interpretation of results is limited by the inherent open-label design.<sup>25</sup>

To address these conceptional limitations, treatment withdrawal or relapse prevention designs have again gained attention. In an earlier study,<sup>26</sup> patients with GAD who responded initially to the selective serotonin reuptake inhibitor paroxetine hydrochloride during 8 weeks of treatment were randomly assigned to continue receiving drug or placebo for an additional 24 weeks. In another study,<sup>27</sup> patients treated with open-label escitalopram oxalate for 12 weeks were followed up for a minimum of 6 months on drug or placebo treatment. Recently, a relapse prevention trial was performed using the selective norepinephrine reuptake inhibitor duloxetine hydrochloride. Twenty-six weeks of open-label study were followed by 26 weeks of drug or placebo treatment.<sup>28</sup>

Although these 3 multicenter, large-sample, pharmaceutical industry-sponsored trials demonstrated better outcome for patients who stayed on active treatment ranging from 8 weeks to 6 months, key questions are how much longer patients should be treated for best clinical outcome and whether there are clinically meaningful differences between various durations of chronic treatment. The present study was designed to clarify the role of long-term anxiolytic therapy in the treatment of chronically anxious patients with GAD. Venlafaxine XR was chosen as representative of the second-generation anxiolytics because it was the first antidepressant approved by the Food and Drug Administration (FDA) for the treatment of GAD.

The 2 main objectives of the present study were the following: (1) to examine the long-term efficacy of venlafaxine XR in patients with chronic GAD who responded therapeutically to an initial 6-month course of venlafaxine XR treatment and were followed up for another 6 months on venlafaxine XR or placebo and (2) to examine whether patients treated for 12 months rather than 6 months with venlafaxine XR experience lower relapse rates over a 6-month placebo period.

## METHODS

### STUDY DESIGN

This 18-month, single-center, relapse prevention study was composed of the following 3 treatment phases: a 6-month, open-label, venlafaxine XR, flexible-dose treatment phase (75-225 mg/d) (phase 1); a 6-month, randomized, double-blind, placebo-controlled relapse phase (phase 2); and a final 6-month, randomized, double-blind, placebo-controlled relapse phase (phase 3) (**Figure 1**). Most patients (n=239) were recruited and seen by our research psychiatrists (B.E., S.K.-K., F.W.L., and M.A.R.) in 4 primary care practices; others (n=95) responded to media advertising and were treated in our central clinic at the University of Pennsylvania Medical Center.

After a screening period of 4 to 28 days, eligible patients were started on venlafaxine XR, 37.5 mg/d, for 1 week, followed by 75 mg/d for the second week. After the second week, flexible dosing was used in a range of 75 to 225 mg/d. Every attempt was made to raise a patient's daily dose to 225 mg by week 8, unless adverse events prevented this increase or the patient was in remission. After 12 weeks of treatment, patients who were unimproved or worse, with a Clinical Global Impressions, improvement (CGI-I), score of 4 or higher, were discontinued from the program as unresponsive. Patients minimally improved (CGI-I score, 3) were continued in the program to assess whether longer than 3 months of treatment may produce further clinical improvement. Patients who did not at least moderately improve (CGI-I score,  $\leq 2$ ) after 6 months of open-label treatment with venlafaxine XR were also discontinued from the study and were treated with their physician's choice of medication.

Responders to 6 months of open-label venlafaxine XR treatment were randomized to double-blind treatment in a 60:40 ratio of drug to placebo. A stratified randomization was used, including level of secondary depressive symptoms at intake (Hamilton Rating Scale for Depression [HAM-D] score,  $\leq 13$  vs  $>13$ ) and improvement status (CGI-I score, 1-2) after 6 months of venlafaxine XR therapy. Patients completing 12 months of venlafaxine XR treatment were further randomized in a 1:3 ratio of drug to placebo for an additional 6-month period or a total of 18 months. Patients already receiving placebo since month 6 (still double blind) continued on placebo in phase 3. The patient's clinical status was monitored bi-weekly for the first 8 weeks and monthly thereafter. A 24-hour telephone number was provided, and patients were encouraged to contact their study psychiatrist between visits with any questions or concerns. A prompt interim visit could be arranged at any time.

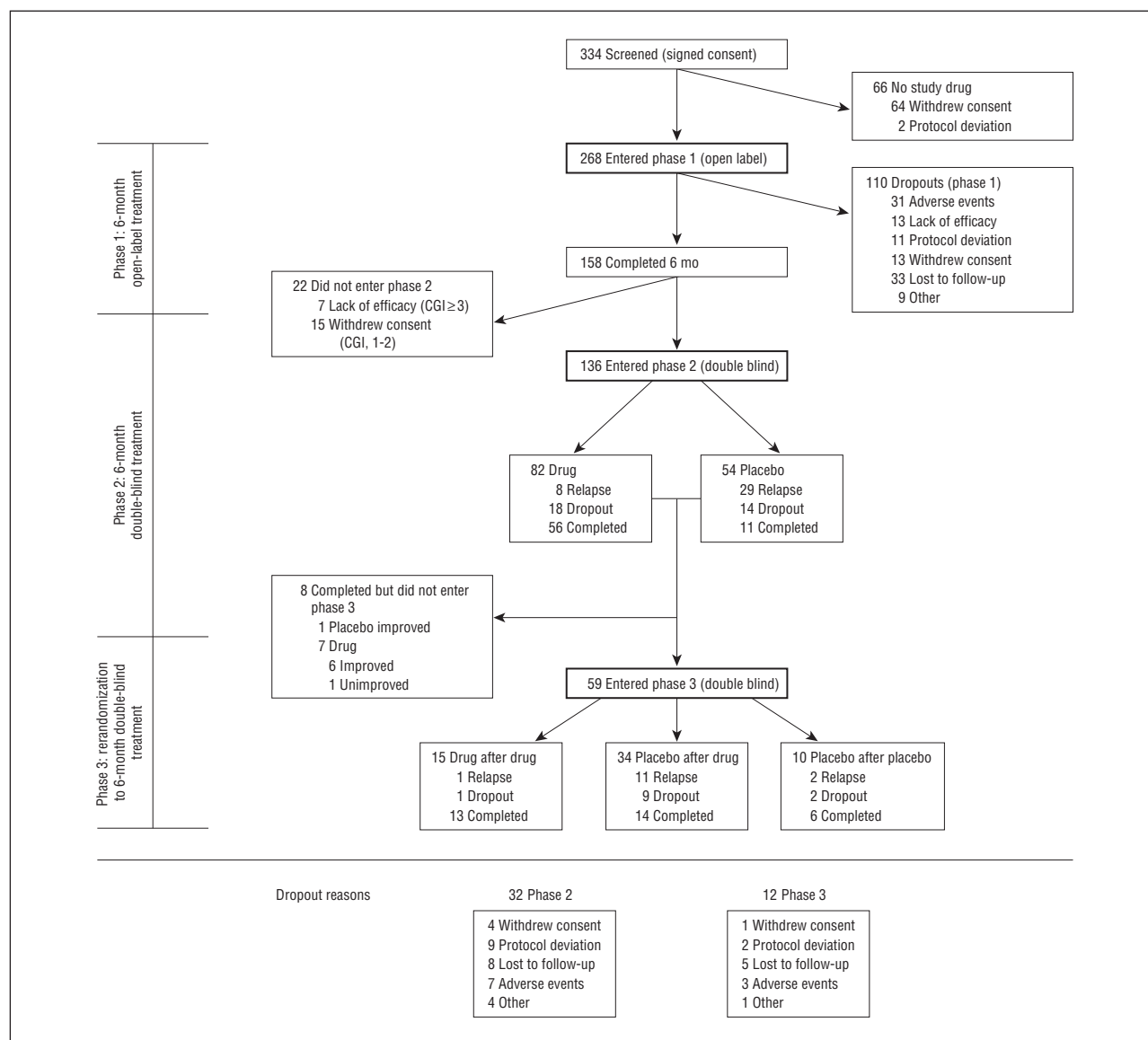
A sample size of 165 was originally planned to enter phase 2 with 100 patients receiving venlafaxine XR and 65 receiving placebo. This proposed sample size had at least 80% power to detect a difference in relapse proportions of 0.22. Because of higher attrition than anticipated, 136 patients were enrolled in phase 2 (82 to venlafaxine XR and 54 to placebo), which had at least 80% power to detect a difference in relapse proportions of 0.24. Similarly, for comparing placebo groups after 6 and 12 months on venlafaxine XR (placebo phase 2 vs phase 3), the observed sample size (54 vs 34) was below the targeted size of 130, which required a difference in relapse proportions of 0.29 to guarantee at least 80% power.

To assure best patient management, after a patient relapsed, dropped out, or completed the trial and after all study procedures were completed, the medication code was broken by a member of the research team uninvolved in the clinical trial. This procedure allowed us to offer patients who relapsed on placebo a return to open-label venlafaxine XR for the remainder of the respective study phase. An opportunity now arose to compare the venlafaxine XR response of these patients who relapsed on placebo with that of patients on venlafaxine XR in the double-blind trial. Because patients were not randomized in this subsample, all data obtained should be viewed as preliminary.

After 6, 12, and 18 months of study treatment or at any time a patient wanted to leave the study, patients were tapered under double-blind conditions over a 4-week period. Study dosage was reduced by 75 mg weekly, with a reduction to 37.5 mg during the last week. Depending on the patient's study drug daily dose, this taper could last from 1 to 3 weeks. To maintain the double blind, patients who continued on venlafaxine XR in relapse phases 2 and 3 went through a sham taper process. Gradual taper was facilitated with the help of a patient diary.

### PATIENT SELECTION

This clinical trial was performed at the University of Pennsylvania Medical Center from February 2005 to September 2009,



**Figure 1.** Patient flowchart. CGI indicates Clinical Global Impressions improvement score.

with approval and oversight by the Institutional Review Board of the University of Pennsylvania. Written informed consent was obtained before performing any study procedures and again before study phases 2 and 3. Informed consent was further enhanced by a patient information sheet that summarized in simple language what the patient would expect in the next study phase. To be included in the study, subjects had to be 18 years or older and meet the criteria for GAD as determined by the Structured Clinical Interview for *DSM-IV* and a psychiatric evaluation. Patients had to have sufficient symptoms to require anxiolytic drug therapy, including a score of at least 20 on the Hamilton Rating Scale for Anxiety (HAM-A) at screen and at baseline and a score of at least 4 on the CGI, severity of illness (CGI-S). Patients were also assessed with the 17-item HAM-D. A HAM-D cutoff score of 18 or less was used to exclude more seriously depressed patients, and a cutoff score of less than 2 on the suicide item of the HAM-D was used to exclude suicidal patients. Patient health was determined by physical examination, medical history, and, if necessary, laboratory tests and electrocardiogram. Exclusion criteria were an eating disorder such as bulimia and anorexia, substance abuse or dependence during the past 6 months, any current anxiety spectrum *DSM-IV* diagnosis

other than GAD, an episode of major depressive disorder in the previous 6 months or depressive symptoms at study intake (HAM-D score,  $>18$ ), or current or past history of dementia, bipolar disorder, schizophrenia, or other psychotic disorders. Positive urine drug screens for amphetamines, cocaine, phencyclidine hydrochloride, methadone hydrochloride, or barbiturates were immediate exclusion criteria. Patients taking opiate-containing pain medication could enter the study if the primary physician substituted such treatment with a nonopiate medication. Occasional use of tetrahydrocannabinol (ie, less than biweekly) was acceptable if the patient was willing to stop use over the first 6 study weeks; this was confirmed by negative drug screens. Patients taking low daily doses of benzodiazepines (diazepam,  $\leq 10$  mg, or its equivalents) or hypnotics were allowed to enter the trial and were tapered off their benzodiazepine during the first 12 weeks of treatment. Benzodiazepine abstinence was confirmed by a full urine drug screen at month 4 of open-label venlafaxine XR treatment, which had to be negative for all drugs tested. No benzodiazepines were allowed in phases 2 and 3. Other exclusion criteria were uncontrolled medical conditions and hypersensitivity to venlafaxine, as well as pregnancy, breastfeeding, or a positive urine

pregnancy test. Fertile patients had to use an accepted contraceptive method, and urine pregnancy tests were performed at regular intervals.

## EFFICACY MEASURES

Patient relapse, our primary outcome, was defined as meeting symptom criteria for a Structured Clinical Interview for *DSM IV* GAD diagnosis and having a HAM-A score of at least 16, having a CGI, a CGI-S score of at least 4 (moderate or higher), and having a CGI-I score of 6 or 7 (worse or very much worse) compared with baseline of the double-blind relapse phase. These symptom levels had to be present for 2 successive visits, spaced 2 weeks apart, with the last visit conducted at least 3 weeks after taper completion, to assure that neither transient anxiety worsening nor temporary drug discontinuation symptoms were considered anxiety relapse. In a few patients, this 2-week interval was reduced to 1 week, but only if the first relapse symptoms were observed at least 1 week before the first relapse evaluation. Three patients who discontinued the study because of symptom worsening during taper and who were unwilling to remain in the double-blind part of the study to participate in a relapse assessment 2 weeks later were not counted as relapsed. HAM-A, CGI-S, and CGI-I<sup>29</sup> and the patient-rated Hospital Anxiety and Depression Scale<sup>30</sup> were assessed at each visit and the HAM-D, Sheehan Disability Scale,<sup>31</sup> and quality of life—assessing General Health Questionnaire<sup>32</sup> every 6 months. Remission was defined as a CGI-I score of 1 or HAM-A score of 7 or less.<sup>33</sup>

## SAFETY AND TOLERABILITY MEASURES

Adverse events (AEs) were assessed at each visit using an open-ended approach, which was facilitated by the use of a physician-completed medication problem checklist. Adverse events were rated by severity, duration, and association with study medication (probably, possibly, or nonrelated). All symptoms considered by the patient to be caused by study treatment, including symptoms that could potentially be considered discontinuation symptoms, were identified as AEs. Vital signs, concomitant illnesses, and concomitant medication were assessed at each study visit. Potential discontinuation symptoms were assessed at selective time points using a patient-completed withdrawal checklist, which was based on a checklist developed by Fava et al.<sup>34</sup> Compliance with study medication intake was assessed by pill count and inquiry.

## STATISTICAL ANALYSIS

The primary efficacy analytic method was time-to-relapse analyses estimated using a discrete-time Cox proportional hazards model.<sup>35</sup> Patients lost to follow-up were treated as censored observations. Survival rates for the 2 conditions were compared using log-rank test. The discrete-time Cox proportional hazards model allows for inclusion of covariates to assess and control for the influence of potential prognostic indexes or confounders as described by Collett.<sup>36</sup> Identified a priori and included in the primary time-to-relapse model were potential confounders, including race/ethnicity (assessed by patient checklist), sex, baseline anxiety score, and CGI-I remission status at the start of the phase.  $\chi^2$  Analyses were used to contrast relapse or responder rates. In the case of small cell sizes, Fisher exact test replaced  $\chi^2$  analysis.

For repeated continuous assessments, longitudinal models adjusting for the correlation of repeated measures within a patient were used. We implemented a specific longitudinal model referred to as a general mixed model (MMANOVA) approach that examines change from baseline to the mean of the postbaseline

monthly assessments within phase, fit with PROC MIXED (SAS; SAS Institute, Cary, North Carolina).<sup>37</sup> MMANOVA retains all non-missing observations; that is, it retains cases even if some data points are missing. Likelihood estimation for mixed models is especially robust with respect to missing data.<sup>38</sup> However, estimates and inferences may be invalid if the missing data or dropout mechanism is not ignorable. To deal with this potential problem, we specified and tested random-effects pattern mixture models. As described by Hedeker and Gibbons<sup>39</sup> and by Guo et al,<sup>40</sup> such models allow us to assess whether important estimates are dependent on dropout patterns and provide overall estimates of treatment effects and contrasts by averaging over the various dropout patterns. For measures acquired at only the start and end of a respective phase, analysis of covariance models were implemented, which estimated treatment contrasts at end point. All analyses controlled for baseline of the respective phase. Tests of baseline differences in demographic and clinical characteristics were investigated using analysis of variance for continuous variables and  $\chi^2$  test of independence or Fischer exact test for categorical variables. Statistical significance was set at  $P < .05$  (2-tailed) for all analyses.

## RESULTS

### STUDY POPULATION

Patient flow through the 18-month study is given in Figure 1. Of 334 patients accepted into the study at screen, 268 patients entered 6-month open-label venlafaxine XR treatment (phase 1), and 158 patients (59.0%) completed this phase. Seven patients were ineligible to enter phase 2, and 15 patients (all improved) withdrew consent. This left 136 patients, or 50.7% of 268 open-label phase 1 patients, to enter the double-blind, 6-month phase 2 relapse phase; of these patients, 59 (43.4%) entered phase 3, the second 6-month, double-blind, relapse phase.

Reasons for early termination are shown in Figure 1 and did not differ significantly in phases 2 and 3 between drug and placebo patients. However, 66 screen dropouts differed from 268 patients entered into the trial on 3 variables. They were younger (mean age, 41.4 vs 47.6 years;  $P < .01$ ), more were employed (66.7% vs 51.5%,  $P < .05$ ), and fewer were of white race/ethnicity (65.2% vs 77.2%,  $P < .05$ ).

**Table 1** gives population demographics for the total population (phase 1) and for patients enrolled in phases 2 and 3. Demographics are similar among these 3 (not independent but patient overlapping) groups.

Only clinically improved patients (CGI-I score, 1-2) entered phase 2 or 3, and their respective remission rates (CGI-I score, 1) when entering phases 2 and 3 were 84.6% and 88.1%, respectively. In contrast, the 6-month last-observation-carried-forward data set remission rate for the total 268 patients was 53.4%, and that for the 6-month completer set ( $n = 158$ ) was 78.6%.

### MEDICATION INTAKE

During the first 6 months of open-label treatment, the mean venlafaxine XR daily dose for the last-observation-carried-forward data set ( $n = 268$ ) at the time of completion or dropout was 155 mg/d (range, 37.5-225 mg/d). The mean venlafaxine XR intakes at 6 months were



**Table 1. Population Demographics<sup>a</sup>**

Demographic	Phase 1 (n=334)	Phase 2 (n=136)	Phase 3 (n=59)
Male sex, %	37.1	37.5	40.7
Age, mean (SD), y	46.3 (16.4)	49.8 (15.8)	53.3 (15.0)
Race/ethnicity, %			
White	74.9	77.9	72.9
Black	22.5	20.6	27.1
Other	2.7	1.5	0
Marital status, %			
Married	46.4	50.0	50.9
Single	35.9	33.1	28.8
Divorced or widowed	17.7	16.9	20.4
Employment status, %			
Employed	62.9	62.6	50.9
Unemployed	10.8	5.9	8.5
Retired	15.6	19.4	27.2
Other	10.7	12.1	13.4
Educational level, %			
<High school	8.1	5.2	8.5
High school	30.8	29.4	25.4
Some college	32.0	29.4	25.4
≥College degree	29.1	36.0	40.7
Duration of anxiety >12 mo, %	100.0	100.0	100.0
Score, mean (SD)			
Hamilton Scale for Anxiety	24.54 (3.75) <sup>b</sup>	4.17 (3.10) <sup>c</sup>	3.89 (3.43) <sup>d</sup>
Hamilton Scale for Depression	13.02 (3.22)	3.71 (3.08)	3.17 (2.45)
Clinical Global Impressions, severity of illness	4.51 (0.74)	1.37 (0.65)	1.27 (0.58)

<sup>a</sup>Due to rounding, percentages may not total 100.<sup>b</sup>Baseline.<sup>c</sup>Month 6.<sup>d</sup>Month 12.

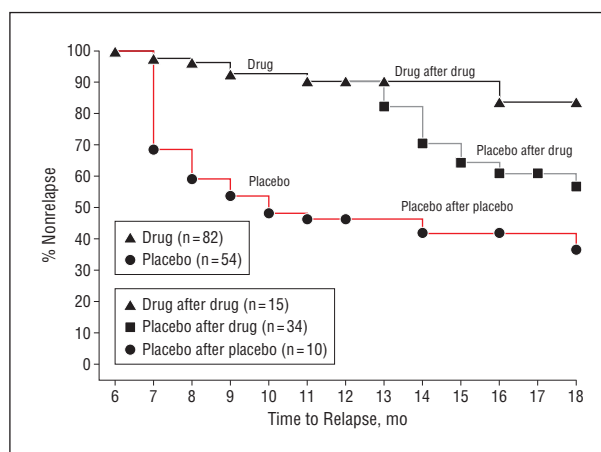
167 mg/d (range, 75-225 mg/d) for 136 patients who entered phase 2 and 158 mg/d (range, 75-225 mg/d) for 59 patients who entered phase 3. The observation that 38.3% of study patients experienced remission improvement only on the highest FDA-approved venlafaxine XR dosage for GAD supports the clinical practice to raise the daily dose of venlafaxine XR to the maximum recommended, namely, 225 mg/d, unless remission is evident at a lower dosage.

## ADVERSE EVENTS

Adverse events were those expected with venlafaxine XR, and AEs that were reported at least once by at least 5% of the study population are given in **Table 2** for all patients who entered treatment (n=268). Incidences of AEs reported in phases 2 and 3 were much lower, did not differ statistically between drug and placebo patients, and included no new AEs. The 2 AEs with the highest frequency in phase 2 were lightheadedness (18.3% in the venlafaxine XR group and 7.4% in the placebo group) and dry mouth (17.1% in the venlafaxine XR group and 12.9% in the placebo group). In phase 3, no AE was reported by more than 3 patients in either treatment group.

**Table 2. Adverse Events Reported by at Least 5% of 268 Study Patients**

Event	No. (%)
Dry mouth	130 (48.5)
Drowsiness	111 (41.4)
Lightheadedness	104 (38.8)
Headache	97 (36.2)
Increased sweating	91 (34.0)
Nausea	89 (33.2)
Insomnia	82 (30.6)
Nightmares	78 (29.1)
Constipation	77 (28.7)
Fatigue	76 (28.4)
Jitteriness	74 (27.6)
Decreased sex drive	68 (25.4)
Flatulence	66 (24.6)
Decreased orgasm	55 (20.5)
Muscle aches	50 (18.7)
Diarrhea	35 (13.1)
Abdominal pain	26 (9.7)
Faintness	21 (7.8)
Delayed orgasm	19 (7.1)
Gas	18 (6.7)



**Figure 2.** Discrete-time Cox proportional hazards model survival analysis over months 6 to 18, where the last observed value without relapse is censored ( $\chi^2=24.83$ ;  $P<.001$ ).

## RELAPSE RATES

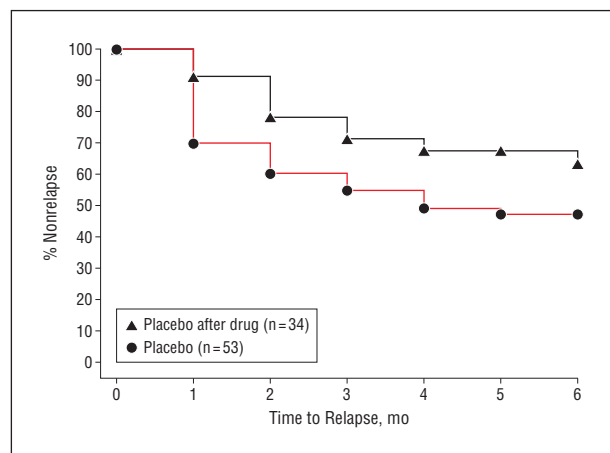
### Venlafaxine XR vs Placebo

After 6 months of open-label venlafaxine XR treatment, significantly more patients who switched to placebo (53.7%) over the next 6 months relapsed compared with patients continuing on venlafaxine XR (9.8%) ( $\chi^2=31.75$ ,  $P<.001$ ). The relapse rates after 12 months of venlafaxine XR treatment were 6.7% for patients on venlafaxine XR for 18 months, 20.0% for patients on placebo for 12 months (months 6-18), and 32.3% for placebo patients who switched at month 12 to placebo ( $\chi^2=3.89$ ,  $P<.14$ ). **Figure 2** shows results of a Cox proportional hazards regression analysis for the combined 12-month relapse data set (Wald  $\chi^2=24.83$ ,  $P=.001$ ). Relapse rates were significantly higher on placebo than on venlafaxine XR. Results of

Kaplan-Meier analyses performed for phases 2 and 3 separately were highly significant for phase 2 ( $\chi^2=29.77$ ,  $P<.001$ ; hazard ratio, 9.73) and, as predicted because of sample size limitation, were of borderline statistical significance for phase 3 ( $\chi^2=3.34$ ,  $P<.07$ ; hazard ratio, 6.86). The study design oversampled the placebo group in phase 3 to allow for a meaningful placebo response comparison between phases 2 and 3.

### Phase 2 vs Phase 3 Placebo

Our second primary hypothesis, predicting lower placebo relapse rates after 12 months than after 6 months of venlafaxine XR treatment, was also confirmed. **Figure 3** shows the results of Kaplan-Meier analysis comparing time to relapse on placebo for patients receiving 6 months vs 12 months of venlafaxine XR treatment. Relapse rates were significantly reduced from 53.7% after 6 months of venlafaxine XR to 32.4% after 12 months of venlafaxine XR (Wald  $\chi^2=4.99$ ,  $P<.03$ ; hazard ratio, 2.34). When adding as covariates the 4 variables predicted to influence treatment outcome, statistical signifi-



**Figure 3.** Kaplan-Meier time to relapse while taking placebo after 6 and 12 months of venlafaxine hydrochloride extended release (XR) treatment ( $\chi^2=4.99$ ;  $P<.03$ ) and when adjusted per protocol for race/ethnicity, sex, severity of anxiety at baseline, and remission (yes or no) at the end of venlafaxine XR treatment ( $\chi^2=7.97$ ,  $P=.005$ ).

cance was slightly increased (Wald  $\chi^2=7.97$ ,  $P=.005$ ; hazard ratio, 2.85).

### Continuous Outcome Variables

Results for the continuous outcome variables (**Table 3**) assessed over time support the primary relapse data. Venlafaxine XR minus placebo differences are greater in phase 2 (after 6 months of venlafaxine XR) than in phase 3 (after 12 months of venlafaxine XR).

Disability and quality of life were assessed only every 6 months, leading to missing data for 30 patients in phase 2 and for 13 patients in phase 3. Therefore, analyzable data are available only for phase 2. Analysis of covariance last-observation-carried-forward analysis confirms our symptom ratings. Adjusted mean (SD) 12-month scores for venlafaxine XR and placebo, respectively, were as follows: 23.73 (6.26) and 28.17 (8.41) for the General Health Questionnaire ( $F_{1,99}=7.99$ ,  $P<.006$ ) and 6.15 (7.82) and 10.26 (8.58) for the Sheehan Disability Scale ( $F_{1,97}=8.15$ ,  $P<.005$ ).

### Rechallenge With Venlafaxine XR Among Patients Who Relapsed While Taking Placebo

Twenty-seven patients who relapsed in phase 2 while on placebo were again placed on open-label venlafaxine XR for the remainder of phase 2 (mean duration, 5.8 months). Clinical outcome was compared between these 27 patients and 74 patients who continued on venlafaxine XR in double-blind phase 2 (**Table 4**). Both patient groups obtained similar positive efficacy outcomes.

### COMMENT

This clinical trial supports the observation that GAD is frequently a chronic illness demanding prolonged treatment. Results confirm the following 2 primary hypotheses: (1) After 6 months of venlafaxine XR treatment, patients continuing on venlafaxine XR for 12 months experience a highly significant lower relapse rate (9.8%) than patients who switched to placebo (53.7%). (2) Patients treated with venlafaxine XR for 12 months before

**Table 3. Contrast of Repeated Continuous Measures**

Measure	Score, Mean (SE)			Statistic	P Value
	Venlafaxine Hydrochloride XR	Placebo	Difference		
<b>Phase 2</b>	<b>(n=82)</b>	<b>(n=54)</b>		<b><math>t_{129}</math></b>	
Hamilton Rating Scale for Anxiety	6.29 (0.60)	11.35 (0.75)	-5.06 (0.82)	-6.22	<.001
Clinical Global Impressions, severity of illness	1.73 (0.14)	2.64 (0.17)	-0.91 (0.14)	-6.47	<.001
Clinical Global Impressions, improvement	1.96 (0.12)	3.29 (0.19)	-1.33 (0.22)	-6.06	<.001
Hospital Anxiety and Depression Scale, anxiety factor	7.43 (0.38)	9.29 (0.44)	-1.86 (0.47)	-3.98	<.001
<b>Phase 3<sup>a</sup></b>	<b>(n=15)</b>	<b>(n=34)</b>		<b><math>t_{41}</math></b>	
Hamilton Rating Scale for Anxiety	5.80 (1.28)	8.42 (1.05)	-2.62 (1.23)	-2.14	.04
Clinical Global Impressions, severity of illness	1.86 (0.26)	2.25 (0.20)	-0.39 (0.27)	-1.44	.16
Clinical Global Impressions, improvement	2.20 (0.41)	2.78 (0.32)	-0.58 (0.43)	-1.35	.18
Hospital Anxiety and Depression Scale, anxiety factor	4.52 (0.67)	6.63 (0.55)	-2.11 (0.70)	-3.01	.005

Abbreviation: XR, extended release.

<sup>a</sup>Placebo after placebo group (n=10) not included in placebo after drug group.

**Table 4. Phase 2 Contrast of Postplacebo Relapse vs Double-blind Venlafaxine XR Groups (Last-Observation-Carried-Forward Data Set)**

Measure	Score, Mean (SE)		<i>t</i> <sub>99</sub> Statistic	P Value
	Postplacebo Relapse Venlafaxine Hydrochloride XR (n=27)	Double-blind Venlafaxine XR (n=74)		
Hamilton Scale for Anxiety	4.74 (0.65)	4.05 (0.47)	0.88	.38
Clinical Global Impressions, improvement	1.15 (0.07)	1.26 (0.09)	-0.70	.48

Abbreviation: XR, extended release.

being shifted to placebo experience a lower relapse rate (32.4%) than patients shifted to placebo after being on venlafaxine XR for only 6 months (53.7%); this difference also was statistically significant. Relapse status was conservatively determined in this study.

An additional preliminary clinical observation was made possible when the welfare of our patients who committed themselves to an 18-month-long clinical trial demanded that we break the study code for each patient at the time of study termination, whenever this occurred. Once all study-related procedures were completed, this allowed us to offer patients who had relapsed on placebo a return to open-label venlafaxine XR. Twenty-seven phase 2 patients elected to do so. Comparing clinical improvement at the end of phase 2 among these patients who were re-challenged on venlafaxine XR with that of patients who remained on venlafaxine XR showed similar degrees of improvement in both venlafaxine XR groups, a great assurance to the clinician. These preliminary additional findings are of clinical relevance for patients who for various reasons prefer not to be on a medication for longer than 6 months. For such patients, tapered medication discontinuation, followed by close observation and swift resumption of medication intake if relapse occurs, may offer an alternative to continuous medication therapy.

There are several limitations to our study. One of the biggest limitations of any long-term treatment study is the increased attrition occurring as a function of trial length. For example, in our study of 268 patients who entered the open-label phase, a phase that lasted 6 months and in which all patients received open-label flexible-dose venlafaxine XR, only 158 patients (59.0%) completed 6 months of treatment, and only 136 patients (50.7%) continued study treatment after 6 months. Therefore, the relapse results of this study are limited to chronically anxious patients who are committed to long-term treatment of their anxiety, are treatment adherent, are able to cope with a slow onset of meaningful improvement, are willing to increase medication daily dose if not fully improved, and are able to tolerate AEs. In our study, patients who persevered with treatment for 6 months experienced a remission rate of 79%, and patients who chose to enter phase 2 had a remission rate of 85%. Remission rates for 6-month completers were 60% at month 3 and 79% at month 6. Remission rates after 12 months of venlafaxine XR were 89.1% for completers and 76.8% for the total venlafaxine XR sample (n=82).

In conclusion, many patients experiencing chronic GAD are in need of prolonged medication treatment to main-

tain the clinical improvement they have achieved. Treatment of GAD with an antidepressant, venlafaxine XR in this case, should continue for at least 12 months at the highest tolerated and effective daily dose, providing remission rates of at least 80%. Furthermore, preliminary data indicate that improved patients who relapse while off their antidepressant medication after at least 6 months of treatment will again most likely respond to a second course of treatment with the same medication. We anticipate that these findings may serve as a pharmacotherapy guide for patients with chronic anxiety.

**Submitted for Publication:** January 28, 2010; final revision received April 28, 2010; accepted June 4, 2010.

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**Financial Disclosure:** During the past 3 years, Dr Rickels received honoraria and served as a consultant or on advisory boards to Cephalon Inc, Hoffman-La Roche Inc, Jazz Pharmaceuticals, Johnson & Johnson, Novartis Pharmaceuticals, Pfizer Inc, Epix (PreDix) Pharmaceuticals, and PGxHealth LLC; Dr Rickels received research grants (issued to the University of Pennsylvania) from Epix Pharmaceuticals, Genaissance Pharmaceuticals Inc (PGxHealth LLC), the National Institute of Mental Health, PamLab, Pfizer Inc, and Wyeth Pharmaceuticals Inc. From 2009 to 2010, Dr Rynn received research support from the National Institute of Mental Health, Boehringer Ingelheim Pharmaceuticals Inc, Wyeth Pharmaceuticals Inc, and Neuropharm Ltd and received royalties from APPI Press.

**Funding/Support:** This research was supported by grant MH065963 from the US Public Health Service (Dr Rickels). Wyeth Pharmaceuticals Inc provided all study medication.

**Additional Contributions:** Tiffany Richardson, BA, and Dana Patsch, BS, assisted with management and quality assurance for this project.

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