Efficacy and Safety of Pregabalin in the Treatment of Generalized Anxiety Disorder: A 6-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Comparison of Pregabalin and Venlafaxine

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Objective: Pregabalin has demonstrated robust, rapid efficacy in reducing symptoms of generalized anxiety disorder (GAD) in 4 placebo-controlled clinical trials. The current study compared the efficacy and safety of pregabalin and venlafaxine in patients diagnosed with moderate to severe GAD.

Method: The study was conducted from December 21, 1999, to July 31, 2001. Outpatients (N = 421) in primary care or psychiatry settings meeting DSM-IV criteria for GAD were randomly assigned to 6 weeks of double-blind treatment with pregabalin 400 or 600 mg/day, venlafaxine 75 mg/day, or placebo. The primary analysis was change in Hamilton Rating Scale for Anxiety (HAM-A) total score from baseline to last-observation-carried-forward (LOCF) endpoint. Secondary analyses included the change in HAM-A psychic (emotional) and somatic (physical) factor scores, significant improvement at week 1, and week 1 improvement sustained at every visit through endpoint.

Results: Pregabalin at both dosages (400 mg/day, $p = .008$; 600 mg/day, $p = .03$) and venlafaxine ($p = .03$) produced significantly greater improvement in HAM-A total score at LOCF endpoint than did placebo. Only the pregabalin 400-mg/day treatment group experienced significant improvement in all a priori primary and secondary efficacy measures. Pregabalin in both dosage treatment groups (400 mg/day, $p < .01$; 600 mg/day, $p < .001$) significantly improved HAM-A total score at week 1, with significant improvement through LOCF endpoint. Statistically significant improvement began at week 2 for venlafaxine. Discontinuation rates due to associated adverse events were greatest in the venlafaxine treatment group: venlafaxine, 20.4%; pregabalin 400 mg/day, 6.2%; pregabalin 600 mg/day, 13.6%; placebo, 9.9%.

Conclusion: Pregabalin was safe, well tolerated, and rapidly efficacious across the physical-somatic as well as the emotional symptoms of GAD in the majority of patients studied in primary care and psychiatric settings.

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Worldwide, anxiety disorders were found by the World Health Organization to be the most common psychiatric disorders in a multistage household probability sample of 14 countries in the Americas, Europe, the Middle East, Africa, and Asia.[1] In addition to being common in psychiatric practice, generalized anxiety disorder (GAD) is the most common anxiety disorder presenting in primary care settings. Nonetheless, GAD is diagnosed in only one third of patients who suffer from the disorder in primary care.[2] While the waxing and waning of symptoms may contribute to the diagnostic challenge,[3] a major reason for poor recognition may be that only a small minority of GAD patients present with the straightforward chief complaint of emotional symptoms, such as anxiety or worry. Instead, in primary care, physical conditions such as somatic symptoms, pain, and insomnia represent the

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most common presenting complaints among GAD patients.[2] The physical-somatic symptoms associated with GAD are often those of greatest concern to patients. Moreover, GAD has been found to produce impairment (e.g., impairments in physical function, role-physical factors, and general health, as well as bodily pain) that is equivalent to or significantly greater than that in patients with nonpsychiatric medical illnesses such as diabetes or recent myocardial infarction. Another important issue is that GAD frequently complicates the clinical presentation of other common medical illnesses such as irritable bowel syndrome,[4,5] other pain syndromes,[6–9] and asthma.[10] From a public health perspective, a 2002 analysis indicated that early treatment of GAD with medication may prevent or delay future episodes of major depression,[11] which is known to be an important clinical risk factor for heightened morbidity and mortality.[12,13]

At present, benzodiazepines and antidepressants are considered first-line therapy for patients suffering from GAD, based on studies conducted in psychiatric settings.[14] Many patients, however, demonstrate less-than-optimal responses to these and other treatments because of combinations of medical comorbidity, slow or inadequate anxiety relief, intolerable side effects, and drug-drug interactions.[15–22]

Pregabalin—a novel medicine approved in Europe for the treatment of peripheral neuropathic pain, in the United States for neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia, and in both Europe and the United States as add-on treatment for partial seizures—is characterized by high-affinity binding to the α_2-δ subunit protein of voltage-gated calcium channels.[23] Pregabalin has a predictable, linear pharmacokinetic profile across its dosing range, and it is rapidly absorbed.[23] Pregabalin is not protein bound, does not inhibit or induce cytochrome P450 enzymes, and exhibits few drug-drug interactions. In randomized, placebo-controlled trials assessing it in the treatment of distinct conditions of the central and peripheral nervous systems, pregabalin has consistently been found to be safe and rapidly efficacious for treating symptoms of painful diabetic peripheral neuropathy,[24–27] postherpetic neuralgia,[27–29] treatment-resistant partial seizures,[30–32] GAD,[33–36] and fibromyalgia syndrome.[37] In view of the consistent findings of significant, robust efficacy in 4 of 5 placebo-controlled trials (references 33–36 and A.C.P., data on file, Pfizer Inc, New York, N.Y., 1998–1999) of pregabalin (3 of which included active comparators[33,34,36]) and a favorable side effect profile in comparison with benzodiazepines,[38,39] our fixed-dose comparison trial was designed to evaluate the efficacy of pregabalin—compared with the serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant venlafaxine—in the treatment of patients with moderate to severe GAD. At the time the study was initiated (1999), venlafaxine was the sole pharmacologic treatment approved for GAD in Europe, at a dosage of 75 mg/day of the immediate-release (IR) formulation. There is no convincing evidence, from short-term studies, of a dose-response effect in the treatment of GAD cited in the label for venlafaxine.[40,41]

METHOD

This was a randomized, double-blind, 4-arm, parallel-group, fixed-dose comparison study of 2 dosages of pregabalin, placebo, and venlafaxine in patients diagnosed with GAD. The study was conducted from December 21, 1999, to July 31, 2001, at 76 centers, 52 of which were primary care centers (the remainder were psychiatric centers), in 5 European countries (Austria, Belgium, Germany, the Netherlands, and the United Kingdom). The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki applicable at the time of the study. For all sites, the respective ethics committees granted approval of the protocol, and after an explanation of the risks and benefits of study participation, written informed consent was obtained from each patient before entry into the study.

Patients

The study sample was recruited from outpatients attending general medical or psychiatric practices. Adult male or female outpatients who were at least 18 years of age and who met DSM-IV diagnostic criteria for primary GAD using the Mini-International Neuropsychiatric Interview (MINI)[42] were eligible for inclusion. At baseline assessment and prior to randomization, patients were required to have a total score ≥ 20 on the Hamilton Rating Scale for Anxiety (HAM-A).[43] To ensure that current symptoms of anxiety rather than those of depression predominated, a score ≥ 9 on the Covi Anxiety Scale[44] and a score ≤ 7 on the Raskin Depression Scale[45] were also required. Patients were excluded from the study if they were diagnosed with any other current Axis I disorders except depression not otherwise specified, dysthymia, simple phobia, or somatization disorder. Additional exclusion criteria included clinically relevant hematologic, autoimmune, endocrine, cardiovascular, renal, hepatic, gastrointestinal, or neurologic disorders; a history of seizure disorder; borderline, avoidant, or antisocial personality disorder; alcohol or substance use disorder within the past 6 months; and patients considered at risk of suicide. Women who were pregnant or lactating were not eligible for the study; also ineligible were women of childbearing potential who were not using a reliable method of contraception.

Other reasons for exclusion were the use of gabapentin or a benzodiazepine within 1 week of the first baseline visit, the use of other psychotropic medications

within 2 weeks prior to study entry, or ongoing psychodynamic or cognitive-behavioral psychotherapy for GAD. Use of corticosteroids (except topical or inhaled corticosteroids < 1000 μg/day), antihypertensive agents, captopril, β-blockers, and psychotropic medication was not permitted during the study. Patients were allowed to take zolpidem for insomnia, but not for more than 2 nights per week or the night before clinic visits.

Study Design

Following a 1-week screening period, patients were randomly assigned to 1 of 4 treatment groups for 6 weeks of double-blind treatment, all administered on a twice-per-day (b.i.d.) dosing schedule: pregabalin 400 mg/day, pregabalin 600 mg/day, venlafaxine 75 mg/day, or matched placebo.

Patients assigned to pregabalin 400 mg/day received 100 mg/day for 2 days, then 200 mg/day for 2 days, before receiving the full dosage of 400 mg/day on day 5. Patients assigned to pregabalin 600 mg/day received 150 mg/day for 2 days, 300 mg/day for 2 days, and 450 mg/day for 2 days, before receiving the full dosage of 600 mg/day after their day 7 visit. Patients assigned to venlafaxine began treatment at the full 37.5 mg b.i.d. dosage. Six weeks of double-blind treatment were followed by a 1-week, double-blind taper and follow-up phase.

Efficacy Analyses

The primary efficacy measure was the change from baseline to endpoint in the total score of the 14-item, clinician-rated HAM-A in the pregabalin and venlafaxine groups compared with placebo. The HAM-A assessment was performed at screening, baseline, and study weeks 1, 2, 3, 4, and 6 (or at the time of early study discontinuation, as with all outcome measures). Secondary efficacy measures included HAM-A total scores (observed cases), analyzed by week; responder rate, as defined by ≥ 50% reduction from baseline in the HAM-A total score; Clinical Global Impression-Improvement scale (CGI-I)[46] score and responder rate (those patients rated as "much improved" or "very much improved" by their clinicians); 17-item, clinician-rated Hamilton Rating Scale for Depression (HAM-D)[47] score; and scores on the Hospital Anxiety and Depression Scale[48] (patient rated) consisting of the anxiety subscale (HADS-A) and the depression subscale (HADS-D).

Safety and Tolerability Analyses

Safety and tolerability were evaluated on the basis of patients' reports of adverse events at each clinic visit and the results of physical examinations, standard laboratory determinations, and electrocardiography (ECG) performed at screening and at the end of the double-blind treatment period. Adverse events were examined by nature, intensity, and relationship to treatment.

Statistical Analyses

The study was designed to enroll a sufficient number of patients to allow 95 evaluable patients per treatment group. The sample size was estimated with a power of 85% to detect a 3-point difference (standard deviation [SD], 7.5) in change in HAM-A score between either of the 2 pregabalin groups and the placebo group using a 2-sided test with an experiment-wise α level of .05.

Primary efficacy and safety analyses were performed on the intent-to-treat (ITT) population, which consisted of all randomized patients who received at least 1 dose of study drug. Only patients with at least 1 postbaseline assessment available were included in the efficacy analyses. Last observation carried forward (LOCF) was used on all primary and secondary outcome measures for the planned analyses, with the exception of analyses conducted to examine early onset, which used observed cases at each assessment. The experiment-wise significance level for the primary efficacy analysis was .05 (2-sided test). All other analyses were evaluated at a .05 significance level (2-sided) for each comparison.

Changes from baseline to endpoint in the HAM-A total score (the primary efficacy variable of the study) were compared between each dose of pregabalin and placebo, as well as between venlafaxine and placebo and (in post hoc analyses) between each pregabalin dose and venlafaxine, using an analysis of covariance (ANCOVA), with treatment and center in the model and baseline scores as covariates. Hochberg's procedure was used to adjust for multiple comparisons for the pregabalin versus placebo comparisons at endpoint. Changes from baseline in HAM-A psychic (e.g., anxiety, tension, worry) and somatic (i.e., muscular somatic symptoms, sensory somatic symptoms, as well as gastrointestinal, cardiovascular, respiratory, genitourinary, and autonomic symptoms) anxiety factor scores; HAM-A ≥ 50% responders; HAM-D, HADS-A, and HADS-D scores; and weekly HAM-A scores (observed-cases values used for the early onset of efficacy evaluation) were also compared. CGI-I scores were compared using an analysis of variance (ANOVA). Logistic regression was used to analyze responders by treatment group. Sustained HAM-A improvement was defined as a ≥ 30% reduction from baseline in HAM-A score sustained from the initial observation of such a reduction to the end of the study. Time to onset of sustained HAM-A improvement was measured in days from baseline to the initial double-blind visit at which sustained HAM-A improvement was observed. A patient must have completed the study to achieve sustained response. Post hoc analyses of change in scores on HAM-A items 1, 2, and 4 and psychic and somatic factor scores were also performed. Placebo-subtracted effect sizes for the HAM-A total score and direct comparisons on the HAM-A total, psychic factor, and somatic factor scores were also calculated post hoc.

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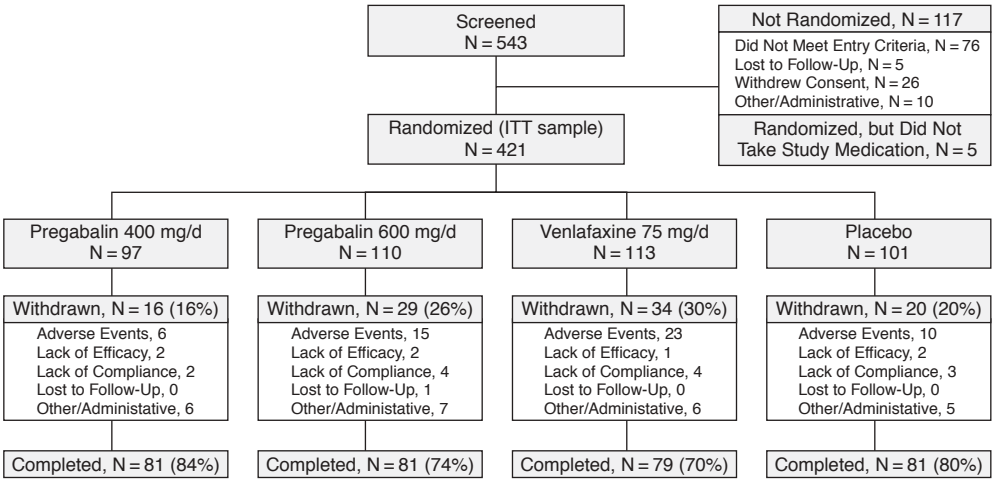
Figure 1. Disposition of Study Patients



Abbreviation: ITT = intent to treat.

Table 1. Baseline Clinical and Demographic Characteristics of 421 Patients With GAD

Characteristic	Pregabalin 400 mg/d (N = 97)	Pregabalin 600 mg/d (N = 110)	Venlafaxine 75 mg/d (N = 113)	Placebo (N = 101)
Female, %	59	65	65	58
Race, %				
White	96.9	100.0	99.1	99.0
Black	0	0	0	0
Asian or Pacific Islander	3.1	0	0	1.0
Other	0	0	0.9	0
Age, mean ± SD, y	45 ± 12	42 ± 12	46 ± 12	43 ± 12
Weight, mean ± SD, kg	75.4 ± 16.8	73.0 ± 16.4	74.9 ± 17.4	75.9 ± 16.4
Education, %				
High school, attended or completed	61	59	62	61
College, attended or completed	17	18	21	21
Graduate, professional, or other	22	23	17	18
HAM-A score, mean ± SD	26.3 ± 4.4	26.5 ± 4.6	26.0 ± 4.6	27.4 ± 5.5
HAM-D score, mean ± SD	12.2 ± 3.6	12.2 ± 4.0	12.0 ± 3.4	12.8 ± 4.9
Duration of current GAD episode, mean ± SD, mo	23 ± 36	16 ± 23	17 ± 31	20 ± 33
No. of prior episodes of GAD, mean ± SD	3 ± 5	4 ± 8	3 ± 4	5 ± 10

Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression.

RESULTS

Baseline Characteristics and Patient Disposition

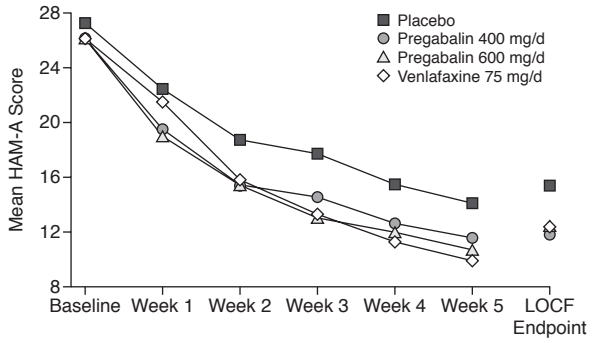
Of the 543 patients who entered the baseline phase, 421 were randomized and received study medication (Figure 1). The baseline demographic and clinical characteristics of the ITT sample are summarized in Table 1. The majority of patients were white, 62.0% were women, and mean age was 44.1 years (SD = 12.3). Mean baseline HAM-A total score ranged from 26.0 to 27.4 across the 4 treatment groups, indicating a population with moderate to severe GAD. Overall, 76.5% of randomized patients completed the study.

There were notable differences in disposition among the 4 treatment groups. Significantly more patients treated with pregabalin 400 mg/day completed the study than did patients treated with venlafaxine ($\chi^2 = 5.32$; $p < .05$). There were, however, no notable differences in demographic or clinical variables between the group of patients who dropped out and those who completed the study. Discontinuation rates due to associated adverse events were venlafaxine 75 mg/day, 20%; pregabalin 400 mg/day, 6%; pregabalin 600 mg/day, 14%; placebo, 7%. Discontinuations for any reason were venlafaxine 75 mg/day, 30%; pregabalin 400 mg/day, 16%; pregabalin 600 mg/day, 26%; placebo, 20%.

Efficacy

HAM-A change score LOCF endpoint analysis showed that efficacy in the pregabalin 400 mg/day,

Figure 2. Efficacy of Pregabalin as Measured by Unadjusted Mean HAM-A Total Score by Week and Treatment Group Versus Placebo (analysis of covariance)[a,b,c]



[a]Efficacy for weeks 1 through 4 and week 6 is based on an observed-cases (available patient) analysis. Sample sizes for each week, respectively, were as follows: pregabalin 400 mg/day (N = 93, 88, 87, 87, and 86), pregabalin 600 mg/day (N = 101, 90, 85, 89, and 84), venlafaxine 75 mg/day (N = 105, 96, 89, 87, and 80), placebo (N = 100, 93, 93, 91, 86). Sample sizes for LOCF endpoint (primary efficacy measure) were as follows: pregabalin 400 mg/day, N = 94; pregabalin 600 mg/day, N = 104; venlafaxine 75 mg/day, N = 110; placebo, N = 100.

[b]ANCOVA significance vs. placebo:

Week 1: pregabalin 400 mg/day, $p < .01$; pregabalin 600 mg/day, $p < .001$.

Week 2: pregabalin 400 mg/day and 600 mg/day, $p < .01$; venlafaxine 75 mg/day, $p < .05$.

Week 3: pregabalin 400 mg/day and 600 mg/day and venlafaxine 75 mg/day, $p < .01$.

Week 4: pregabalin 400 mg/day, $p < .05$; pregabalin 600 mg/day and venlafaxine 75 mg/day, $p < .01$.

Week 6: pregabalin 400 mg/day, $p = .0505$; pregabalin 600 mg/day and venlafaxine 75 mg/day, $p < .01$.

LOCF endpoint: pregabalin 400 mg/day, $p < .01$; pregabalin 600 mg/day and venlafaxine 75 mg/day, $p < .05$.

[c]ANCOVA significance vs. venlafaxine 75 mg/day:

Week 1: Pregabalin 400 mg/day, $p < .01$; pregabalin 600 mg/day, $p < .001$.

Abbreviations: ANCOVA = analysis of covariance, HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward.

pregabalin 600 mg/day, and venlafaxine 75 mg/day treatment groups was significantly superior to that in the placebo group ($p = .008$, $p = .03$, and $p = .03$, respectively) (Figure 2, Table 2). Treatment with pregabalin was associated with substantial overall improvement of general anxiety symptoms based on placebo-controlled effect sizes for reduction in the total HAM-A score: pregabalin 400 mg/day, 0.38; pregabalin 600 mg/day, 0.31; venlafaxine 75 mg/day, 0.31.

Consistent with the objectively scored HAM-A ratings, the change in patient-rated HADS-A subscale score, which measures subjective report of improvement of anxiety symptoms, demonstrated significant improvement for all 3 active treatments at endpoint (Table 3). The proportion of patients with a ≥ 50% reduction in HAM-A score at endpoint was significant and comparable for pregabalin 400 mg/day (61%; $p = .02$) and venlafaxine 75 mg/day (62%; $p = .01$), but was not significant for pregabalin 600 mg/day (58%; $p = .06$) when compared with placebo (45%).

Onset of improvement of anxiety symptoms was measured at the first patient visit in the study at week 1 of double-blind treatment. Early and sustained improvement—defined as the first week at which patients achieved ≥ 30% improvement in HAM-A total score with a significant level at every time point thereafter—was observed at both pregabalin dosage levels. Among completers, sustained improvement at week 1 was experienced by 33% of patients treated with pregabalin 400 mg/day, 46% of patients treated with pregabalin 600 mg/day, 23% of those treated with venlafaxine 75 mg/day, and 29% of those who received placebo. Significant improvement in mean ± SE HAM-A total score was achieved at the first assessment at week 1 with pregabalin 400 mg/day ($–7.0 \pm 0.6$; $p < .01$) and 600 mg/day ($–7.7 \pm 0.6$; $p < .001$) compared with placebo ($–4.8 \pm 0.6$), but was not achieved at this time point in the venlafaxine 75 mg/day treatment group ($p = .86$). Pregabalin in both treatment groups demonstrated significantly greater improvement in HAM-A total score at week 1 than did venlafaxine in post hoc direct comparisons (pregabalin 400 mg/day vs. venlafaxine 75 mg/day, $p = .005$; pregabalin 600 mg/day vs. venlafaxine 75 mg/day, $p = .0002$). Significant improvement in HAM-A total score was achieved beginning at week 2 on venlafaxine 75 mg/day compared with placebo.

In the assessment of improvement of the emotional anxiety symptoms as indicated on the HAM-A psychic factor score, significant efficacy compared with placebo was found at week 1 in both pregabalin treatment groups, but not in the venlafaxine 75-mg/day group (Figure 3). In addition, improvement in HAM-A psychic factor score at week 1 associated with pregabalin 600 mg/day was significantly greater than that associated with venlafaxine 75 mg/day ($p = .0007$) in the post hoc comparison. At LOCF endpoint on the HAM-A psychic factor, significantly greater efficacy versus placebo was demonstrated among all 3 treatment groups (Figure 4).

On the HAM-A somatic factor score, only pregabalin 400 mg/day was associated with significant efficacy versus placebo at week 1 and LOCF endpoint. Both pregabalin groups were also associated with significantly greater improvement in somatic symptoms at week 1 than was venlafaxine 75 mg/day ($p = .002$ for pregabalin 400 mg/day; $p = .002$ for pregabalin 600 mg/day vs. venlafaxine 75 mg/day).

As anxiety, worry, and tension are considered to be cardinal symptoms of the diagnosis of GAD, improvement of these individual symptoms in pregabalin-treated patients versus placebo-treated patients was assessed. Patients treated with pregabalin 400 mg/day, pregabalin 600 mg/day, and venlafaxine 75 mg/day all demonstrated

Table 2. Change From Baseline in HAM-A Total Score and HAM-A Psychic and Somatic Factor Scores in Patients With Generalized Anxiety Disorder[a,b]

	Study Treatment Groups				Pairwise Comparison vs Placebo		
Efficacy Variable	Pregabalin 400 mg/d (N = 94)	Pregabalin 600 mg/d (N = 104)	Venlafaxine 75 mg/d (N = 110)	Placebo (N = 100)	Pregabalin 400 mg/d	Pregabalin 600 mg/d	Venlafaxine 75 mg/d
HAM-A total score							
Week 1	–7.0 ± 0.6	–7.7 ± 0.6	–4.6 ± 0.6	–4.8 ± 0.6	< .01	< .001	.86
LOCF endpoint	–14.7 ± 0.8	–14.1 ± 0.8	–14.1 ± 0.8	–11.6 ± 0.8	.008	.03	.03
HAM-A psychic factor							
Week 1	–3.6 ± 0.3	–4.4 ± 0.3	–2.9 ± 0.3	–2.4 ± 0.3	.01	< .001	.26
LOCF endpoint	–7.7 ± 0.5	–7.7 ± 0.4	–7.8 ± 0.4	–5.9 ± 0.4	.006	.005	.003
HAM-A somatic factor							
Week 1	–3.4 ± 0.3	–3.4 ± 0.3	–1.9 ± 0.3	–2.3 ± 0.3	.03	.03	.40
LOCF endpoint	–7.0 ± 0.4	–6.4 ± 0.4	–6.4 ± 0.4	–5.6 ± 0.4	.02	.15	.14

[a]Week 1 values are based on observed cases at those assessments. Endpoint values are intent-to-treat–LOCF.
[b]Values are expressed as mean ± SE.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward.

Table 3. Additional Efficacy Analyses for Patients With Generalized Anxiety Disorder[a]

	Study Treatment Groups				Pairwise Comparison vs Placebo		
Efficacy Variable[b]	Pregabalin 400 mg/d (N = 94)	Pregabalin 600 mg/d (N = 104)	Venlafaxine 75 mg/d (N = 110)	Placebo (N = 100)	Pregabalin 400 mg/d	Pregabalin 600 mg/d	Venlafaxine 75 mg/d
HADS anxiety subscale							
Baseline	13.5 ± 0.3	13.5 ± 0.3	13.0 ± 0.3	13.8 ± 0.3			
Change at LOCF endpoint	–5.5 ± 0.5	–5.1 ± 0.5	–5.5 ± 0.4	–3.7 ± 0.5	.006	.03	.004
HAM-A anxiety item (#1)							
Baseline	2.8 ± 0.1	2.9 ± 0.1	2.8 ± 0.1	2.9 ± 0.1			
Change at week 1	–0.8 ± 0.1	–0.9 ± 0.1	–0.7 ± 0.1	–0.5 ± 0.1	.003	< .001	.05
Change at LOCF endpoint	–1.6 ± 0.1	–1.5 ± 0.1	–1.5 ± 0.1	–1.2 ± 0.1	.007	.02	.006
HAM-A tension item (#2)							
Baseline	2.7 ± 0.1	2.8 ± 0.1	2.8 ± 0.1	2.8 ± 0.1			
Change at week 1	–0.7 ± 0.1	–0.9 ± 0.1	–0.7 ± 0.1	–0.5 ± 0.1	.06	< .001	.16
Change at LOCF endpoint	–1.6 ± 0.1	–1.5 ± 0.1	–1.6 ± 0.1	–1.2 ± 0.1	.003	.01	.004
HAM-A insomnia item (#4)							
Baseline	2.2 ± 0.1	2.1 ± 0.1	2.1 ± 0.1	2.2 ± 0.1			
Change at week 1	–0.8 ± 0.1	–0.9 ± 0.1	–0.4 ± 0.1	–0.2 ± 0.1	< .001	< .001	.088
Change at LOCF endpoint	–1.4 ± 0.1	–1.4 ± 0.1	–1.0 ± 0.1	–0.8 ± 0.1	< .001	< .001	.12
CGI-I at LOCF endpoint	2.6 ± 0.1	2.7 ± 0.1	2.5 ± 0.1	3.0 ± 0.1	.04	.07	.006
CGI-I responders at LOCF endpoint, N (%)	53 (56.4)	61 (58.7)	67 (60.9)	42 (42.0)	.04	.02	.005
HADS depression subscale							
Baseline	9.5 ± 0.4	9.2 ± 0.4	8.9 ± 0.4	9.9 ± 0.4			
Change at LOCF endpoint	–3.0 ± 0.4	–2.6 ± 0.4	–2.9 ± 0.4	–1.8 ± 0.4	.02	.11	.04
HAM-D total score							
Baseline	12.1 ± 0.3	12.1 ± 0.3	11.9 ± 0.3	12.6 ± 0.3			
Change at LOCF endpoint	–5.3 ± 0.5	–4.9 ± 0.5	–5.1 ± 0.5	–3.0 ± 0.5	.001	.006	.002

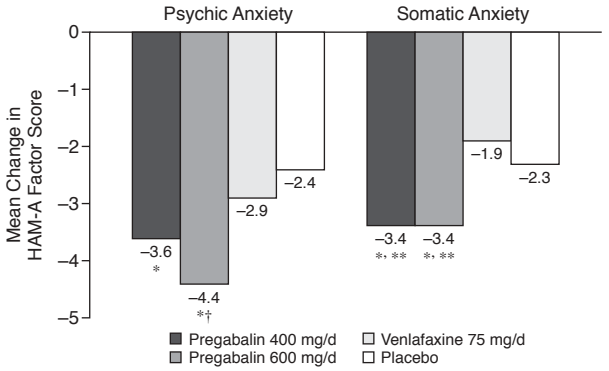
[a]Week 1 values are based on observed cases at those assessments. Endpoint values are intent-to-treat–LOCF.
[b]Values shown as mean ± SE unless otherwise noted.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, HADS = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

significantly greater improvement at LOCF endpoint compared with those who received placebo on HAM-A item 1 (anxiety, worry) and item 2 (tension).

Beneficial effects of pregabalin on sleep disturbances commonly associated with GAD—including insomnia and fatigue on waking—are captured in evaluation of change in score on item 4 of the HAM-A. Pregabalin 400 mg/day (–1.4, $p < .001$) and 600 mg/day (–1.4, $p < .001$) were significantly superior to placebo (–0.8), and each pregabalin dosage showed a substantial advantage over venlafaxine 75 mg/day (–1.0, $p = .12$ vs. placebo). The improved sleep associated with pregabalin use was observed as early as the first assessment at week 1 and remained significant at every visit through endpoint. Venlafaxine 75 mg/day was associated with significant improvement of insomnia at weeks 3 and 4 of treatment, but not at LOCF endpoint.

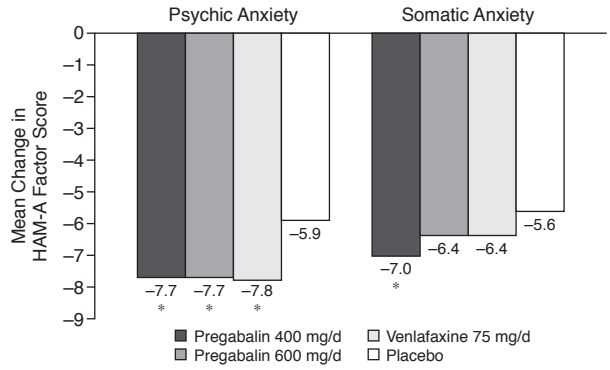
Change in patients' overall status was evaluated with the clinician-rated CGI-I. Treatment with pregabalin 400 mg/day and treatment with venlafaxine 75 mg/day were associated with significantly greater improvement than placebo in mean CGI-I score. In addition, the proportion of patients who were CGI-I responders—those patients rated as "much improved" or "very much improved" by

Figure 3. Week 1 Improvement (observed cases) in HAM-A Psychic and Somatic Anxiety Factor Scores for Pregabalin Versus Venlafaxine



*p < .05 vs. placebo.
**p < .01 vs. venlafaxine.
†p < .001 vs. venlafaxine.
Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

Figure 4. Efficacy of Pregabalin as Measured by Change in HAM-A Psychic and Somatic Factor Scores at LOCF Endpoint



*p < .05 vs. placebo.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward.

Table 4. Adverse Events (AEs) Reported by More Than 5% of Patients in Any Treatment Group (ordered by greatest incidence in pregabalin 600-mg/day group)

	Pregabalin 400 mg/d (N = 97)		Pregabalin 600 mg/d (N = 110)		Venlafaxine 75 mg/d (N = 113)		Placebo (N = 101)	
AE	Reported AE, N (%)	Discontinued Because of AE, N (%)	Reported AE, N (%)	Discontinued Because of AE, N (%)	Reported AE, N (%)	Discontinued Because of AE, N (%)	Reported AE, N (%)	Discontinued Because of AE, N (%)
Dizziness	22 (22.7)	1 (1.0)	29 (26.4)	8 (7.3)	14 (12.4)	5 (4.4)	7 (6.9)	0
Somnolence	13 (13.4)	0	15 (13.6)	3 (2.7)	4 (3.5)	1 (0.9)	3 (3.0)	0
Nausea	9 (9.3)	2 (2.1)	14 (12.7)	3 (2.7)	31 (27.4)	11 (9.7)	8 (7.9)	1 (1.0)
Headache	7 (7.2)	1 (1.0)	9 (8.2)	3 (2.7)	10 (8.8)	2 (1.8)	13 (12.9)	2 (2.0)
Constipation	7 (7.2)	0	7 (6.4)	0	7 (6.2)	2 (1.8)	2 (2.0)	0
Dry mouth	5 (5.2)	0	5 (4.5)	0	8 (7.1)	0	2 (2.0)	0
Diarrhea	4 (4.1)	0	5 (4.5)	2 (1.8)	5 (4.4)	2 (1.8)	6 (5.9)	0
Asthenia	5 (5.2)	0	4 (3.6)	0	14 (12.4)	3 (2.7)	6 (5.9)	1 (1.0)
Insomnia	1 (1.0)	0	3 (2.7)	0	8 (7.1)	0	5 (5.0)	0
Infection	9 (9.3)	0	3 (2.7)	0	3 (2.7)	0	4 (4.0)	0
Vomiting	4 (4.1)	1 (1.0)	2 (1.8)	2 (1.8)	9 (8.0)	5 (4.4)	1 (1.0)	0

their clinicians—at the end of treatment was significantly greater in all 3 treatment groups versus placebo.

Symptoms of depression often complicate clinical outcomes in patients diagnosed with GAD. Response to treatment on the HAM-D was examined. Treatment with pregabalin 400 mg/day, pregabalin 600 mg/day, and venlafaxine 75 mg/day was associated with significantly greater endpoint improvement compared with placebo on the HAM-D total score. Mean ± SE reductions in HAM-D score from baseline to LOCF endpoint were –5.3 ± 0.5 for pregabalin 400 mg/day, –4.9 ± 0.5 for pregabalin 600 mg/day, –5.1 ± 0.5 for venlafaxine 75 mg/day, and –3.0 ± 0.5 for placebo. Significant endpoint improvement relative to placebo in reduction of depressive symptoms was also achieved on the patient-rated HADS-D subscale for pregabalin 400 mg/day and venlafaxine 75 mg/day. Mean ± SE change from baseline to LOCF endpoint was –3.0 ± 0.4 for pregabalin 400 mg/day, –2.9 ± 0.4 for venlafaxine 75 mg/day, and –1.8 ± 0.4 for placebo.

Tolerability

Pregabalin, dosed at 400 mg/day and 600 mg/day, was generally well tolerated in this study, as was the 75-mg/day dose of venlafaxine (Table 4). The most common adverse events experienced by patients in the pregabalin groups were dizziness, somnolence (daytime sedation), and nausea; the most common adverse events in the venlafaxine 75-mg/day treatment group were nausea, dizziness, and asthenia. Headache was most common in the placebo group.

Fewer patients in the pregabalin treatment groups reported severe adverse events or discontinued because of adverse events than did those in the venlafaxine 75-mg/day treatment group. The proportion of patients who reported severe adverse events was 12% in the venla-

Table 5. Duration of Common Treatment-Emergent Adverse Events in Patients With Generalized Anxiety Disorder[a]

Adverse Event	Pregabalin 400 mg/d (N = 97)	Pregabalin 600 mg/d (N = 110)	Venlafaxine 75 mg/d (N = 113)	Placebo (N = 101)
Dizziness				
Total, %	23	26	12	7
Median day of onset[b]	1	1	1	4
Median duration, d	9	10	8	9
Somnolence				
Total, %	13	14	4	3
Median day of onset	2	1	1	1
Median duration, d	13	13	21	21
Nausea				
Total, %	9	13	27	8
Median day of onset	8	1	0	8
Median duration, d	4	11	4	14
Asthenia				
Total, %	5	4	12	6
Median day of onset	0	8	1	1
Median duration, d	9	32	8	16

[a]All-causality, with incidence = 10%; adverse event not included unless greater than placebo in at least 1 active treatment group.
[b]Number of days after first dose. Day 0 was the first day subject took study drug.

faxine 75-mg/day group, 9% in the pregabalin 600-mg/day group, 5% in the pregabalin 400-mg/day group, and 6% in the placebo group. The median onset of adverse events with pregabalin was during the dose-escalation period (Table 5). Tolerance to most adverse events developed rapidly, with remission of most adverse events occurring within 2 weeks of dosage stabilization. Somnolence as a treatment-emergent adverse event was reported by 13% of patients treated with pregabalin 400 mg/day and 14% of patients treated with pregabalin 600 mg/day. In comparison, somnolence was reported by 4% of patients treated with venlafaxine 75 mg/day and by 3% of those treated with placebo. Median day of onset of somnolence was day 2 for the pregabalin 400-mg/day group and day 1 for the pregabalin 600-mg/day, venlafaxine 75-mg/day, and placebo groups. The somnolence associated with pregabalin had a median duration of 13 days and appeared to be more transient than that observed with venlafaxine 75 mg/day or placebo, for which the median duration was 21 and 20.5 days, respectively.

The proportion of patients who discontinued due to associated adverse events was 20.4% in the venlafaxine 75-mg/day group, 13.6% in the pregabalin 600-mg/day group, 9.9% in the placebo group, and 6.2% in the pregabalin 400-mg/day group. The attrition rate due to discontinuations associated with adverse events in the venlafaxine 75-mg/day group was significantly greater than that in the pregabalin 400-mg/day group ($\chi^2 = 8.80$; $p < .01$).

No clinically relevant changes in vital signs, laboratory values, or ECG findings were observed. The mean ± SD change from baseline in weight was 1.0 ± 2.1 kg with pregabalin 400 mg/day, 1.6 ± 2.5 kg with pregabalin 600 mg/day, –0.2 ± 2.5 kg with venlafaxine 75 mg/day, and 0.6 ± 2.3 kg with placebo. One serious adverse event was considered related to treatment with pregabalin 400 mg/day: an "accidental fall" associated with dizziness. One serious adverse event—a "manic reaction"—occurred in the placebo group and was considered to be "possibly related" to treatment.

DISCUSSION

The results of this fixed-dose, randomized, controlled trial of pregabalin conducted in primary care and psychiatric specialty settings demonstrate that pregabalin provides robust efficacy in the treatment of GAD, encompassing improvement of psychic symptoms such as anxiety, worry, tension, and sleep disturbances as well as physical, somatic symptoms that characteristically manifest with generalized anxiety. At both dosages studied, pregabalin treatment was associated with significant LOCF endpoint improvement that was comparable to that observed with venlafaxine 75 mg/day. Only the pregabalin 400-mg/day treatment group experienced significant efficacy on all a priori primary and secondary efficacy measures.

The significant advantage compared with placebo was observed at the first clinical assessment at 1 week. This early onset of effect is seen in all doses of pregabalin compared to placebo in all short-term clinical trials conducted in GAD,[49] indicating a robust effect.

The present study represents the fifth positive randomized, placebo-controlled study in the short-term treatment of GAD with pregabalin.[33–36] Two of these positive studies included lorazepam as an active control,[33,34] 1 included alprazolam,[36] and the present study included venlafaxine (the other positive study[35] did not include an active control). In the single study that did not show separation of pregabalin from placebo at endpoint, lorazepam was included as an active control, and it, too, did not separate from placebo at endpoint, suggesting that the results from this study may be discounted (A.C.P., data on file, Pfizer Inc, New York, N.Y., 1998–1999).

A consistent pattern of findings in this study among the different efficacy measures demonstrates that, in both pregabalin treatment groups, there is a rapid, sustained, beneficial effect of pregabalin on symptoms of generalized anxiety. Beginning with the first assessments as early as week 1 and continuing to the end of the trial, anxiety symptoms were substantially improved in patients treated with pregabalin relative to placebo as evaluated with the HAM-A total score.

In general, licensed antidepressant treatments for GAD, such as paroxetine[18,19] and venlafaxine,[50–52] have been found to be more effective in treating the psychic (emotional) symptoms of anxiety, such that significant differences from placebo are often reported on the psy-

chic factor but only in rare instances on the somatic factor. In the present study, pregabalin appeared to be effective for treating both the psychic and the physical-somatic anxiety symptoms of GAD at endpoint, while venlafaxine 75 mg/day did not show efficacy for treating somatic symptoms of anxiety in comparison with placebo. It is conceivable that more patients would have responded to higher doses of venlafaxine. The early response with both dosages of pregabalin—which was further supported by the significant differences from placebo of pregabalin in both treatment arms on both psychic and somatic anxiety factors as early as week 1—was not shared by venlafaxine 75 mg/day. With venlafaxine early in treatment, the reduction in the somatic factor score was similar to placebo. It is possible that the somatic factor score was influenced by somatic adverse drug effects of venlafaxine, such as nausea, sweating, and palpitations. Based on these data, pregabalin may be preferred to venlafaxine to achieve both significantly earlier response and significantly greater efficacy against both psychic and somatic symptoms.

Early onset of anxiety relief is critical to the successful treatment of patients suffering from severe anxiety. In the assessment of early onset of anxiolytic effect, only pregabalin demonstrated significant improvement as early as week 1, the first HAM-A assessment, which persisted to the end of the study. Treatment resulted in significantly greater sustained improvement on the HAM-A and all secondary measures as early as week 1 and at every visit during the double-blind treatment phase. In particular, significantly greater improvement at week 1 for pregabalin 400 mg/day in direct post hoc comparison with venlafaxine 75 mg/day as well as placebo was also achieved on the HAM-A somatic factor. Previously, benzodiazepines have demonstrated rapid, clinically meaningful anxiolytic efficacy in some randomized, placebo-controlled trials in the treatment of GAD.[16]

The rapid (as early as week 1) onset of efficacy demonstrated by pregabalin in the current study is consistent with the results of its previous placebo-controlled comparator trials. Efficacy relative to placebo as early as week 1 has been found for dosages of pregabalin within the 200- to 600-mg/day range.[33–36] A recent study showed a significantly higher rate of early sustained response (from week 1 to endpoint) with pregabalin 300, 450, and 600 mg/day, but not with alprazolam 1.5 mg/day, compared with placebo, and pregabalin 300 mg/day achieved significantly greater early improvement than alprazolam.[36]

The efficacy seen in the present study in the pregabalin 400-mg/day treatment group was superior to that in the other treatment groups, as it was consistently significant versus placebo on the primary outcome measure (change in HAM-A score) at all study visits and at LOCF endpoint on all secondary outcomes, including the HAM-A psychic and somatic factors scores, the anxiety and tension items (1 and 2) of the HAM-A, and the CGI-I, in addition to the HADS anxiety and depression subscales. Pregabalin 600 mg/day and venlafaxine 75 mg/day were also significantly superior to placebo at LOCF endpoint on the HAM-A total score, but results were less robust on secondary outcome measures.

To the best of our knowledge, superior efficacy on improvement of somatic symptoms in a direct comparison to an active agent has been seen in only 2 studies. The benzodiazepine diazepam was associated with greater efficacy in comparison with buspirone on the HAM-A somatic factor score,[53] and, in a second study, diazepam was more effective than imipramine and trazodone at week 2 on the HAM-A somatic factor score.[54]

Some of the more favorable overall response may be attributable to the documented beneficial effects of pregabalin on sleep, which have been consistently observed in several clinical trials.[24–29,37] A post hoc analysis of the insomnia item of the HAM-A demonstrated a significant improvement in insomnia seen with both dosages of pregabalin at week 1 and at endpoint compared with placebo. Relief of sleep disturbances early in the treatment of GAD is important to well-being and adherence to treatment, as complaints of insomnia in GAD are common and insomnia is regarded in DSM-IV-TR as a core diagnostic feature of GAD.[55] This advantage may be reflective, however, of the more frequent reports of somnolence among patients treated with pregabalin than with venlafaxine. The effect of the somnolence (which was transient in most patients in the pregabalin groups) associated with pregabalin use remains to be characterized. In a study of healthy volunteers, however, sedation seen with pregabalin use was not associated with the broad spectrum and severity of cognitive impairment observed with alprazolam, and brake reaction time was better than that when subjects received placebo.[38,39]

Dizziness (described as lightheadedness) was the most frequently reported side effect with both doses of pregabalin (400 mg, 22.7%; 600 mg, 26.4%) compared with a rate of 6.9% with placebo. For comparison, the rate of dizziness with venlafaxine was 12.4%. Somnolence (daytime sedation) with pregabalin occurred at a rate of 13.4% to 13.6%, compared to 3.0% with placebo. Venlafaxine, which is thought to disturb sleep, understandably had a lower rate of somnolence (3.5%) and did not differ from placebo. Pregabalin was associated with a lower incidence of insomnia (400 mg, 1.0%; 600 mg, 2.7%) than venlafaxine (7.1%) or placebo (5.0%). There was a greater incidence of nausea with venlafaxine (27.4%) than with placebo (7.9%), pregabalin 400 mg/day (9.3%), or pregabalin 600 mg/day (12.7%). Asthenia also occurred more frequently with venlafaxine (12.4%) than with pregabalin, which did not differ from placebo in asthenia incidence.

Both pregabalin and venlafaxine were found to be safe in this study; the salient between-drug difference in toler-

ability was that overall attrition and attrition due to adverse events were significantly lower with pregabalin 400 mg/day compared with venlafaxine 75 mg/day. Attrition with pregabalin 600 mg/day was intermediate between pregabalin 400 mg/day and venlafaxine 75 mg/day.

Because mild depressive-type symptoms frequently complicate the clinical presentation of GAD, the secondary outcome of improvement of depressive symptoms was evaluated. Venlafaxine is a licensed antidepressant with efficacy established in placebo-controlled studies and, as expected, venlafaxine 75 mg/day significantly improved the depressive symptoms found in these patients with a primary diagnosis of GAD. Pregabalin demonstrated comparable antidepressant effect: treatment with pregabalin at both dosages resulted in improvement in the HAM-D total score that was significant versus placebo and comparable in magnitude to that observed with venlafaxine 75 mg/day at the end of week 6. Pregabalin has not yet been directly tested in placebo-controlled studies in major depressive disorder, and in view of these findings, it would be interesting to assess its efficacy in that disorder.

The Results in Context

The past 8 years have witnessed a renewed interest in the treatment of generalized anxiety disorder—with the completion of at least a dozen placebo-controlled studies evaluating the efficacy of SSRI and SNRI antidepressants as anxiolytic agents—to provide clear alternatives to the benzodiazepines. Fewer placebo-controlled trials provide comparative data on the efficacy of 2 drugs in GAD, though such trials provide useful information for clinical decision-making. In one active-comparator trial, similar efficacy was reported for imipramine, trazodone, and diazepam, but faster onset and greater efficacy were reported for diazepam in treating symptoms of somatic anxiety.[54] Another comparator trial found no significant difference between venlafaxine extended release (XR) and buspirone relative to placebo in either speed of onset or overall anxiolytic effect on change from baseline to LOCF endpoint in the total HAM-A score.[50] Overall, these studies have supported clinical observation suggesting faster onset of action for benzodiazepines and relatively later onset for antidepressants and other classes of medications in the treatment of generalized anxiety symptoms. The results of the present study support this distinction and, furthermore, show that pregabalin is associated with significantly earlier improvement of both psychic and somatic symptoms, including insomnia, compared with venlafaxine 75 mg/day and placebo.

Study Limitations

Several possible study limitations should be noted. First, the IR formulation of venlafaxine was used at a fixed dosage of 75 mg/day. At the time the study was designed (early 1999), the XR formulation of venlafaxine was not available, and the 75-mg/day dosage of the IR formulation was the only dosage indicated in Europe. Because the IR and XR formulations are the same chemical entity, it may be assumed that the XR formulation would perform similarly to the IR formulation used in this study. The selection of the dose of venlafaxine 75 mg/day was based on this being the dose at which venlafaxine was licensed for GAD, and no dose-response relationship has been established for venlafaxine in short-term treatment in GAD across its dosing range of 75 to 225 mg/day.[40,41] In the absence of a clear-cut dose-response relationship in short-term treatment with venlafaxine, there seems little reason to use greater doses that are known to be associated with increased side effects. It is possible that in long-term treatment, doses greater than 75 mg may be useful, as shown in a post hoc analysis,[56] but this has not yet been clearly established.

A limitation of the study is its length of 6 weeks. This relatively short period would not identify the possible very late responses that have been reported in studies of longer duration. However, the responses observed with pregabalin occurred early in treatment, so the duration of 6 weeks is sufficient to test efficacy adequately, and the results may, therefore, generalize to short-term treatment. The study was designed to investigate the efficacy of pregabalin in short-term treatment and not to investigate efficacy in long-term treatment, for which a separate study would be needed. The efficacy of pregabalin has now been established in a long-term maintenance treatment study (A.C.P., data on file, Pfizer Inc, New York, N.Y., 1999–2001). Finally, formal investigation of possible discontinuation symptoms at the end of the study was not undertaken in this study. Such a study has been carried out and is the subject of a separate paper (A.C.P., in preparation).

CONCLUSION

At endpoint, the anxiolytic efficacy of pregabalin was comparable to that of venlafaxine 75 mg/day, but pregabalin demonstrated a significantly more rapid onset of action and more consistent improvement across both psychic and somatic anxiety symptom clusters. Pregabalin demonstrated anxiolytic efficacy that was comparable to that of venlafaxine 75 mg/day among patients diagnosed with GAD who also had high levels of pretreatment depressive symptoms, and it effectively reduced the depressive symptoms themselves. Pregabalin 400 mg/day was better tolerated than either pregabalin 600 mg/day or venlafaxine 75 mg/day, as evidenced by fewer discontinuations due to adverse events and fewer adverse events in this treatment group. Pregabalin, at the higher end of its dosing range, appeared to be somewhat better tolerated than venlafaxine, even though the latter drug was administered at doses of 75 mg/day.

There are now 5 placebo-controlled studies in GAD demonstrating robust efficacy of pregabalin for the treatment of both psychic and somatic symptoms of anxiety—4 previous trials[33–36] and the current study. Furthermore, all 5 studies confirm that pregabalin is associated with rapid onset (by week 1) of anxiolytic efficacy. Our study suggests additional areas of potential benefit; in particular, improvement of sleep disturbances associated with GAD and treatment of depressive symptoms in major depression could be promising clinical avenues. In light of the newly defined mechanism of action of pregabalin, its modulatory effect on neurotransmitter release appears to confer on pregabalin the ability to improve sleep, without causing the reduction in restorative slow-wave sleep associated with benzodiazepines or selective serotonin/norepinephrine reuptake inhibitors.[57] As recently reviewed,[58] anxiety, pain, and insomnia represent the most commonly occurring triad of suffering for which central nervous system drugs are prescribed worldwide. Pregabalin, with its novel pharmacology, may offer a unique treatment for overlap between generalized anxiety, physical-somatic symptoms, and associated sleep disturbances, and its full scope of efficacy for these symptoms needs to be further explored in clinical trials.

Drug names: alprazolam (Xanax, Niravam, and others), buspirone (BuSpar and others), captopril (Capoten and others), diazepam (Valium and others), gabapentin (Neurontin and others), imipramine (Tofranil and others), lorazepam (Ativan and others), paroxetine (Paxil, Pexeva, and others), pregabalin (Lyrica), trazodone (Desyrel and others), venlafaxine (Effexor), zolpidem (Ambien).

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REFERENCES

1. The World Health Organization Mental Health Survey Consortium. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. JAMA 2004;291:2581–2590
2. Wittchen HU, Kessler RC, Beesdo K, et al. Generalized anxiety and depression in primary care: prevalence, recognition, and management. J Clin Psychiatry 2002;63(suppl 8):24–34
3. Rynn MA, Brawman-Mintzer O. Generalized anxiety disorder: acute and chronic treatment. CNS Spectr 2004;9:716–723
4. Blanchard EB, Scharff L, Schwarz SP, et al. The role of anxiety and depression in the irritable bowel syndrome. Behav Res Ther 1990;28: 401–405
5. Lydiard RB. Irritable bowel syndrome, anxiety, and depression: what are the links? J Clin Psychiatry 2001;62(suppl 8):38–45
6. Walker EA, Keegan D, Gardner G, et al. Psychosocial factors in fibromyalgia compared with rheumatoid arthritis, 1: psychiatric diagnoses and functional disability. Psychosom Med 1997;59:565–571
7. Epstein SA, Kay G, Clauw D, et al. Psychiatric disorders in patients with fibromyalgia: a multicenter investigation. Psychosomatics 1999;40: 57–63
8. Verri AP, Proietti Cecchini A, Galli C, et al. Psychiatric comorbidity in chronic daily headache. Cephalalgia 1998;18(suppl 21):45–49
9. Clark MR, Heinberg LJ, Haythornthwaite JA, et al. Psychiatric symptoms and distress differ between patients with postherpetic neuralgia and peripheral vestibular disease. J Psychosom Res 2000;48:51–57
10. Nascimento I, Nardi AE, Valenca AM, et al. Psychiatric disorders in asthmatic outpatients. Psychiatry Res 2002;110:73–80
11. Goodwin RD, Gorman JM. Psychopharmacologic treatment of generalized anxiety disorder and the risk of major depression. Am J Psychiatry 2002;159:1935–1937
12. Murphy JM, Monson RR, Olivier DC, et al. Affective disorders and mortality: a general population study. Arch Gen Psychiatry 1987;44: 473–480
13. Frasure-Smith N, Lespérance F, Juneau M, et al. Gender, depression, and one-year prognosis after myocardial infarction. Psychosom Med 1999; 61:26–37
14. Roy-Byrne PP, Wagner A. Primary care perspectives on generalized anxiety disorder. J Clin Psychiatry 2004;65(suppl 13):20–26
15. Woods JH, Katz JL, Winger G. Benzodiazepines: use, abuse, and consequences. Pharmacol Rev 1992;44:151–347
16. Rickels K, Rynn M. Pharmacotherapy of generalized anxiety disorder. J Clin Psychiatry 2002;63(suppl 14):9–16
17. Sramek JJ, Zarotsky V, Cutler NR. Generalised anxiety disorder: treatment options. Drugs 2002;62:1635–1648
18. Pollack MH, Zaninelli R, Goddard A, et al. Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry 2001;62:350–357
19. Rickels K, Zaninelli R, McCafferty J, et al. Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. Am J Psychiatry 2003;160:749–756
20. Stahl SM. Don't ask, don't tell, but benzodiazepines are still the leading treatments for anxiety disorder [Brainstorms]. J Clin Psychiatry 2002; 63:756–757
21. IMS. IMS National Prescription Audit and National Disease Therapeutic Index (NDTI): Moving Annual Total Nov 2003. Fairfield, Conn: IMS; 2003. Available at: http://www.imshealth.com/ims/portal/front/articleC/0,27777,6599_18731_40044561,00.html. Access verified April 5, 2006
22. Grimsley SR. Anxiety disorders. In: Young LY, Koda-Kimble MA,

Kradjan WA, et al, eds. Applied Therapeutics: The Clinical Use of Drugs. 6th ed. Vancouver, BC: British Columbia Therapeutics; 1995:73-1–73-31
23. Gee NS, Brown JP, Dissanayake VU, et al. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the a_2-d subunit of a calcium channel. J Biol Chem 1996;271:5768–5776
24. Rosenstock J, Tuchman M, LaMoreaux L, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004;110:628–638
25. Lesser H, Sharma U, LaMoreaux L, et al. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 2004;63:2104–2110
26. Richter RW, Portenoy R, Sharma U, et al. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. J Pain 2005;6:253–260
27. Freynhagen R, Strojek K, Griesing T, et al. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005;115:254–263
28. Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2003;60:1274–1283
29. Sabatowski R, Gálvez R, Cherry DA, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled trial. Pain 2004; 109:26–35
30. French JA, Kugler AR, Robbins JL, et al. Dose-response trial of pregabalin adjunctive therapy in patients with partial seizures. Neurology 2003;60:1631–1637
31. Arroyo S, Anhut H, Kugler R. Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled dose-response study in adults with partial seizures. Epilepsia 2004;45:20–27
32. Beydoun A, Uthman BM, Kugler AR, et al. Safety and efficacy of two pregabalin regimens for add-on treatment of partial epilepsy. Neurology 2005;64:475–480
33. Feltner DE, Crockatt JG, Dubovsky SJ, et al. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. J Clin Psychopharmacol 2003;23:240–249
34. Pande AC, Crockatt JG, Feltner DE, et al. Pregabalin in generalized anxiety disorder: a placebo-controlled trial. Am J Psychiatry 2003;160: 533–540
35. Pohl RB, Feltner DE, Fieve RR, et al. Efficacy of pregabalin in the treatment of generalized anxiety disorder: double-blind, placebo-controlled comparison of BID versus TID dosing. J Clin Psychopharmacol 2005; 25:151–158
36. Rickels K, Pollack MH, Feltner DE, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry 2005;62:1022–1030
37. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:1264–1273
38. Hindmarch I, Dawson J, Stanley N. A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. Sleep 2005;28:187–193
39. Hindmarch I, Trick L, Ridout F. A double-blind, placebo- and positive-internal-controlled (alprazolam) investigation of the cognitive and psychomotor profile of pregabalin in healthy volunteers. Psychopharmacology 2005;183:133–143
40. Meoni P, Salinas E, Brault Y, et al. Pattern of symptom improvement following treatment with venlafaxine XR in patients with generalized anxiety disorder. J Clin Psychiatry 2001;62:888–893
41. Wyeth Pharmaceuticals Inc. Effexor (venlafaxine hydrochloride) tablets. Full prescribing information. Available at: http://www.wyeth.com/content/getfile.asp?id=99. Access verified March 14, 2006
42. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33
43. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
44. Lipman R, Covi L. Outpatient treatment of neurotic depression: medication and group psychotherapy. In: Spitzer R, Klein DL, eds. Evaluation of the Psychological Therapies. Baltimore, Md: Johns Hopkins UP; 1976:181–202
45. Raskin A, Schulterbrandt J, Reatig N, et al. Replication of factors of psychopathology in interview, ward behaviour and self-report ratings of hospitalized depressives. J Nerv Ment Dis 1969;148:87–98
46. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
47. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
48. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–370
49. Montgomery SA, Rickels K, Bielski RJ, et al. Pregabalin in generalized anxiety disorder: speed of onset. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
50. Davidson JR, DuPont RL, Hedges D, et al. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. J Clin Psychiatry 1999;60:528–535
51. Rickels K, Pollack MH, Sheehan DV, et al. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. Am J Psychiatry 2000;157:968–974
52. Allgulander C, Hackett D, Salinas E. Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: twenty-four-week placebo-controlled dose-ranging study. Br J Psychiatry 2001;179:15–22
53. Rickels K, Weisman K, Norstad N, et al. Buspirone and diazepam in anxiety: a controlled study. J Clin Psychiatry 1982;43:81–86
54. Rickels K, Downing R, Schweizer E, et al. Antidepressants for the treatment of generalized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry 1993;50: 884–895
55. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
56. Montgomery SA, Mahe V, Haudiquet V, et al. Effectiveness of venlafaxine, extended release formulation, in the short-term and long-term treatment of generalized anxiety disorder: results of a survival analysis. J Clin Psychopharmacol 2002;22:561–567
57. Salín-Pascual RJ, Galicia-Polo L, Drucker-Colín R. Sleep changes after four consecutive days of venlafaxine administration in normal volunteers. J Clin Psychiatry 1997;58:348–350
58. Ghodse H. Pain, anxiety, and insomnia: a global perspective on the relief of suffering. Br J Psychiatry 2003;183:15–21

