

Pregabalin for Treatment of Generalized Anxiety Disorder

A 4-Week, Multicenter, Double-blind, Placebo-Controlled Trial of Pregabalin and Alprazolam

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Background: Pregabalin inhibits release of excess excitatory neurotransmitters, presumably by binding to the α_2 - δ subunit protein of widely distributed voltage-dependent calcium channels in the brain and spinal cord.

Objective: To assess the anxiolytic efficacy of pregabalin in patients with generalized anxiety disorder.

Design: Double-blind, placebo-controlled, active-comparator trial. Patients were randomized to 4 weeks of treatment with pregabalin, 300 mg/d (n=91), 450 mg/d (n=90), or 600 mg/d (n=89); alprazolam, 1.5 mg/d (n=93); or placebo (n=91).

Setting: Psychiatry research and clinic settings.

Patients: Outpatients meeting the DSM-IV criteria for generalized anxiety disorder, with a baseline Hamilton Anxiety Rating Scale (HAM-A) total score of 20 or greater.

Main Outcome Measures: Change from baseline to end point in total HAM-A score in the pregabalin and alprazolam groups compared with the placebo group. The end point response criterion was 50% or greater reduction in the HAM-A total score.

Results: Pregabalin and alprazolam produced a significantly greater reduction in mean \pm SE HAM-A total score at last-observation-carried-forward end point compared with placebo (-8.4 ± 0.8): pregabalin, 300 mg (-12.2 ± 0.8 , $P < .001$), 450 mg (-11.0 ± 0.8 , $P = .02$), and 600 mg (-11.8 ± 0.8 , $P = .002$), and alprazolam (-10.9 ± 0.8 , $P = .02$). By week 1 and at last-observation-carried-forward end point, the 3 pregabalin groups and the alprazolam group had significantly ($P < .01$) improved HAM-A psychic anxiety symptoms compared with the placebo group. Compared with the placebo group, HAM-A somatic anxiety symptoms were also significantly ($P < .02$) improved by the 300- and 600-mg pregabalin groups, but not by the 450-mg pregabalin (week 1, $P = .06$; week 4, $P = .32$) and the alprazolam groups (week 1, $P = .21$; week 4, $P = .15$). Of the 5 treatment groups, the 300-mg pregabalin group was the only medication group that differed statistically in global improvement at treatment end point not only from the placebo group but also from the alprazolam group.

Conclusion: Pregabalin was significantly more efficacious than placebo for the treatment of psychic and somatic symptoms of generalized anxiety disorder and was well tolerated by most study patients.

Arch Gen Psychiatry. 2005;62:1022-1030

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GENERALIZED ANXIETY DISORDER (GAD) is among the most common psychiatric illnesses, with a 12-month prevalence estimated to range from 3% to 5% and a lifetime prevalence of 4% to 7%.¹ The prevalence of GAD in the primary care setting is even higher, reflecting the degree of health care use associated with the illness: approximately 8% of all primary care visits are by patients with GAD, with an additional 4% just missing the full diagnostic criteria.²⁻⁴ While psychic symptoms of anxiety, tension, and worry are cardinal symptoms, a wide array of autonomic, musculoskeletal, gastrointestinal, and respiratory

symptoms contribute substantially to the clinical picture. Surveys suggest that these varied physical somatic symptoms (including painful somatic manifestations) associated with anxiety, together with insomnia, represent the presenting complaint of more than 3 of 4 patients with GAD in the primary care setting.⁵

Generalized anxiety disorder is a chronic illness, with a modal age of onset in the late teenaged years to the early 20s and a typical illness duration of greater than 10 years.¹ The chronicity of GAD is associated with significant levels of functional disability and quality-of-life impairment that is comparable to what is reported for major depression.^{2,3,6,7}

Pregabalin, a structural analogue of γ -aminobutyric acid, is a novel compound with broad-spectrum efficacy in the treatment of distinct medical conditions, as suggested by findings from studies of diabetic neuropathy,^{8,9} postherpetic neuralgia,^{10,11} and partial epilepsy.^{12,13} In addition, evidence from 2 dose-finding studies^{14,15} suggests that pregabalin may also have efficacy in GAD.

Pregabalin is rapidly absorbed (time of occurrence for maximum drug concentration, 1 hour) and has linear kinetics across its therapeutic dose range.¹⁶ Pregabalin is not protein bound. It has an elimination half-life of 6 hours and is primarily (92%) renally excreted (89% as the parent compound). Pregabalin does not inhibit cytochrome P450 enzymes, nor do these enzymes alter its pharmacokinetics.

Pregabalin represents a potentially new class of anxiolytic agents for the treatment of GAD, with a mechanism of action that is different from the benzodiazepines and from all other anxiolytic agents. Pregabalin is inactive at γ -aminobutyric acid_A, γ -aminobutyric acid_B, or benzodiazepine receptors; does not bind to presynaptic or postsynaptic serotonin receptors; and does not inhibit reuptake of serotonin or norepinephrine.¹⁷ Instead, pregabalin binds to the α_2 - δ subunit protein of voltage-gated calcium channels and acts as a presynaptic inhibitor of the release, in stimulated neurons, of various excitatory neurotransmitters.¹⁸⁻²¹ In animal models, chemical alterations to the pregabalin structure that reduce binding to α_2 - δ subunits also reduce anticonvulsant, analgesic, and anxiolytic activity.²² These results suggest that high-affinity binding of pregabalin to the α_2 - δ subunit may be required for its anxiolytic, analgesic, and anticonvulsant activities in animal models.

The present study was undertaken to test the hypothesis that pregabalin is rapidly effective in the treatment of anxiety symptoms in patients diagnosed as having GAD. Alprazolam, the most commonly prescribed anxiolytic agent for GAD in the United States,²³ was used as a benchmark active comparator to assess the efficacy, rapidity of onset, and tolerability of pregabalin.

METHODS

STUDY DESIGN

This was a double-blind placebo-controlled comparison of the efficacy and tolerability of 3 fixed dosages of pregabalin (300, 450, and 600 mg/d) vs alprazolam (1.5 mg/d) in the treatment of GAD. Patients who met the study enrollment criteria completed a 1-week drug-free screening period, during which no placebo was administered and prohibited medications were washed out; then, patients were randomized, in blocks of 10, to 4 weeks of double-blind study treatment. At the conclusion of the 4-week double-blind treatment period, medication was discontinued during a 1-week taper period, followed by a 1-week medication-free period, during which patients were examined for the occurrence of discontinuation symptoms.

Pregabalin treatment was initiated at 300 mg/d for all 3 dosages; for patients assigned to 450 and 600 mg of pregabalin, the dosage was titrated to 450 mg/d on day 4; and for those assigned to 600 mg of pregabalin, the dosage was titrated to

600 mg/d on day 7. Treatment with alprazolam was initiated at 0.5 mg/d and was increased to 1.0 mg/d on day 4 and to 1.5 mg/d on day 7. Study drug was administered in divided doses using a 3 times a day schedule.

The study was conducted at 29 US centers based on Good Clinical Practices guidelines and in accordance with the Declaration of Helsinki. The protocol was approved at each center by the appropriate institutional review board, and written informed consent was obtained from each patient before enrollment.

PATIENT SELECTION

Patients were recruited through clinic referrals and from advertisements in local media. Male or female outpatients who were 18 years or older, met the DSM-IV²⁴ criteria for GAD based on a structured Mini-International Neuropsychiatric Interview,²⁵ and had screening and baseline scores of 20 or greater on the Hamilton Anxiety Rating Scale (HAM-A)²⁶ and 9 or greater on the Covi Anxiety Scale were eligible for enrollment.²⁷ Patients were excluded for any of the following reasons: (1) a Raskin Depression Scale²⁸ score of greater than 7; (2) being a fertile woman having a positive pregnancy test result, not using a medically accepted contraceptive, or currently nursing; (3) current or past history of bipolar, schizophrenic, schizoaffective, psychotic, or factitious disorder and dementia; (4) current but not lifetime major depressive disorder, social anxiety disorder, panic disorder with or without agoraphobia, obsessive-compulsive disorder, posttraumatic or acute stress disorders, and eating disorders at the diagnostic threshold but not sub-threshold level and alcohol or other substance dependence and/or abuse; (5) positive urine drug screen result (including benzodiazepines); (6) any clinically significant acute or unstable medical condition or clinically significant electrocardiographic (ECG) result or laboratory abnormalities; (7) concurrent psychotherapy for GAD, unless undergoing stable treatment for longer than 3 months; (8) concomitant treatment with a psychotropic medication during the study and for at least 2 weeks before the screening visit (5 weeks for fluoxetine) (zolpidem tartrate, 5 mg, for up to 2 nights per week was permitted during the study as needed for extreme sleeplessness, except for the night before a scheduled clinic appointment); (9) current or past history of a seizure disorder or requiring anticonvulsant therapy for any indication; or (10) suicide risk either currently or based on history.

The screening evaluation consisted of a psychiatric history and assessment of current status, including completion of the Mini International Neuropsychiatric Interview, a structured diagnostic interview, the HAM-A, the Raskin Depression Scale, and the Covi Anxiety Scale. A medical evaluation was performed, including a review of systems, an ECG, a physical examination, and laboratory testing (clinical chemistry test, hematologic analysis, urinalysis, urine drug screen, and serum pregnancy test).

EFFICACY MEASURES

The primary efficacy measure was the mean change from baseline to end point in the total score on the 14-item clinician-rated HAM-A.²⁶ The HAM-A assessment was performed at the screening and baseline visits; at study weeks 1, 2, 3, and 4 (or at study discontinuation, if premature); and, for a subgroup of patients, also during the taper period.

Secondary efficacy measures consisted of the following: the 17-item clinician-rated Hamilton Depression Rating Scale (HAM-D),²⁹ completed at the screening visit, at baseline, and at week 4; and the investigator-rated Clinical Global Impression Im-

provement Scale (CGI-I),³⁰ completed at weeks 1, 2, 3, and 4. The HAM-A psychic anxiety (items 1-6 and 14) and somatic anxiety (items 7-13) factors were evaluated. Items 1 (anxiety/worry) and 2 (tension) of HAM-A were also analyzed, because these items represent key criteria for the diagnosis of GAD and because they have been widely reported in recent GAD clinical trials.^{31,32} The Endicott Work Productivity Scale was included as a quality-of-life assessment scale.³³

SAFETY AND TOLERABILITY MEASURES

Spontaneously reported or observed adverse events were recorded with regard to time of onset, duration, severity, action taken, and outcome. Use of concomitant medications was recorded in terms of daily dosage, stop and start dates, and reason for use. Compliance was monitored by counts of returned medication, and patients were counseled if they were noncompliant.

Vital signs were obtained at each visit. The 20-item patient-rated Physician Withdrawal Checklist (PWC),³⁴ designed to evaluate benzodiazepine withdrawal symptoms, was completed at week 4 and at 2 follow-up visits. The ECG, physical examination, and laboratory testing were repeated at the end of 4 weeks of double-blind treatment (or at the time of early discontinuation).

STATISTICAL ANALYSES

All statistical analyses were performed using SAS statistical software, version 6.12,³⁵ for the intent-to-treat (ITT) population, composed of all randomized patients who received at least 1 dose of study medication. This sample excludes 2 pregabalin, 300 mg/d, 3 pregabalin, 450 mg/d, 4 pregabalin, 600 mg/d, 5 alprazolam, and 6 placebo group patients with no postrandomization efficacy assessments. It was hypothesized that patients in the pregabalin treatment groups would show a statistically significant reduction in the HAM-A score at treatment end point compared with those in the placebo group. A sample size of 97 evaluable patients per treatment group would provide 85% power to detect a mean difference of 3.5 (SD, 7) in the HAM-A score between placebo and pregabalin (300, 450, or 600 mg/d), with an experimentwise α level of .05. Last-observation-carried-forward (LOCF) analysis was used on all primary and secondary outcome measures for the planned analyses. In addition, some analyses used observed case data. Analyses of HAM-A and HAM-D change scores from baseline to end point, HAM-A and CGI-I responders, and PWC data were planned a priori. Other analyses were post hoc.

The HAM-A change score from baseline to end point was analyzed using an analysis of covariance model that included the effects of treatment and center, with baseline HAM-A total score as a covariate.³⁶ Least squares means and 95% confidence intervals were calculated, and an adjustment³⁷ for multiple comparisons was used to test the treatment effect in each pregabalin treatment group vs the placebo group. For a given efficacy parameter, patients with no postrandomization data were not included in its analyses (the “n” values in our tables and figures reflect the number of patients with data for that parameter). To check the robustness of the primary analysis, a rank analysis of covariance was used, with worst-rank imputation for patients with no postrandomization data. Weekly HAM-A change scores were analyzed separately by analysis of covariance using a model that included the effects of treatment and center, with baseline HAM-A total score as a covariate (observed cases). A repeated-measures model was also used to analyze change in HAM-A total score by treatment-interaction factors in the model.

The treatment effects of pregabalin and alprazolam on the HAM-D total score, the HAM-A somatic and psychic anxiety

subscales, and the HAM-A anxiety and tension items were evaluated by analyses of covariance, with treatment and center in the model and baseline scores as covariates ($\alpha = .05$, 2-sided).

Patients' response to pregabalin was also evaluated by analyzing the percentage of patients who were considered HAM-A and CGI-I responders. A HAM-A responder was defined as a patient with a 50% or greater decrease in HAM-A total score from baseline to end point. Logistic regression, adjusting for center, was performed to compare the percentage of HAM-A responders by treatment group in the ITT population ($\alpha = .05$, 2-sided).^{38,39} A CGI-I responder was defined as a patient who was rated as “very much improved” or “much improved” at end point. The CGI-I responder rate was analyzed in the same manner as the HAM-A responder rate.

Rebound anxiety, as distinguished from relapse of anxiety, was evaluated post hoc by the assessment of change in HAM-A total score from the week 4 visit (end of treatment) to follow-up visit 1 (1 week after the end of double-blind treatment) and to the second follow-up visit (2 weeks after the end of double-blind treatment). The HAM-A assessments during study drug discontinuation (follow-up visits 1 and 2) were added based on a protocol amendment that was approved when 80% of the ITT population had already completed study participation. Rebound anxiety, an early indicator of benzodiazepine withdrawal symptoms, was defined as a HAM-A score greater than the baseline value at the first follow-up visit with a subsequent decrease in HAM-A score by the second follow-up visit.^{40,41} The severity of benzodiazepinelike withdrawal symptoms was evaluated by an analysis of variance performed on the PWC total score obtained at follow-up weeks 1 and 2.

RESULTS

PATIENT CHARACTERISTICS AND DISPOSITION

A total of 696 patients were screened, of whom 454 were randomized and received study medication and, thus, composed the ITT safety sample (**Figure 1**). Four hundred thirty-four patients composed the efficacy sample, ie, those with postrandomization efficacy data. Baseline demographic and clinical characteristics are summarized in **Table 1**. There were no notable differences in baseline characteristics among the 5 study treatment groups. At end point, significantly more patients taking 300 mg of pregabalin completed study treatment (Figure 1) compared with those taking alprazolam ($\chi^2_1 = 7.54$, $P < .01$), placebo ($\chi^2_1 = 8.87$, $P < .01$), or 600 mg of pregabalin ($\chi^2_1 = 6.63$, $P = .02$). Attrition data are also shown in Figure 1. There were no notable differences in demographic or clinical variables between the group of patients who dropped out and those who completed the study. Only 9 patients took as-needed doses of zolpidem (placebo group, n = 2; 450-mg pregabalin group, n = 3; and alprazolam group, n = 4).

EFFICACY END POINTS

For the primary end point, change in HAM-A score, the LOCF end point analysis showed that all 3 doses of pregabalin and alprazolam had significantly greater efficacy than placebo (**Table 2**). The 3 pregabalin treatment groups, and the alprazolam group, also demonstrated significant efficacy compared with the placebo group based on an LOCF end point analysis of all sec-

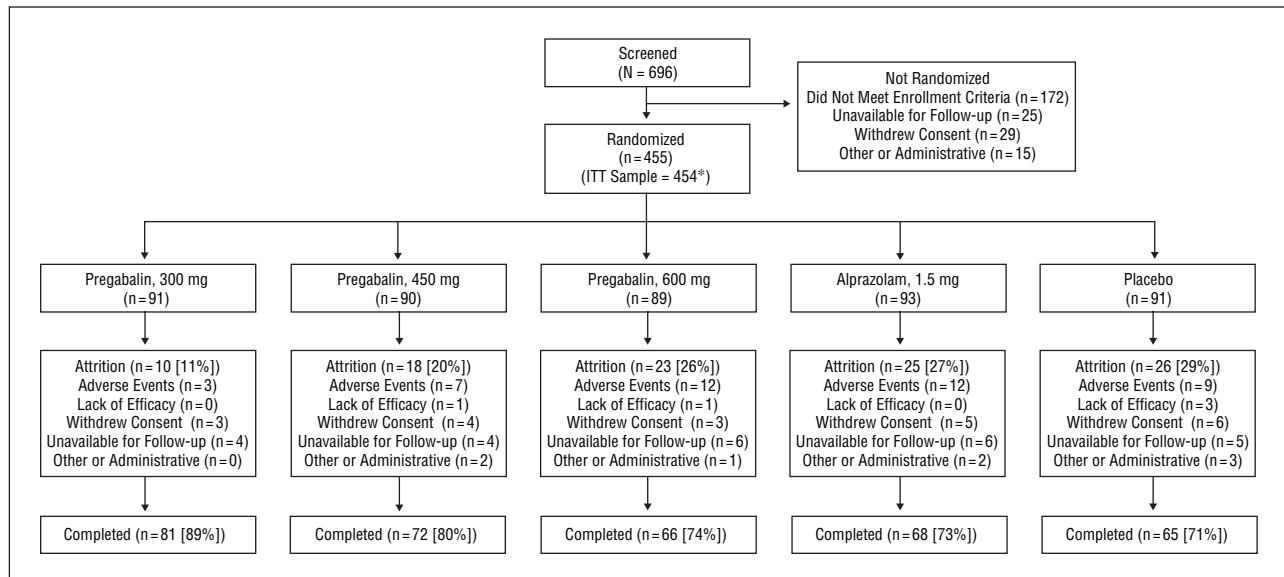


Figure 1. Patient disposition. The asterisk indicates that one patient assigned to receive pregabalin, 450 mg/d, did not receive the study medication and, thus, is not included in the intent-to-treat (ITT) sample.

Table 1. Baseline Clinical and Demographic Characteristics of the Patient Sample*

Characteristic	Pregabalin, mg/d			Alprazolam, 1.5 mg/d (n = 93)	Placebo (n = 91)
	300 (n = 91)	450 (n = 90)	600 (n = 89)		
Female sex	58 (64)	53 (59)	60 (67)	61 (66)	57 (63)
Age, y†	38 ± 10	38 ± 12	39 ± 12	40 ± 12	41 ± 12
White race	67 (74)	66 (73)	71 (80)	63 (68)	68 (75)
Education‡					
High school, attended or completed	37 (41)	42 (47)	44 (49)	50 (54)	51 (56)
College, attended or completed	38 (42)	38 (42)	37 (42)	34 (37)	33 (36)
Graduate or professional school	16 (18)	10 (11)	8 (9)	9 (10)	7 (8)
Unemployed	4 (4)	8 (9)	9 (10)	12 (13)	7 (8)
Duration of GAD, y†	12 ± 12	12 ± 13	14 ± 13	12 ± 12	13 ± 12
Age at onset, y†	26 ± 11	27 ± 11	26 ± 13	29 ± 13	29 ± 14

Abbreviation: GAD, generalized anxiety disorder.

*Data are given as number (percentage) of each group unless otherwise indicated.

†Data are given as mean ± SD.

‡Percentages may not total 100 because of rounding.

ondary outcome measures (**Table 3**), including the CGI-I, the HAM-A psychic and somatic factors, HAM-A items 1 (anxiety/worry) and 2 (tension), and the HAM-D. The only exception was that pregabalin, 450 mg, and alprazolam did not achieve significance on the HAM-A somatic anxiety factor. The mixed-models analysis of HAM-A change score demonstrated results consistent with the primary analysis (**Figure 2**). A worst-rank analysis, which included the 20 randomized patients with no efficacy data, was conducted for the 4-week LOCF data set and gave similar results for the Wilcoxon (2-sample) rank sum test and the Kruskal-Wallis tests (pregabalin, 300 and 600 mg, differed from placebo for both tests at $P < .001$; and pregabalin, 450 mg, and alprazolam at $P < .02$).

Significantly more patients treated with the 300- and 600-mg doses of pregabalin were treatment responders

compared with placebo-treated patients at LOCF end point, based on a priori HAM-A and CGI-I responder criteria (**Figure 3**). Patients treated with alprazolam also showed significantly higher end point responder rates than placebo-treated patients based on CGI-I but only at a statistical trend level ($P < .10$) in the HAM-A responder criterion. Patients taking 450 mg of pregabalin differed from those taking placebo at a statistical trend level ($P < .10$) in both outcome measures. Significantly more patients taking pregabalin, 300 mg, were CGI-I and HAM-A responders than those taking alprazolam ($P < .05$) (**Figure 3**).

All 3 assigned treatment groups of pregabalin and the alprazolam group demonstrated significantly greater efficacy than the placebo group as early as week 1 on the HAM-A total score, the HAM-A psychic factor, HAM-A items 1 (anxiety/worry) and 2 (tension), and CGI-I

Table 2. Primary Efficacy Measure: Change From Baseline to End Point in Total HAM-A Score*

Treatment Group	No. of Subjects†	Least Squares Mean	SE	Difference From Placebo	Treatment Comparisons for Active Treatment vs Placebo	
					95% Confidence Interval	P Value
Pregabalin, mg/d						
300	89	-12.25	0.77	-3.89	-6.05 to -1.73	<.001
450	87	-11.00	0.78	-2.65	-4.82 to -0.48	.02
600	85	-11.79	0.80	-3.43	-5.62 to -1.25	.002
Alprazolam, 1.5 mg/d	88	-10.91	0.78	-2.55	-4.72 to -0.39	.02
Placebo	85	-8.35	0.79	NA	NA	NA

Abbreviations: HAM-A, Hamilton Anxiety Rating Scale; NA, data not applicable.
 *The results are from an analysis of covariance (last observation carried forward).
 †Reflects number of patients with postrandomization HAM-A data.

Table 3. Efficacy Variables at Baseline, Change at Week 1, and LOCF End Point*

Efficacy Variable	Study Treatment Group†					P Value (Pairwise Comparison vs Placebo)			
	Pregabalin, mg/d			Alprazolam, 1.5 mg/d, (n = 88)	Placebo (n = 85)	Pregabalin, mg/d			Alprazolam, 1.5 mg/d
	300 (n = 89)	450 (n = 87)	600 (n = 85)			300	450	600	
HAM-A Data									
Total score									
Baseline	25.0 ± 0.4	24.6 ± 0.4	25.2 ± 0.4	24.9 ± 0.4	24.6 ± 0.4	NA	NA	NA	NA
Week 1‡	-8.9 ± 0.6	-8.5 ± 0.6	-8.9 ± 0.6	-7.2 ± 0.6	-5.2 ± 0.6	<.001	<.001	<.001	.02
LOCF end point	-12.2 ± 0.8	-11.0 ± 0.8	-11.8 ± 0.8	-10.9 ± 0.8	-8.4 ± 0.8	<.001	.02	.002	.02
Psychic factor score									
Baseline	13.8 ± 0.2	13.8 ± 0.2	13.9 ± 0.2	13.8 ± 0.2	13.7 ± 0.2	NA	NA	NA	NA
Week 1‡	-5.0 ± 0.3	-5.1 ± 0.4	-5.0 ± 0.4	-4.0 ± 0.4	-2.7 ± 0.4	<.001	<.001	<.001	.01
LOCF end point	-6.6 ± 0.4	-6.3 ± 0.4	-6.3 ± 0.5	-6.0 ± 0.4	-4.3 ± 0.5	<.001	.002	.002	.007
Somatic factor score									
Baseline	11.1 ± 0.3	10.8 ± 0.3	11.2 ± 0.3	11.1 ± 0.3	10.9 ± 0.3	NA	NA	NA	NA
Week 1‡	-3.9 ± 0.3	-3.5 ± 0.4	-3.8 ± 0.3	-3.2 ± 0.3	-2.6 ± 0.3	.006	.06	.009	.21
LOCF end point	-5.6 ± 0.4	-4.6 ± 0.4	-5.4 ± 0.4	-4.9 ± 0.4	-4.1 ± 0.4	.005	.32	.02	.15
Anxiety item score (No. 1)									
Baseline	2.9 ± 0.04	2.8 ± 0.04	2.9 ± 0.04	2.8 ± 0.04	2.9 ± 0.04	NA	NA	NA	NA
Week 1‡	-1.0 ± 0.1	-1.0 ± 0.1	-1.0 ± 0.1	-0.8 ± 0.1	-0.6 ± 0.1	<.001	<.001	<.001	.04
LOCF end point	-1.3 ± 0.1	-1.2 ± 0.1	-1.2 ± 0.1	-1.1 ± 0.1	-0.8 ± 0.1	<.001	.02	.02	.03
Tension item score (No. 2)									
Baseline	2.9 ± 0.04	2.8 ± 0.05	2.9 ± 0.05	2.8 ± 0.04	2.9 ± 0.04	NA	NA	NA	NA
Week 1‡	-1.0 ± 0.1	-1.1 ± 0.1	-1.0 ± 0.1	-0.9 ± 0.1	-0.6 ± 0.1	.001	<.001	.001	.04
LOCF end point	-1.3 ± 0.1	-1.2 ± 0.1	-1.3 ± 0.1	-1.2 ± 0.1	-0.9 ± 0.1	.007	.03	.01	.05
CGI-I Data									
Week 1‡	2.9 ± 0.09	2.9 ± 0.09	2.9 ± 0.09	3.1 ± 0.09	3.4 ± 0.09	<.001	<.001	<.001	.003
LOCF end point	2.4 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	3.1 ± 0.1	<.001	.02	.003	.004
HAM-D Data									
Total score§									
Baseline	12.9 ± 0.4	13.2 ± 0.4	13.2 ± 0.4	13.5 ± 0.4	13.1 ± 0.4	NA	NA	NA	NA
LOCF end point	-5.7 ± 0.5	-4.4 ± 0.5	-4.3 ± 0.5	-4.9 ± 0.5	-2.7 ± 0.5	<.001	.02	.03	.004

Abbreviations: CGI-I, Clinical Global Impression Improvement Scale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; LOCF, last observation carried forward; NA, data not applicable.

*Based on an analysis of covariance of change from baseline, with terms for center, baseline, and treatment.

†Data are given as mean ± SE for baseline and change scores (for on-treatment visits).

‡Efficacy is based on an observed case (available patient) analysis. Week 1 sample sizes were as follows: pregabalin, 300 mg/d, n = 86; pregabalin, 450 mg/d, n = 83; pregabalin, 600 mg/d, n = 83; alprazolam, 1.5 mg/d, n = 82; and placebo, n = 81.

§HAM-D sample sizes. For pregabalin, 300 mg/d, n = 84; pregabalin, 450 mg/d, n = 83; pregabalin, 600 mg/d, n = 80; alprazolam, 1.5 mg/d, n = 82; and placebo, n = 80.

||Sample sizes may vary on some measures by up to 2 patients because of missing values.

(Table 3). On the HAM-A total score, the 300- and 600-mg doses of pregabalin demonstrated significantly greater improvement ($P < .05$ for both doses) at week 1 when compared with alprazolam.

Current depressive disorder was a reason for exclusion from the study. Nevertheless, the mean baseline HAM-D score was 13, indicating either a mild degree of depressive symptoms in many patients or endorsement

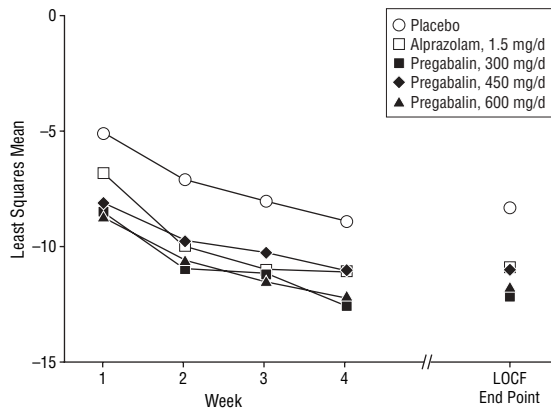


Figure 2. Repeated-measures analysis of change in Hamilton Anxiety Rating Scale (HAM-A) total score. Data are based on a repeated-measures model with an interaction term for week ($F_{3,428}=44.9, P<.001$) and treatment ($F_{4,428}=5.47, P<.001$). Baseline HAM-A scores for the groups were as follows: pregabalin, 300 mg/d, 24.9; pregabalin, 450 mg/d, 24.5; pregabalin, 600 mg/d, 25.0; alprazolam, 1.5 mg/d, 24.8; and placebo, 24.5. Efficacy for weeks 1 through 4 is based on an observed case (available patient) analysis. Respective sample sizes for weeks 1 through 4 and last-observation-carried-forward (LOCF) end point were as follows: pregabalin, 300 mg/d, n=86, 77, 81, 78, and 89; pregabalin, 450 mg/d, n=83, 78, 75, 65, and 87; pregabalin, 600 mg/d, n=83, 75, 68, 67, and 85; alprazolam, 1.5 mg/d, n=82, 77, 76, 61, and 88; and placebo, n=81, 77, 74, 66, and 85. At LOCF end point, vs placebo, $P<.001$ for pregabalin, 300 mg/d; $P=.02$ for pregabalin, 450 mg/d, and alprazolam, 1.5 mg/d; and $P=.002$ for pregabalin, 600 mg/d.

of HAM-D anxiety items. No evidence was found for pregabalin or alprazolam to cause depression. In fact, all study treatments, compared with placebo, were associated with statistically significant greater end point reduction of the HAM-D total score (Table 3).

The Endicott Work Productivity Scale mean \pm SE scores at baseline ranged from 35.7 ± 1.8 for the placebo group to 39.5 ± 1.9 for all 5 treatment groups, similar to a score of 39.4 for patients with major depressive disorder.³³ Because the scale was appropriate only for working patients, this led to a substantial decrease in sample size from 434 patients with an efficacy rating on the HAM-A to 266 patients with a rating on the Endicott Work Productivity Scale. The mean \pm SE reduction in Endicott Work Productivity Scale total score from baseline to end point was highest for pregabalin, 600 mg (12.9 ± 1.9); followed by reductions of 10.6 ± 1.6 for pregabalin, 450 mg; 9.1 ± 1.9 for pregabalin, 300 mg; 7.2 ± 1.7 for alprazolam; and 7.2 ± 1.7 for placebo. Only pregabalin, 600 mg, demonstrated significantly greater improvement in work productivity than placebo ($P<.03$), while pregabalin, 450 mg, did so at a statistical trend level ($P<.14$).

TOLERABILITY AND SAFETY

Pregabalin was generally well tolerated for each of the 3 fixed doses (Table 4). The proportion of patients during the active treatment phase who discontinued because of adverse events was 3% (n=3) for those taking pregabalin, 300 mg; 8% (n=7) for those taking pregabalin, 450 mg; 15% (n=13) for those taking pregabalin, 600 mg; 14% (n=13) for those taking alprazolam, 1.5 mg/d; and 10% (n=9) for those taking placebo ($\chi^2_4=7.31, P<.20$).

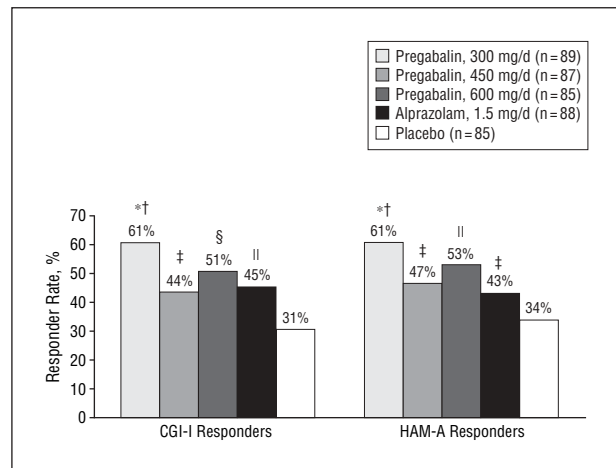


Figure 3. Last observation carried forward end point analysis of Clinical Global Impression Improvement Scale (CGI-I) and Hamilton Anxiety Rating Scale (HAM-A) responder rates at week 4. A responder in each group is defined as having the following: a CGI-I score of 2 or less (much or very much improved) ($\chi^2_3=17.1, P<.01$) and a 50% or greater reduction from baseline in the HAM-A total score ($\chi^2_3=14.0, P<.01$). For CGI-I responders in the pregabalin, 450 mg/d, group, n=88. Sample sizes reflect the number of patients with postrandomization efficacy parameter data. The asterisk indicates $P<.001$ vs placebo; dagger, $P<.05$ vs alprazolam; double dagger, $P<.10$ vs placebo; section mark, $P<.01$ vs placebo; parallel mark, $P<.05$ vs placebo; and paragraph mark, $P=.10$ vs placebo.

The most frequent adverse events (somnolence, dizziness, and dry mouth) were most often rated mild or moderate. The median duration of somnolence in the ITT population was shortest in the placebo group (8.5 days); followed by pregabalin, 300 mg (11 days); pregabalin, 600 mg (13 days); pregabalin, 450 mg (16 days); and alprazolam (17 days). The median durations of dizziness in the 3 pregabalin groups were 5, 9, and 10 days, respectively; for the alprazolam group, 9 days; and for the placebo group, 13 days.

The mean \pm SE increase in weight from baseline to the 4-week end point was 1.1 ± 0.2 kg for those taking pregabalin, 300 mg; 1.4 ± 0.2 kg for those taking pregabalin, 450 mg; 1.9 ± 0.2 kg for those taking pregabalin, 600 mg; 0.9 ± 0.3 kg for those taking alprazolam; and 0.1 ± 0.2 kg for those taking placebo ($F_{4,363}=8.13, P<.001$). All the medication groups, including alprazolam, differed significantly from the placebo group ($P=.01$ for alprazolam; $P<.002$ for 300-mg pregabalin; $P<.001$ for 450- and 600-mg pregabalin groups).

Two serious adverse events occurred during the study treatment, 1 in the placebo group and 1 in the alprazolam group; neither was judged to be treatment related. No adverse events occurred resulting from ECG findings, and treatment-emergent ECG changes were not clinically meaningful and occurred at similar low frequencies across all treatment groups. No clinically significant changes in vital signs (blood pressure, heart rate, or respiratory rate) or laboratory values were noted for any treatment group during this study.

The PWC was used to assess potential benzodiazepineline withdrawal symptoms occurring after either abrupt discontinuation of pregabalin, 300 mg, or a taper (4-7 days) of pregabalin, 450 mg, pregabalin, 600 mg, or alprazolam. At follow-up visit 1, the mean \pm SE PWC

Table 4. Rates of Most Common Adverse Events During Treatment With Pregabalin, Alprazolam, and Placebo*

Adverse Event	Pregabalin, mg/d			Alprazolam, 1.5 mg/d (n = 93)	Placebo (n = 91)
	300 (n = 91)	450 (n = 90)	600 (n = 89)		
Somnolence	35	36	37	42	15
Dizziness	37	34	35	15	9
Dry mouth	18	16	21	4	8
Incoordination	4	11	15	3	0
Infection	10	14	15	8	9
Nausea	10	13	10	9	10
Blurred vision	8	10	8	4	3
Asthenia	7	10	7	13	2
Constipation	2	12	3	3	5

*Data are given as percentage of each group. These are all-causality events, with an incidence of 10% or greater; an adverse event was not included unless greater than placebo in at least one active treatment group.

total score was similar across all treatment groups: placebo (14.3 ± 1.16); pregabalin, 300 mg (15.2 ± 1.08); pregabalin, 450 mg (15.7 ± 1.20); pregabalin, 600 mg (15.1 ± 1.14); and alprazolam (15.3 ± 1.15). At follow-up visit 2, the mean \pm SE PWC total score was similar across all treatment groups, except for pregabalin, 600 mg; placebo (15.8 ± 1.70); pregabalin, 300 mg (14.8 ± 1.14); pregabalin, 450 mg (15.2 ± 1.17); pregabalin, 600 mg (19.4 ± 1.24) ($P < .04$ vs placebo); and alprazolam (15.7 ± 1.19).

As mentioned in the "Statistical Analysis" subsection, only 89 patients had the HAM-A score assessed post-taper: 52 were in the 3 pregabalin groups, 21 were in the alprazolam group, and 16 were in the placebo group. Of those 89 patients, only 3 (1 each in the placebo, pregabalin, 300 mg, and pregabalin, 450 mg, groups) met the criteria for rebound anxiety in a post hoc analysis consisting of a HAM-A total score greater than baseline at the first follow-up visit, with a decrease in the HAM-A score at the second follow-up visit.

COMMENT

The results of this fixed-dose 4-week study demonstrate that pregabalin is effective in the treatment of GAD. Pregabalin treatment was associated with significant end point improvement on the HAM-A that was comparable to alprazolam at all 3 doses.

The anxiolytic efficacy of pregabalin was notable for its early onset, comparable to alprazolam, with statistically significant improvement occurring by week 1 in the HAM-A total score and the HAM-A psychic and somatic anxiety factor scores. The rapid onset of efficacy, and the significant improvement on HAM-A psychic and somatic symptom factor scores, distinguishes pregabalin from alprazolam—which was not efficacious for reducing somatic symptoms at week 1. To our knowledge, no anxiolytic agent has demonstrated equivalent or earlier onset of anxiolytic efficacy than a high-potency benzodiazepine in a double-blind, placebo-controlled, comparator trial.^{32,42-44} It is possible, though, that more aggressive titration during the first week, and a daily dose higher than 1.5 mg after week 1, might have further in-

creased response to alprazolam.⁴⁵ Yet, a high attrition due to adverse events (14%) suggests that a higher daily dose of alprazolam might not have been clinically acceptable. In fact, the 1.5-mg/d dosage of alprazolam used in the present study is the average dosage used in the primary care setting.⁴⁶ In all 3 pregabalin treatment groups and in the alprazolam group, there was no evidence of worsening of depressive symptoms evaluated by the total HAM-D score at end point.

Pregabalin's lack of protein binding or activity at any P450 enzymes suggests a favorable drug-drug interaction profile. Its rapid absorption (time of occurrence for maximum drug concentration, 1 hour), rapid onset of anxiolytic effect, and equivalent efficacy across the full range of psychic and somatic symptoms of anxiety suggest a favorable clinical profile that is distinct from selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor therapies for GAD.

Overall, pregabalin was well tolerated across a dosing range of 300 to 600 mg/d. Discontinuations during pregabalin treatment due to adverse events increased with increasing pregabalin dose, and the 300-mg dose was fully efficacious, with no apparent increase in efficacy with increasing dose. Most adverse events were mild to moderate, with onset during titration to the assigned fixed dose. Adverse events generally showed rapid tolerance, typically within 2 weeks. The pregabalin groups experienced a dose-related weight gain, with weight gain in the 300-mg pregabalin group being similar to that of the alprazolam group (1.1 and 0.9 kg, respectively). The increase in the PWC score beyond that of those taking placebo during the second follow-up week for the 600-mg pregabalin group did not seem to be clinically significant and was much lower than that previously reported for patients experiencing benzodiazepine withdrawal.³⁴ No rebound anxiety was noted during discontinuation. This profile is in contrast to the occurrence of discontinuation symptoms and rebound anxiety when therapeutic doses of benzodiazepines are abruptly discontinued after 4 weeks of therapy.^{40,41} Pregabalin, 300 mg, demonstrated efficacy comparable to or better than pregabalin, 450 or 600 mg, and alprazolam, while having the lowest attrition (completion rate, 89%). Thus,

pregabalin, 300 mg/d, seems to be the preferred choice for most patients.

The present study has several limitations. First, the duration of study treatment was short. The investigators believed that 4 weeks would be adequate to test the anxiolytic effects of pregabalin while also serving the ethical need to minimize the duration of treatment exposure to placebo. While 4 weeks was sufficient for pregabalin to demonstrate robust and significant efficacy vs placebo, inspection of the week 3 to 4 HAM-A slopes indicates that improvement had not yet reached an asymptote. Studies of longer duration need to be developed to provide adequate assessment of long-term clinical efficacy and safety, and to assess whether pregabalin causes discontinuation effects with prolonged use. Second, common to most GAD clinical trials, patients with current depression or other anxiety disorders were excluded. We did include, however, all lifetime anxiety and depressive comorbid disorders and all subthreshold anxiety and depressive disorders. Third, from a clinical standpoint, the fixed-dose study design was a limitation. Fixed-dose studies seem to underestimate the efficacy of a compound,⁴⁷ while resulting in higher levels of adverse events, because titration is forced and dose adjustment is not permitted. Finally, the sample sizes per treatment group (89-93) were 30% to 50% smaller than in many recent GAD treatment studies (this was not a limitation). In conclusion, the results of this study confirm the anxiolytic efficacy of pregabalin suggested by 2 previous dose-finding studies,^{14,15} assessed in the daily dose range of 300 to 600 mg, with the lowest daily dosage of 300 mg being the most efficacious and best-tolerated one.

Submitted for Publication: April 5, 2004; final revision received February 15, 2005; accepted March 24, 2005.

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Financial Disclosure: Dr Rickels has received honoraria and served as a consultant or on advisory boards to Biovail, Cephalon, Inc, DOV Pharmaceuticals, Eli Lilly & Co, Hoffmann-La Roche, MediciNova, Merck & Co, Inc, Novartis Pharmaceuticals, Pfizer Inc, Pharmacia, Pherin Pharmaceuticals, PreDix Pharmaceuticals, Sanofi-Synthelabo, and Wyeth; and has received research grants (issued to the University of Pennsylvania) from Merck & Co, Inc, Somerset Pharmaceuticals, Inc, AstraZeneca, Bristol-Myers Squibb, National Institute of Mental Health, Novartis Pharmaceuticals, Johnson & Johnson, Wyeth, Kramer-Fabre, Cephalon, Inc, GlaxoSmithKline, Pfizer Inc, Biovail, and Sanofi-Synthelabo. Dr Pollack has been on the advisory boards of Bristol-Myers Squibb, Cephalon, Inc, Forest Laboratories, GlaxoSmithKline, Janssen, Eli Lilly & Co, Novartis Pharmaceuticals, Otsuka Pharmaceuticals, Pfizer Inc, PreDix, Roche Laboratories, Sepracor, UCB Pharma, and Wyeth; has received research grants from Cephalon, Inc, Forest Laboratories, GlaxoSmithKline, Janssen, Eli Lilly & Co, Pfizer Inc, UCB Pharma, and Wyeth; and has been a speaker for Forest Laboratories, GlaxoSmithKline, Janssen, Eli Lilly & Co, Pfizer Inc, Solvay Pharmaceuticals, Inc, and Wyeth. Dr

Zimbroff has received grant or research contracts and support from Merck & Co, Inc, Pfizer Global Research & Development, Bristol-Myers Squibb, Forest Laboratories, DOV Pharmaceuticals, Organon, Solvay Pharmaceuticals Inc, GlaxoSmithKline, Sanofi-Synthelabo, Cephalon, Inc, Novartis Pharmaceuticals, and Wyeth; has been a paid consultant to Bristol-Myers Squibb; and has been a member of the speakers' bureau of Bristol-Myers Squibb, Otsuka Pharmaceuticals, and Pfizer Inc. Dr Lydiard served as a consultant for AstraZeneca, Eli Lilly & Co, Novartis Pharmaceuticals, Pfizer Inc, Roche Pharmaceuticals, Sanofi-Synthelabo, Solvay Pharmaceuticals, Inc, and Wyeth; has received research support from Cephalon, Inc, Forest Laboratories, GlaxoSmithKline, Jazz Pharmaceuticals, Eli Lilly & Co, MediciNova, UCB Pharma, and Wyeth; and has been a speaker for Forest Laboratories, GlaxoSmithKline, Eli Lilly & Co, Pfizer Inc, and Wyeth. **Funding/Support:** This study was supported by Pfizer Inc, New York, NY.

Previous Presentation: This study was presented in part at the 155th annual meeting of the American Psychiatric Association, May 21, 2002, Philadelphia, Pa; and the 40th annual meeting of the American College of Neuropsychopharmacology, December 12, 2001, Waikoloa, Hawaii.

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