

# Efficacy and Tolerability of Paroxetine for the Long-Term Treatment of Generalized Anxiety Disorder

Fabrizio Stocchi, M.D., Ph.D.; Giampetro Nordera, M.D., Ph.D.;  
Riitta H. Jokinen, M.D.; Ulla M. Lepola, M.D., Ph.D.; Karen Hewett, Ph.D.;  
Heather Bryson, Ph.D.; and Malini K. Iyengar, Ph.D.,  
for the Paroxetine Generalized Anxiety Disorder Study Team

**Background:** Paroxetine has demonstrated efficacy in depression and anxiety disorders, including generalized anxiety disorder (GAD). This 32-week study evaluated the maintained efficacy and safety of paroxetine in GAD by assessing the potential for relapse after discontinuation of medication.

**Method:** Adults (N = 652) with DSM-IV GAD and a Clinical Global Impressions-Severity of Illness (CGI-S) score  $\geq 4$  received paroxetine (20–50 mg/day) for 8 weeks. Patients whose CGI-S score had decreased by at least 2 points to  $\leq 3$  at week 8 were randomly assigned to double-blind treatment with paroxetine (N = 278) or placebo (N = 288) for a further 24 weeks. The primary efficacy parameter was the proportion of patients relapsing (an increase in CGI-S score of at least 2 points to a score  $\geq 4$  or withdrawal resulting from lack of efficacy) during double-blind treatment.

**Results:** Significantly fewer paroxetine than placebo patients relapsed during the 24-week double-blind phase (10.9% vs. 39.9%;  $p < .001$ ). Placebo patients were almost 5 times more likely to relapse than paroxetine patients (estimated hazard ratio = 0.213 [95% CI = 0.1 to 0.3];  $p < .001$ ). Statistical significance in favor of paroxetine was demonstrated for all secondary efficacy parameters, including functional status. Twice as many paroxetine patients as placebo patients (73%) achieved remission. Paroxetine was well tolerated, with no unexpected adverse events reported.

**Conclusion:** Paroxetine was found to be effective and well tolerated for both the short- and long-term treatment of DSM-IV GAD. Continued treatment with paroxetine significantly reduced the potential for relapse of GAD symptoms.

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Received Dec. 13, 2001; accepted Aug. 2, 2002. From the Institute of Neurology, Istituto Ricerca Carattere Scientifico Neuromed, Pozzilli, Italy (Dr. Stocchi); Casa di Cura Villa Margherita, Vicenza, Italy (Dr. Nordera); Psychiatric Research Clinic of Turku, Turku, Finland (Dr. Jokinen); Department of Psychiatry, Oulu University, Psychiatric Research Clinic of Kuopio, Kuopio, Finland (Dr. Lepola); Glaxo-SmithKline Pharmaceuticals, New Frontiers Science Park, Harlow, United Kingdom (Drs. Hewett and Bryson); and GlaxoSmithKline Pharmaceuticals, Upper Providence, Pa. (Dr. Iyengar).

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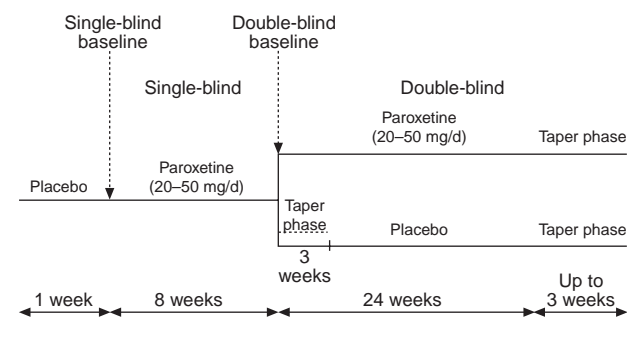
Corresponding author and reprints: Fabrizio Stocchi, M.D., Istituto Ricerca Carattere Scientifico Neuromed, Via Atinense 18, 86077 Pozzilli, Isernia, Italy (e-mail: fabstocc@tin.it).

Generalized anxiety disorder (GAD) is a disabling and chronic disorder.<sup>1–3</sup> It is characterized by persistent, unspecific anxiety and worry of a minimum of 6 months' duration.<sup>4</sup> Patients also suffer from somatic anxiety features such as tension, restlessness, fatigue, difficulty concentrating, irritability, and sleep disturbance.<sup>5</sup> Epidemiologic studies have shown that the lifetime prevalence of GAD is around 5% to 6%,<sup>3</sup> with 12-month prevalence estimates in the range of 1.5% to 3%, depending on the DSM criteria used.<sup>2–4</sup>

Treatment of anxiety disorders has previously relied on drugs such as the benzodiazepines or buspirone. Benzodiazepines, while effective anxiolytics, are limited in their use by their association with tolerance and patient dependence,<sup>6,7</sup> especially with long-term use, as is often required with GAD. Buspirone exhibits similar efficacy in GAD to that of the benzodiazepines,<sup>8,9</sup> but without the risk of addiction.

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have shown utility in the treatment of many anxiety disorders, including panic disorder, social anxiety disorder/phobia, and obsessive-compulsive disorder (OCD),<sup>10–12</sup> and a number of agents in these classes have been investigated in GAD. There is considerable evidence to support the efficacy of TCAs in the treatment of GAD<sup>13,14</sup>; however, the SSRIs are increasingly considered first-line treatment for many anxiety disorders. Controlled clinical trials have demonstrated that the SSRI paroxetine and the serotonin and norepi-

Figure 1. Study Design



nephre reuptake inhibitor venlafaxine are effective in treating patients who meet DSM-IV criteria for GAD.<sup>15–20</sup> Short-term studies have shown paroxetine (20–50 mg/day) to be effective and well tolerated for the treatment of GAD,<sup>17,20</sup> improving both core symptoms of anxiety (worry and tension) and functional disability.

As GAD is a chronic disorder, studies assessing the efficacy and safety of paroxetine in the extended treatment of this condition are essential. We report here the results of a large, multicenter, double-blind, 32-week study that evaluated the maintained efficacy and safety of paroxetine in the treatment of GAD by assessing the potential for relapse after discontinuation of medication.

## METHOD

### Study Design

This 32-week multicenter study comprised an 8-week single-blind paroxetine treatment phase (20–50 mg/day flexible dose) followed by a 24-week double-blind treatment phase during which patients were randomly assigned either to remain on treatment with paroxetine or to receive placebo (Figure 1).

Following an initial screening visit, patients fulfilling the study inclusion criteria entered a 1-week single-blind placebo run-in phase to evaluate their suitability for entry into the study and to eliminate early placebo responders. Patients who scored 4 or more (moderately ill to extremely ill) on the Clinical Global Impressions-Severity of Illness (CGI-S)<sup>21</sup> and who met the baseline inclusion criteria entered the 8-week single-blind paroxetine treatment phase. Paroxetine treatment was initiated at 20 mg once daily for 2 weeks with flexible daily dosing thereafter in the range of 20 to 50 mg/day.

Following the single-blind treatment phase, patients whose CGI-S score had decreased by at least 2 points to a score of 3 or less (no illness or only mild illness) were classified as responders and were randomly assigned to either remain on paroxetine treatment (at the dose level at which they completed the single-blind treatment phase) or

receive placebo for the 24-week double-blind treatment phase. A computer-generated randomization list was used to randomize the patients in a 1:1 ratio.

Study visits were scheduled for baseline; at weeks 1, 2, 3, 4, 6, and 8 (single-blind treatment phase); and at weeks 12, 16, 20, 24, 28, and 32 (double-blind treatment phase).

Before the study began, the protocol was approved by the appropriate regulatory authority and an independent ethics committee. The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki (1999), and all patients provided written informed consent prior to the start of the study.

### Study Population

Outpatients from 47 centers in Italy, Finland, Norway, Sweden, Denmark, Hungary, Greece, and the Czech Republic were recruited. Eligible patients had to be 18 years or older and have a primary diagnosis of GAD according to DSM-IV criteria (300.02). To establish the diagnosis, each patient was given a psychiatric interview that included the Mini-International Neuropsychiatric Interview for DSM-IV.<sup>22</sup> In addition, patients had to have the following minimum scores at screening and at baseline: (1) Hamilton Rating Scale for Anxiety (HAM-A)<sup>23</sup> total score of  $\geq 20$ , (2) HAM-A score  $\geq 2$  on items 1 (anxious mood) and 2 (tension), and (3) Montgomery-Asberg Depression Rating Scale (MADRS)<sup>24</sup> score of  $< 18$ . In addition, patients aged over 65 years had to be able to tolerate a paroxetine starting dose of at least 20 mg/day and be without renal or hepatic impairment.

Patients who satisfied the selection criteria but whose CGI-S score decreased by 2 points between screening and baseline or was 3 or less (no illness or only mild illness) at baseline were not allowed to continue in the study. Patients who had a reduction greater than 20% in HAM-A total score from screening to the baseline visit were also precluded from entering the study.

Patients were excluded from the study if they had any of the following conditions currently or diagnosed during the 6 months prior to screening: major depressive episode (DSM-IV 296.2x, 296.3x), panic disorder (DSM-IV 300.01, 300.21), social phobia (DSM-IV 300.23), agoraphobia (DSM-IV 300.22), posttraumatic stress disorder (DSM-IV 309.81), OCD (DSM-IV 300.3), and eating disorders (DSM-IV 307.1, 307.51). Patients were excluded if they met DSM-IV criteria for substance abuse (alcohol or drugs) or substance dependence within the previous 6 months. Patients were excluded if they were currently diagnosed with dysthymia (DSM-IV 300.4) or diagnosed with dysthymia within the previous 6 months as a predominant psychiatric condition relative to GAD. Women who were pregnant, lactating, or of childbearing potential and not practicing clinically acceptable contraception were also excluded.

## Study Treatments

In the single-blind treatment phase, all patients received paroxetine, 20 mg, once daily for at least 2 weeks. Thereafter, the dose could be increased no more frequently than once a week by 10 mg/day to a maximum of 50 mg once daily at the investigator's discretion according to clinical response and tolerability.

Patients randomly assigned to receive paroxetine during the double-blind treatment phase continued to receive paroxetine for 24 weeks at the same dose they were receiving at the end of the single-blind treatment phase (upward titration of the dose to maintain efficacy during the double-blind treatment phase was not permitted). Patients randomly assigned to receive placebo in the double-blind treatment phase underwent a 3-week taper phase. All patients randomly assigned to placebo received the first dose of placebo medication at the start of week 4 of the double-blind phase.

A dosage reduction to the next lowest level (10 mg less) consequent to an adverse event was permitted at the investigator's discretion from week 2 of the single-blind treatment phase onward. On resolution of the adverse event, the patient was allowed to return to the original dose. Patients requiring a dosage reduction prior to the week 2 single-blind treatment phase visit were withdrawn from the study. Patients requiring more than 1 dosage reduction throughout the study were also withdrawn.

Patients who discontinued paroxetine treatment (1) on completion of the single-blind treatment phase, (2) at the end of the study, or (3) on early withdrawal from the study after more than 2 weeks of study medication entered a taper phase lasting up to 3 weeks. Patients commenced the taper phase at 1 level below their final paroxetine dose level, and paroxetine doses of > 20 mg/day were then reduced by 10-mg/day increments at weekly intervals to 20 mg/day.

## Efficacy Parameters and Assessments

The primary efficacy parameter was the proportion of patients relapsing during the double-blind treatment phase. Relapse was defined as an increase of at least 2 points on the CGI-S (relative to the patient's score at the end of the single-blind treatment phase) to a score of 4 or more, or withdrawal resulting from lack of efficacy.

Secondary efficacy parameters included time to relapse during the double-blind treatment phase and mean change from baseline in HAM-A scores (total, items 1 and 2, and somatic and psychic subscale scores), Sheehan Disability Scale (SDS)<sup>25</sup> scores (total and family, social, and work item scores), and MADRS score.

The CGI-S, CGI-Global Improvement, and HAM-A assessments were made at baseline; weeks 1, 2, 3, 4, 6, and 8 (single-blind treatment phase); and weeks 12, 16, 20, 24, 28, and 32 (double-blind treatment phase), or at the time of early withdrawal from the study. SDS and

MADRS assessments were performed at baseline, week 8 (single-blind phase), and weeks 20 and 32 (double-blind phase), or at the time of early withdrawal from the study.

## Safety Assessments

Adverse events were monitored throughout the study by asking, at every study visit, a non-leading question such as, "Have you felt different in any way since your last visit?" Vital signs and laboratory monitoring were also performed at baseline, at week 8 (single-blind treatment phase), and at week 32 (double-blind treatment phase), or at the time of early withdrawal from the study.

## Data Analysis

It was estimated that approximately 50% of the placebo patients would relapse during the double-blind treatment phase. A total of 220 randomized patients were required to provide 90% power (with 5% level of significance) to detect a difference of 25% between the paroxetine and placebo groups in the proportion of patients who would relapse during the double-blind treatment phase. Assuming a 10% dropout rate during the screening phase and 40% of patients continuing into the double-blind treatment phase, 612 patients were required for screening.

For the double-blind treatment phase, the proportions of patients relapsing and responding were analyzed using logistic analysis with treatment, investigational region, and treatment-by-region interaction effects. In the analyses, "region" refers to centers in northern, southern, and eastern Europe, and these were defined before the analysis was performed. Time to relapse was measured from the start of the double-blind treatment phase and was analyzed using a Cox proportional hazards model with treatment and investigational region effects. Analyses of variance with treatment, investigational region, and treatment-by-region interaction effects were used to assess mean change from baseline in efficacy variables. Interactions were tested at a significance level of  $p < .1$ , and main effects were tested at a significance level of  $p < .05$ .

The primary analysis population as presented in this article was based on the intent-to-treat (ITT) population (all patients who received treatment and had at least 1 efficacy assessment) and the last-observation-carried-forward (LOCF) dataset. Observed case (OC) data were also analyzed. Baseline values used in the computation of change from baseline variables refer to the week 8 (or last available) assessment of the patient in the single-blind treatment phase.

For the primary efficacy variable only, an additional analysis was conducted based on the per-protocol population (patients not identified as protocol violators and who had at least 1 on-therapy CGI assessment).

A post hoc analysis was conducted to estimate the proportion of patients who achieved remission during the single-blind and double-blind treatment phases. The pro-

**Table 1. Demographic Data for the 8-Week Single-Blind and 24-Week Double-Blind Phases (intent-to-treat population)**

Variable	Single-Blind Phase (paroxetine) (N = 652)	Double-Blind Phase	
		Paroxetine (N = 274)	Placebo (N = 287)
Sex, N (%)			
Female	416 (63.8)	172 (62.8)	186 (64.8)
Male	236 (36.2)	102 (37.2)	101 (35.2)
Race, N (%)			
White	651 (99.8)	273 (99.6)	287 (100.0)
Black	1 (0.2)	1 (0.4)	0 (0.0)
Age, y			
Mean (SD)	43.2 (13.1)	43.0 (12.7)	43.7 (13.1)
Range	18.0–83.0	20.0–79.0	18.0–78.0
Weight, kg			
Mean (SD)	69.7 (13.1)	69.4 (14.0)	70.1 (12.4)
Range	40.0–130.0	40.0–130.0	44.7–103.7
Age at onset of GAD, mean (SD), y	37.2 (14.3)	37.7 (13.6)	38.2 (14.2)
Duration of GAD, mean (SD), y	6.5 (9.2)	5.7 (8.6)	6.0 (8.3)
Previously used medication, N (%)			
SSRI	17 (2.6)	8 (2.9)	5 (1.7)
Benzodiazepine	108 (16.6)	47 (17.2)	47 (16.4)
Tricyclic antidepressant	12 (1.8)	3 (1.1)	6 (2.1)

Abbreviations: GAD = generalized anxiety disorder, SSRI = selective serotonin reuptake inhibitor.

portion of patients who achieved remission was analyzed by logistic analysis model with treatment and region effects. Remission is an important component of the response status and represents a state in which the patient is virtually symptom-free. For this analysis, remission was defined according to the criteria described by Ballenger<sup>26</sup> (HAM-A total score  $\leq 7$ ). The results of this analysis were not adjusted for HAM-A score.

## RESULTS

### Demographic Characteristics

A total of 652 patients entered the single-blind paroxetine treatment phase, and 566 entered the double-blind treatment phase (278 randomly assigned to paroxetine and 288, to placebo). Although 568 patients completed the single-blind phase, only 566 were randomly assigned to treatment, as 1 patient withdrew consent after completion of the single-blind phase and another was lost to follow-up. The intent-to-treat safety population consisted of 274 paroxetine-treated patients and 287 placebo-treated patients; 4 patients in the paroxetine group and 1 in the placebo group were excluded from this population because they had no safety assessment data for the double-blind phase. The intent-to-treat efficacy population consisted of 274 paroxetine-treated patients and 286 placebo-treated patients; 4 patients in the paroxetine group and 2 in the placebo group were excluded because they had no CGI assessment data during the double-blind phase.

**Table 2. Patients Who Completed the Study and Who Were Withdrawn During the 8-Week Single-Blind and 24-Week Double-Blind Treatment Phases, N (%)**

Group	Single-Blind Phase (paroxetine) (N = 652)	Double-Blind Phase	
		Paroxetine (N = 274)	Placebo (N = 287)
Completed study	568 (87.1)	216 (78.8)	147 (51.2)
Withdrawn from study			
Reason for withdrawal			
Adverse event	28 (4.3)	7 (2.6)	8 (2.8)
Lack of efficacy	20 (3.1)	26 (9.5)	101 (35.2)
Deviation from protocol	8 (1.2)	5 (1.8)	9 (3.1)
Lost to follow-up	12 (1.8)	12 (4.4)	8 (2.8)
Other reason	16 (2.5)	8 (2.9)	14 (4.9)
Total withdrawn	84 (12.9)	58 (21.2)	140 (48.8)

The 2 double-blind treatment groups were well matched for key demographic characteristics and illness history at baseline (Table 1). There were no marked differences at the double-blind baseline between the 2 treatment groups on any of the CGI-S, HAM-A, SDS, or MADRS efficacy parameters. With regard to psychiatric history, the most common comorbidity in both groups was major depressive episode: 6.9% in the paroxetine group and 4.9% in the placebo group. Dysthymia was experienced by just 4 patients (1.5%) in the paroxetine group; no patients in the placebo group had a history of this condition.

Of the 566 patients entering the double-blind treatment phase, 363 completed the study (216 paroxetine patients and 147 placebo patients) (Table 2). The most common reason for early withdrawal from the study during the double-blind phase in both treatment groups was lack of efficacy: 26 paroxetine-treated patients (9.5%) compared with 101 placebo patients (35.2%).

The mean dose of paroxetine at endpoint was 28.1 mg/day for the single-blind treatment phase and 28.4 mg/day for the double-blind treatment phase.

### Relapse

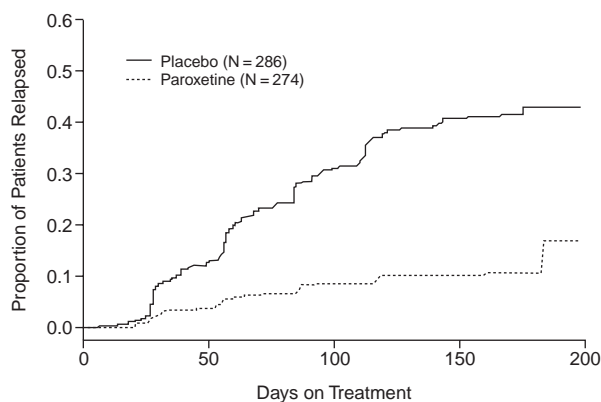
Paroxetine-treated patients were significantly less likely to relapse than placebo patients; only 10.9% of paroxetine-treated patients relapsed during the double-blind treatment phase compared with 39.9% of placebo patients (treatment difference:  $-28.9\%$  [95% CI =  $-35.7\%$  to  $-22.1\%$ ];  $p < .001$ ). The proportion of patients relapsing during the double-blind treatment phase was not influenced by duration of GAD, gender, or baseline HAM-A score.

The analysis based on the per-protocol population confirmed the results from the ITT population: 10.7% of patients in the paroxetine group relapsed during the double-blind treatment phase compared with 41.2% in the placebo group (treatment difference:  $-30.5\%$  [95% CI =  $-38.0\%$  to  $-23.1\%$ ];  $p < .001$ ).

Patients switched to placebo after 8 weeks of paroxetine treatment in the single-blind phase were 4.7 times



**Figure 2. Time to Relapse During Double-Blind Treatment Phase (Kaplan-Meier curve)**



more likely to relapse than those who continued to receive paroxetine (estimated hazard ratio 0.213 [95% CI = 0.1 to 0.3];  $p < .001$ ) (Figure 2). The process of relapse in both treatment groups was gradual over the course of the study.

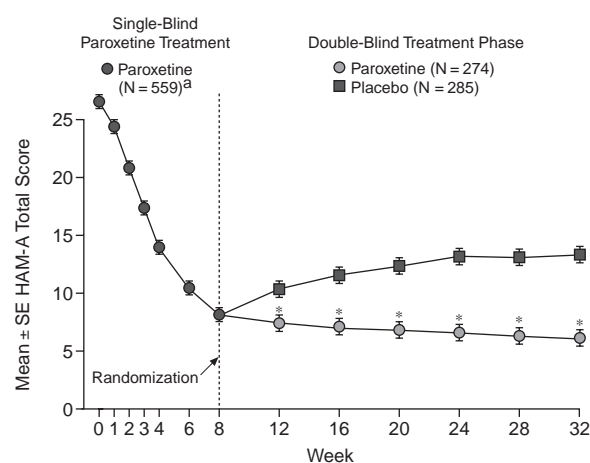
The proportions of patients relapsing by region were as follows: east Europe: paroxetine, 4/38 (10.53%); placebo, 9/43 (20.93%); north Europe: paroxetine, 18/96 (18.75%); placebo, 49/100 (49.00%); south Europe: paroxetine, 8/140 (5.71%); placebo, 56/143 (39.16%). Covariate analysis revealed a statistically significant ( $p = .0717$ ) quantitative treatment-by-region interaction for the proportion of patients relapsing during the double-blind treatment phase: larger treatment differences were observed in the northern and southern European regions compared with the eastern European region. This finding implies that differences among the regions were due to a variable magnitude only. The significant quantitative treatment-by-region interaction merely summarizes the differences in the rates of relapse in each region. One notes, however, that paroxetine is consistently associated with fewer relapses (regardless of region). A treatment benefit for paroxetine was observed in all regions, but was significantly different among the regions.

### Continued Improvement in Associated Symptomatology

All patients improved during the single-blind treatment phase. During the double-blind treatment phase, paroxetine-treated patients continued to improve, whereas those switched to placebo deteriorated.

**HAM-A total score.** The mean HAM-A total score was markedly decreased at the end of the 8-week single-blind phase, indicating that patients had moderate-to-severe symptoms of GAD at study entry that were reduced to mild symptoms after 8 weeks of paroxetine treatment (Figure 3).

**Figure 3. Mean HAM-A Total Scores During the Single-Blind and Double-Blind Treatment Phases**



<sup>a</sup>Five hundred fifty-nine patients in the single-blind treatment phase continued to the double-blind treatment phase. One patient in the intent-to-treat efficacy population had no postrandomization HAM-A assessment and is not included in this analysis.

\* $p < .001$ .

Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, SE = standard error of mean.

During the double-blind treatment phase, patients who remained on paroxetine treatment continued to improve, as shown by a further decrease in mean HAM-A total score (Figure 3). However, patients switched to placebo deteriorated—the mean HAM-A total score for placebo patients increased by 4.8. The treatment difference at week 32 ( $-6.7$ ) was highly statistically significant ( $p < .001$ ) (Table 3).

The LOCF dataset in the relevant phase (single-blind or double-blind) takes into account the scores from patients who withdrew from the study in that phase for any reason by forwarding data from a previous visit. Data were not carried forward from the single-blind phase to the double-blind phase. Conversely, the OC dataset at a given visit contains only those scores recorded at that visit. The mean change in HAM-A total score at week 32 in the OC dataset was  $-3.3$  for the paroxetine group and  $0.2$  for the placebo group (treatment difference:  $-3.5$  [95% CI =  $-4.7$  to  $-2.2$ ];  $p < .001$ ). Therefore, even those placebo patients doing sufficiently well to remain in the double-blind treatment phase did not improve after stopping paroxetine, whereas those patients who continued on paroxetine treatment showed further improvement and continued to benefit from maintained treatment.

**HAM-A items 1 (anxious mood) and 2 (tension) scores.** At the single-blind baseline, the HAM-A item 1 mean score was 2.7 (SD 0.6), and the item 2 mean score was 2.7 (SD 0.6); following 8 weeks of paroxetine treatment, the scores had decreased to 1.0 (SD 0.8) and 1.0 (SD 0.9), respectively. During the double-blind treatment

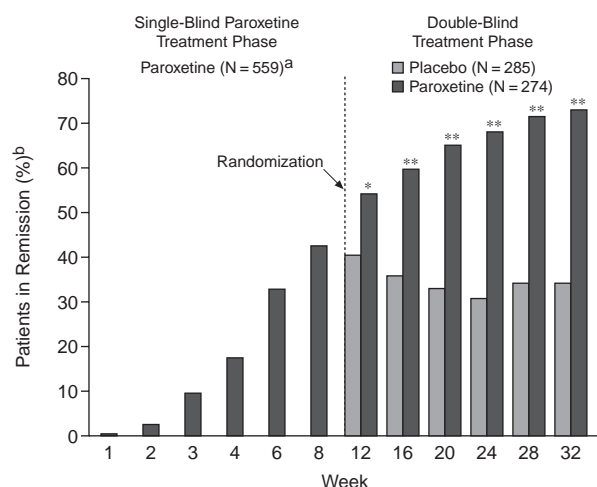
Table 3. Mean Change in HAM-A Score From Double-Blind Treatment Phase Baseline at Week 32 (LOCF)

HAM-A Score	Placebo (N = 285) <sup>a</sup>		Paroxetine (N = 274)		Placebo vs. Paroxetine		
	Mean	SE	Mean	SE	Difference	95% CI <sup>b</sup>	p Value <sup>b</sup>
Total	4.8	0.5	-1.9	0.6	-6.7	-8.2 to -5.1	< .001
Item 1	0.7	0.1	-0.1	0.1	-0.8	-0.9 to -0.6	< .001
Item 2	0.6	0.1	-0.1	0.1	-0.7	-0.9 to -0.5	< .001
Somatic subscale	1.7	0.3	-1.2	0.3	-2.9	-3.6 to -2.1	< .001
Psychic subscale	3.1	0.3	-0.7	0.3	-3.8	-4.7 to -2.9	< .001

<sup>a</sup>One patient in the intent-to-treat efficacy population had no postrandomization HAM-A assessment and is excluded from this analysis.

<sup>b</sup>p Values and CIs reported for difference in mean change from baseline using analysis of variance with treatment, region, and treatment-by-region interaction effects. All p values shown are significant (< .05).

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

Figure 4. Proportion of Patients Experiencing Remission (HAM-A score  $\leq 7$ ) From Symptoms of GAD

<sup>a</sup>Five hundred fifty-nine patients in the single-blind treatment phase continued to the double-blind treatment phase. One patient in the intent-to-treat efficacy population had no postrandomization HAM-A assessment and is not included in this analysis. Of the intent-to-treat population of 650 patients in the single-blind treatment phase, 276 (42.5%) achieved remission by week 8.

<sup>b</sup>Not adjusted for baseline HAM-A score.

\*p < .01.

\*\*p < .001.

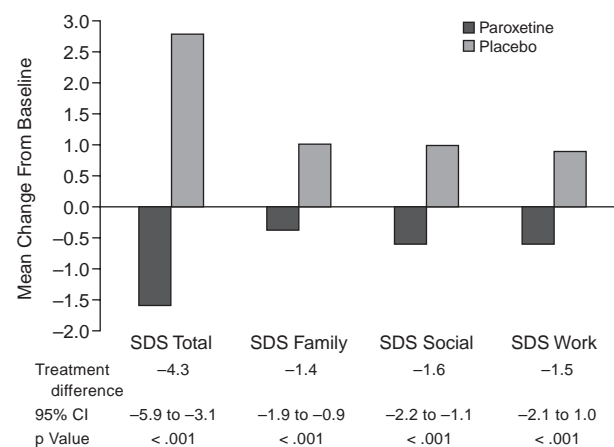
Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety.

phase, the HAM-A items 1 and 2 scores continued to improve in the paroxetine-treated patients but deteriorated in the placebo patients (Table 3).

**HAM-A somatic and psychic subscale scores.** The mean HAM-A somatic subscale score decreased from 12.4 (SD 3.6) to 4.8 (SD 4.5) at the end of the 8-week single-blind phase. Similarly, the mean HAM-A psychic subscale score decreased from 14.1 (SD 2.4) to 5.0 (SD 4.2) at the end of this treatment phase.

During the double-blind treatment phase, both psychic and somatic symptoms continued to improve in patients maintained on treatment with paroxetine, whereas these symptoms deteriorated in patients switched to placebo. The difference between treatment groups for both HAM-A somatic and psychic subscales was statistically

Figure 5. Mean Change on the SDS Total Score and Family, Social, and Work Item Scores Relative to Baseline During the Double-Blind Treatment Phase



significant at each timepoint assessed. At week 32, paroxetine-treated patients had experienced a decrease in mean HAM-A somatic and psychic subscale scores of 1.2 (SE 0.3) and 0.7 (SE 0.3), respectively. Mean HAM-A somatic and psychic subscale scores for placebo patients at week 32, however, had increased by 1.7 (SE 0.3) and 3.1 (SE 0.3), respectively. The treatment differences at week 32 for both the HAM-A somatic and psychic subscales were highly statistically significant ( $p < .001$ ) (Table 3).

## Remission

Following 8 weeks of single-blind treatment with paroxetine, 42.5% of patients were in remission from GAD symptoms as defined by a HAM-A total score  $\leq 7$ . At the end of the double-blind treatment phase, 73.0% of paroxetine patients randomly assigned to paroxetine achieved remission compared with only 34.4% of the patients switched to placebo ( $p < .001$ ) (Figure 4).

## Disability

The mean SDS total score decreased during the 8 weeks of treatment with paroxetine in the single-blind phase from 16.0 (SD 6.2) at baseline to 7.4 (SD 5.6) at week 8.

**Table 4. Most Frequently Reported ( $\geq 5\%$ ) Treatment-Emergent Adverse Events During the 8-Week Single-Blind Treatment Phase**

Adverse Event	Paroxetine (N = 652) N (%)
Nausea	140 (21.5)
Headache	80 (12.3)
Insomnia	62 (9.5)
Asthenia	57 (8.7)
Sweating	54 (8.3)
Somnolence	50 (7.7)
Dry mouth	43 (6.6)
Diarrhea	37 (5.7)
Dizziness	33 (5.1)
Abnormal ejaculation	27 (11.4)
Impotence	13 (5.5)

**Table 5. Most Frequently Reported ( $\geq 5\%$ ) Treatment-Emergent Adverse Events During the 24-Week Double-Blind Treatment Phase**

Adverse Event	Paroxetine (N = 274) N (%)	Placebo (N = 287) N (%)
Headache	19 (6.9)	15 (5.2)
Infection	17 (6.2)	15 (5.2)
Respiratory disorder	15 (5.5)	6 (2.1)
Sweating	14 (5.1)	16 (5.6)
Insomnia	11 (4.0)	16 (5.6)
Dizziness	8 (2.9)	27 (9.4)

During the double-blind treatment phase, patients who continued on paroxetine treatment experienced a further improvement in their disability scores, whereas those switched to placebo deteriorated. At week 32, treatment differences in the mean change from the double-blind baseline in SDS total score and SDS family, social, and work item scores were statistically significant in favor of paroxetine compared with placebo (each  $p < .001$ ) (Figure 5).

### Depressive Symptoms

The mean MADRS score at the single-blind baseline was 12.0 (SD 3.4). At the double-blind phase baseline, mean MADRS values were 4.6 (SD 0.2) for paroxetine and 4.7 (SD 0.2) for placebo. At week 32, the mean (SE) change from baseline was  $-0.2$  (0.4) and  $3.2$  (0.4) for paroxetine and placebo, respectively. The treatment difference at week 32 ( $-3.4$ ) was statistically significant (95% CI =  $-4.4$  to  $-2.3$ ,  $p < .001$ ).

### Safety

**Single-blind treatment phase.** A total of 51.8% of patients reported an adverse event during the single-blind treatment phase. In keeping with the known safety profile of paroxetine, the most common treatment-emergent adverse events during the single-blind treatment phase were nausea, headache, and insomnia (Table 4).

**Double-blind treatment phase.** Overall, 35.0% of paroxetine-treated patients and 34.8% of placebo patients reported an adverse event during the double-blind treatment phase. The incidence of adverse events during the double-blind treatment phase was low (Table 5). The most frequent treatment-emergent adverse events for paroxetine-treated patients were headache, infection, and respiratory disorder. For placebo patients, the most frequent treatment-emergent adverse events were dizziness, sweating, and insomnia, which may well be associated with the cessation of paroxetine treatment after the single-blind treatment phase.

### Weight Gain

The mean increase in weight at the end of the study from the single-blind baseline was 1.3 kg (SD 4.4 kg) (2.9 lb [SD 9.8 lb]) for paroxetine and 0.4 kg (SD 3.3 kg) (0.9 lb [SD 7.3 lb]) for placebo. At study end, patients' weights ranged from 42.0 to 109.0 kg (93.3–242.2 lb) in the paroxetine group and from 45.0 to 107.0 kg (100.0–237.8 lb) in the placebo group. There was no clinically significant difference between the treatment groups in the proportion of patients experiencing a  $\geq 7\%$  increase in weight during the study (9.1% paroxetine, 5.9% placebo).

The incidence of weight gain reported as an adverse event during the double-blind treatment phase was also low, occurring in 5/274 paroxetine-treated patients (1.8%) and 1/287 placebo patients (0.3%).

## DISCUSSION

Ours is the first randomized, placebo-controlled study in GAD published to date that specifically investigated relapse prevention over the long term. The efficacy of paroxetine in the short-term treatment of GAD has been well established in 4 randomized clinical trials.<sup>16,17,20,27</sup> The primary objective of the present study was to evaluate the long-term efficacy of paroxetine by assessing the potential for relapse after discontinuation of treatment. A secondary aim of this study was to investigate the long-term safety of paroxetine in the treatment of GAD.

For patients randomly assigned to placebo at the end of the initial 8-week single-blind paroxetine treatment phase, the risk of relapse was nearly 5 times greater than for those who continued to receive paroxetine. A clinically important benefit of continued paroxetine treatment in the management of GAD was demonstrated by the further improvement in anxiety symptoms over the 24-week double-blind phase. Moreover, the proportion of patients achieving remission from GAD symptoms also continued to increase with paroxetine treatment. At the end of the study, more than twice as many paroxetine-treated patients were in remission compared with placebo patients.

This study clearly shows that cessation of paroxetine after 8 weeks does not lead to rebound of the underlying

anxiety disorder (a potential concern when stopping any psychotropic drug). An efficacy assessment undertaken 1 week after paroxetine cessation (i.e., week 4 for placebo patients during the double-blind phase) showed only a small mean increase in HAM-A scores, while the mean HAM-A scores in these patients continued to increase throughout the 24-week double-blind phase in a gradual manner. The lack of an abrupt rebound effect is also demonstrated by the gradual rate of relapse in the placebo group (Figure 2).

SDS total and subscale scores showed a statistically significant benefit for paroxetine compared with placebo ( $p < .001$ ). As paroxetine maintains the improvement of anxiety symptoms, so the functional status of the patient concurrently improves.

Studies assessing long-term treatment with paroxetine in depression<sup>28,29</sup> and other anxiety disorders<sup>11,30,31</sup> have demonstrated that it is well tolerated. Adverse events reported during the present study were consistent with those in other indications and confirm the favorable safety profile of paroxetine. In the double-blind treatment phase, similar proportions of paroxetine and placebo patients withdrew because of adverse effects (2.6% vs. 2.8%).

Long-term treatment with paroxetine in this study population of patients with DSM-IV GAD was not associated with an increased incidence of clinically significant weight gain compared with placebo. This finding corroborates the findings of 2 long-term studies conducted in patients with panic disorder<sup>11</sup> and in depressive outpatients,<sup>32</sup> where the incidence of weight gain was substantially lower with paroxetine than with the TCA comparator.

A possible shortcoming of the current study is that the study population is limited to patients with a primary diagnosis of GAD according to DSM-IV criteria (300.02). This represents an exclusive population that is unlikely to be similar to that encountered by physicians in the course of their consultations. The majority of patients with GAD show substantial comorbidity,<sup>33</sup> and the extrapolation of our results to patients in the community suffering from GAD must be made with an awareness of potential differences between the 2 populations. However, paroxetine has proven long-term efficacy in most Axis I disorders, including depression,<sup>28,29</sup> panic disorder,<sup>11</sup> OCD,<sup>30</sup> and social anxiety disorder.<sup>31</sup>

Recently, studies reporting the short- and long-term efficacy of venlafaxine in GAD have been published.<sup>15,18,19,34,35</sup> In a 28-week placebo-controlled, maintenance-design study in 251 outpatients with GAD, venlafaxine extended release (75–225 mg/day) significantly improved anxiety symptoms assessed using HAM-A and CGI-S scores ( $p < .001$ ).<sup>18</sup> However, unlike the present study, functionality was not assessed, and therefore the ability of long-term venlafaxine to improve aspects of daily functioning was not addressed.

## CONCLUSION

The results of this study clearly demonstrate the maintained efficacy of paroxetine in the long-term treatment of GAD. Patients in the placebo group were almost 5 times more likely to relapse than patients on continuous paroxetine treatment, and twice as many (70%) paroxetine-treated patients as placebo patients were considered to be in remission from GAD at the end of the double-blind phase of this study. The tolerability of paroxetine was excellent, and, coupled with its well-documented efficacy in the treatment of major depression, the most frequent comorbid condition in GAD, paroxetine is a logical choice for the long-term medical management of this common and disabling psychiatric disorder.

*Drug names:* buspirone (BuSpar and others), paroxetine (Paxil), venlafaxine (Effexor).

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