Paroxetine in the Treatment of Generalized Anxiety Disorder: Results of a Placebo-Controlled, Flexible-Dosage Trial

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Background: The objective of this randomized, double-blind, placebo-controlled study was to investigate the efficacy and safety of paroxetine in outpatients with generalized anxiety disorder (GAD).

Method: Male and female outpatients 18 years and older who met DSM-IV criteria for GAD and had baseline scores of at least 20 on the Hamilton Rating Scale for Anxiety (HAM-A) were randomly assigned to treatment with paroxetine (20–50 mg/day) or placebo for 8 weeks. The primary efficacy variable was the mean change from baseline in the total score of the HAM-A. Additional key efficacy variables were the change from baseline in the scores of the HAM-A items anxious mood and tension, the anxiety subscale of the Hospital Anxiety and Depression Scale, and the Sheehan Disability Scale (SDS). The proportions of patients fulfilling response and remission criteria at week 8 were also determined.

Results: The intent-to-treat population included 324 patients. At week 8, compared with the placebo group (N = 163), the paroxetine group (N = 161) had a significantly greater reduction of GAD symptoms on all of the above-mentioned efficacy variables. On the HAM-A anxious mood item, which encompasses the cardinal symptoms of GAD, significantly greater efficacy was observed from week 1 and on the SDS significantly greater improvement was documented in the domain "social life" as early as week 4 for paroxetine compared with placebo. In both the last-observation-carried-forward and completer data sets, significantly greater proportions of paroxetine-treated patients achieved response or remission by week 8. Treatment with paroxetine was well tolerated, and the number and type of adverse events recorded in the paroxetine group correspond to the known safety profile of this medication.

Conclusion: Paroxetine in doses of 20 to 50 mg once daily is effective in the treatment of patients with GAD. Improvement of core symptoms of GAD occurs early and is associated with significant reduction in disability after only 8 weeks of treatment.

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Since the introduction of generalized anxiety disorder (GAD) into psychiatric nosology in DSM-III,[1] this diagnostic entity has been substantially modified and refined in the 2 succeeding DSM editions. On the basis of the DSM field trials and other research,[2] GAD has developed from a residual syndrome encompassing "persistent" anxiety, motor tension, apprehension, hypervigilance, and autonomic symptoms, all occurring for only 1 month and in the absence of another disorder,[1] into a more precisely defined disorder in DSM-IV, in which "uncontrollable" anxiety or worry, chronicity, and functional impairment are emphasized.[3,4]

As documented in the Epidemiologic Catchment Area (ECA) study, GAD is associated with significant impairment in psychosocial function as well as negative impact on quality of life.[5,6] Affected patients experience diminished emotional health and social life, as well as vocational impairment, increased reliance on public assistance, and low ratings on measures of life satisfaction.[7] Patients with GAD frequently present in primary care settings because of a range of associated somatic symptoms and tend to use high levels of medical resources.[8,9] Untreated GAD is associated with negative health outcomes, including elevated medical utilization and increased morbidity and mortality.[10–12]

Pharmacologic treatment options for GAD include benzodiazepines, buspirone, and antidepressants. Benzodiazepines are commonly used for treatment of anxiety, but their use is limited by their lack of efficacy for comorbid depression, as well as concerns, in the absence of well-controlled data, about the potential for tolerance, abuse, and dependence with long-term use.[13,14] Buspirone is approved for the treatment of anxiety, and although it is well tolerated, its use is complicated by the need for daily multiple dosing, delayed onset of activity, limited spectrum of action, and concerns about efficacy and patient satisfaction in clinical practice.[15,16] Tricyclic antidepressants such as imipramine are effective for GAD, but their use is constrained by a side effect profile that limits compliance.[17,18] Other antidepressants, including trazodone and nefazodone, may also be effective for GAD,[17,19] but have not been well studied for this indication. Recently published studies report the efficacy of venlafaxine extended release (XR) for the treatment of GAD,[20–22] and this agent recently received U.S. Food and Drug Administration approval for this indication. However, given the prevalence and associated distress and disability of GAD, there is a clear need in clinical practice for alternative effective and well-tolerated pharmacotherapies.

Over the last decade, extensive clinical research has demonstrated that the selective serotonin reuptake inhibitor (SSRI) paroxetine is an effective antidepressant[23,24] with a broad spectrum of anxiolytic activity, having demonstrated efficacy in the treatment of panic disorder,[25] obsessive-compulsive disorder (OCD),[26] and social anxiety disorder.[27] Preliminary clinical work has also indicated that paroxetine is effective in alleviating the symptoms of GAD: in a randomized trial involving 81 nondepressed outpatients with GAD, Rocca et al.[28] compared paroxetine with imipramine and the benzodiazepine 2'-chlordesmethyldiazepam. As measured by changes in the Hamilton Rating Scale for Anxiety (HAM-A) and the Clinical Global Impressions-Severity of Illness scale (CGI-S), the benzodiazepine was more effective than the other drugs during the first 2 weeks of treatment, but was consistently surpassed thereafter by both imipramine and paroxetine, which led to continued improvement of GAD symptoms up to the 8-week study endpoint.

On the basis of this previous research and the positive effects of paroxetine in other anxiety disorders, an 8-week, multicenter, placebo-controlled study investigating the efficacy of paroxetine for the treatment of GAD in nondepressed outpatients was conducted. The results of this study are reported here. In addition to examining measures of changes in anxiety symptoms, this study is one of the first to evaluate improvement in functional impairment in patients receiving treatment for GAD.

METHOD

This was a randomized, double-blind, parallel-group, placebo-controlled, flexible-dosage study of outpatients (N = 326) with GAD. The study was conducted at 35 outpatient clinics in the United States and Canada.

Patient Selection

Outpatients of both sexes who were at least 18 years old were eligible for inclusion into the study if they fulfilled the DSM-IV criteria for GAD as determined by psychiatric evaluation, which included the Mini-International Neuropsychiatric Interview.[29] Because paroxetine has been safely used in elderly populations,[30] there was no upper age limit for patients considered for the study. At the initial (screening) and baseline assessments, the patients were required to have a total score ≥ 20 on the 14-item HAM-A[31] and a score ≥ 2 on HAM-A items 1 (anxious mood) and 2 (tension). Patients who were diagnosed with any other Axis I disorder or who had a score of 17 or greater on the Montgomery-Asberg Depression Rating Scale[32] at the initial or baseline assessments were excluded, as were patients who met DSM-IV criteria for substance abuse or substance dependence within the previous 6 months. The following minimum discontinuation periods were required for psychoactive medications: antidepressants and herbal medications, 4 weeks; hypnotics and sedatives, 2 weeks; depot neuroleptics, 12 weeks. Patients who had electroconvulsive therapy or formal psychotherapy within the 3 months prior to the initial assessment were also excluded. Individuals with an untreated coexisting medical condition and women of childbearing potential who did not practice a reliable method of contraception were not eligible for the study.

The study protocol was approved by the appropriate institutional review board at each of the centers. Written informed consent from each patient was obtained before any study procedures were carried out.

Study Flow

Patients who met the eligibility criteria at the initial assessment underwent a 1-week, single-blind, placebo run-in phase. At the subsequent (baseline) assessment, patients were randomly assigned to double-blinded study medication if there was no significant reduction on the HAM-A total score (defined as ≥ 20% reduction of the initial score) and all other inclusion criteria were met. Subjects who were noncompliant during the placebo run-in week or had unresolved clinically significant abnormalities in hematology, blood chemistry, electrocardiogram (ECG), or physical examination findings were excluded. The double-blind treatment lasted 8 weeks. Patients randomly assigned to paroxetine started treatment at 10 mg/day for the first week and received 20 mg/day during the second week. Patients who could not tolerate the study medication during the first 2 weeks were removed from the study. After week 2, the paroxetine dosage could be increased every 7 days by 10 mg/day up to 50 mg/day. During the study treatment, only a single dos-

age reduction (because of physical illness or an adverse event) was allowed in patients taking at least 30 mg/day (or placebo equivalent). Concomitant medication for sleep disturbance was not allowed at any time during the study.

Efficacy Variables and Safety Assessments

Efficacy assessments were performed at the end of weeks 1 through 6 and at week 8. Prior to study start, all clinicians functioning as HAM-A raters underwent training to ensure consistency of application of this instrument.

The primary efficacy variable was the mean change from baseline in the total score of the HAM-A. A number of secondary efficacy measures were chosen to evaluate paroxetine's effects on GAD symptomatology and impairment: the change from baseline score in HAM-A item 1 (anxious mood) and item 2 (tension); the change in scores on the psychic and somatic symptom subscales of the HAM-A; the anxiety subscale score of the patient-rated Hospital Anxiety and Depression Scale (HAD)[33]; and the change from baseline score on the CGI-S. The change from baseline in illness-related impairment was assessed at baseline and weeks 4 and 8 using the Sheehan Disability Scale (SDS), which documents the patient's perception of impairment within the 3 domains of work, social life, and family life.[34] The level of impairment is measured by a separate visual analogue scale for each of the domains on a scale of 0 ("no impairment") to 10 ("very severe impairment"), thus giving a total score from 0 to 30. The SDS has been validated in patients with depression and panic disorder and has been shown to be sensitive to change in drug trials in psychiatry.[35] Patients with panic disorder and social anxiety disorder have been found to have mean SDS scores of approximately 16 and 18, respectively, corresponding to a condition of moderate impairment. Reduction in the total score by 30% or greater is considered meaningful improvement in functional status.[34,35] Response to treatment was defined by a score of 1 ("very much improved") or 2 ("much improved") on the CGI-Global Improvement scale (CGI-I), while remission, which represents complete or near-complete symptom resolution, was defined by a HAM-A total score of 7 or less.[36]

At each assessment visit, information concerning adverse events was obtained from spontaneous patient reports and investigator inquiry and/or physical examination. The evaluation of safety was based on documented adverse events and the results of scheduled physical examinations, ECGs, and laboratory tests.

Data Analysis

The key comparison of interest was paroxetine versus placebo in the intent-to-treat (ITT) population from the last-observation-carried-forward (LOCF) data set, in which the last available data from patients dropping out of the study are carried to all successive timepoints. The ITT population was defined as those patients who were randomly assigned to study medication and had at least 1 postbaseline efficacy assessment. The protocol-defined study endpoint was week 8.

For continuous efficacy variables (i.e., all efficacy parameters except response), comparisons between paroxetine and placebo were based on the change from baseline scores. These were analyzed by analysis of variance (ANOVA) using the general linear models procedure in Statistical Analysis System (SAS) version 6.12. The dichotomous response data were analyzed via logistic analysis using the categorical model procedure (CATMOD) of SAS with treatment in the model, with the proportion of patients responding being compared among the treatments. All hypothesis tests were 2-sided. The effect of interactions was assessed during the model building process at the 10% level of significance. All other statistical tests were performed at the 5% significance level, with 95% confidence intervals (CIs) constructed around the differences between paroxetine and placebo. All analyses, with the exception of the determination of remission rates, were prospectively defined. For response and remission, the results of the analyses of both the LOCF and study-completer (observed-case) data sets are presented to give a fuller picture of the potential range of treatment outcomes.

RESULTS

Patients

Three hundred and thirty-one subjects completed the 1-week placebo run-in phase and were randomly assigned to double-blind study medication at the baseline visit. Of these, 7 patients had no postbaseline efficacy assessment and were therefore excluded from the efficacy analysis. The mean baseline demographic and clinical characteristics of the 324 patients who made up the ITT population are presented in Table 1. The mean age of the placebo group was slightly greater than that of the paroxetine group, but the difference, although statistically significant, is not considered clinically meaningful. In the paroxetine group, the mean SDS total score at baseline was greater than that in the placebo group; because both means fall into the moderately severe category, this difference is not considered clinically relevant. Otherwise, the treatment groups were comparable with regard to the distribution of gender and race and were also very similar with respect to age at onset of GAD, duration of GAD symptoms, and baseline psychometric measures.

There was no substantial difference between the 2 treatment groups with respect to the number of patients completing 8 weeks of treatment (78.9% [127/161] of paroxetine patients and 81.6% [133/163] of placebo pa-

Table 1. Demographic and Baseline Clinical Characteristics of Randomized Patients in the Intent-to-Treat Population[a]

Characteristic[b]	Placebo (N = 163)	Paroxetine (N = 161)	p Value
Age, y, mean (range)	41.3 (19–80)	39.7 (19–69)	.001
Gender, %			
Male	33.7	39.1	.374
Female	66.3	60.9	
Race, %			…
African American	4.3	3.2	
Asian	0.6	0.6	
White	81.6	85.7	
Other	13.5	10.5	
Age at onset of GAD symptoms, y	30.7 (1.2)	28.7 (1.1)	.227
Duration of GAD symptoms, y	10.2 (0.9)	11.1 (1.0)	.087
HAM-A score			
Total	24.1 (0.30)	24.2 (0.30)	.803
Anxiety item (item 1)	2.6 (0.05)	2.7 (0.04)	.433
Tension item (item 2)	2.6 (0.04)	2.6 (0.04)	.990
Psychic anxiety subscale	13.6 (0.20)	13.6 (0.20)	.998
Somatic anxiety subscale	10.5 (0.20)	10.6 (0.20)	.750
HAD anxiety subscale score	12.6 (0.30)	12.5 (0.30)	.954
CGI-S score	4.3 (0.04)	4.2 (0.04)	.478
SDS total score	13.6 (0.40)	14.8 (0.50)	.047

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, GAD = generalized anxiety disorder, HAD = Hospital Anxiety and Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, SDS = Sheehan Disability Scale.
[b]All values shown as mean (SE) unless otherwise specified.

tients). The mean ± SD dosage of paroxetine during the study was 26.8 ± 7.5 mg/day. The paroxetine dosage at endpoint was evenly distributed among 4 dosage levels: 26% of patients attained 20 mg/day, 26% attained 30 mg/day, 20% attained 40 mg/day, and 26% attained 50 mg/day. Three paroxetine patients withdrew during the first week of the study while receiving 10 mg/day.

Efficacy

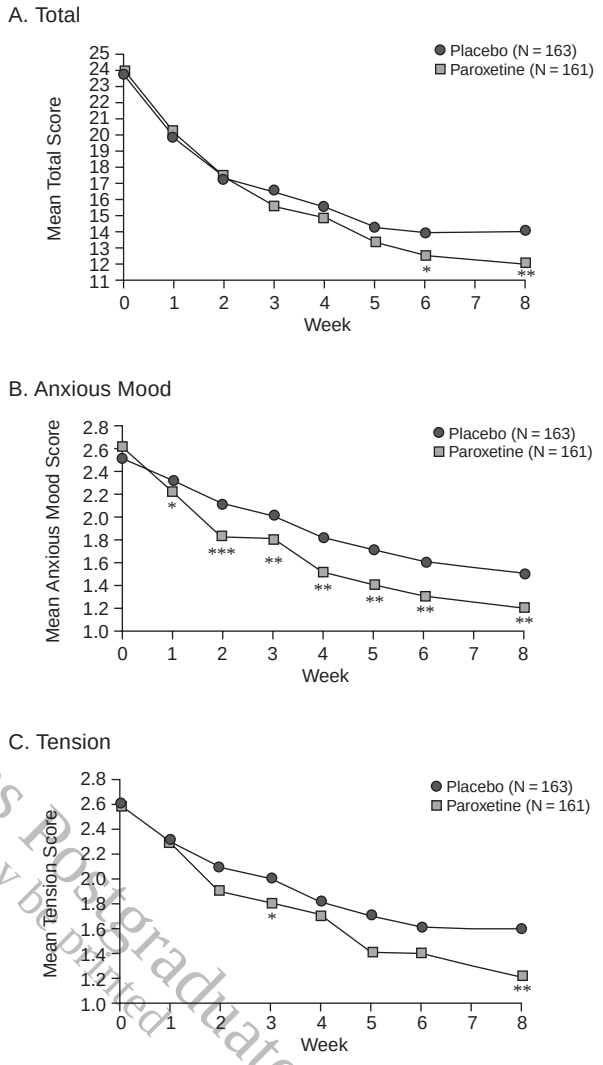
Figure 1 shows the mean at each assessment timepoint for the HAM-A total score and the mean scores for items 1 (anxiety item) and 2 (tension item). Compared with the placebo group, the paroxetine group had significantly greater reduction of anxiety symptoms. This is evident in HAM-A total score (panel A) at weeks 6 ($p < .05$) and 8 ($p < .01$) and in the scores that measure central features of GAD (anxious mood, panel B; tension, panel C). With respect to the HAM-A anxious mood item, which includes "worries" and "fearful anticipation" and thus the cardinal symptoms of GAD, significant improvement in the paroxetine group was observed from week 1.

Results in favor of paroxetine were also observed in the psychic and somatic anxiety subscales of the HAM-A (adjusted mean differences at endpoint: psychic anxiety –1.7, 95% CI = –2.7 to –0.6; somatic anxiety –0.6, 95% CI = –1.4 to 0.2). Only for the psychic anxiety subscale was the difference from placebo significant ($p = .002$).

From the perspective of a general assessment of the patients' condition, there was a significantly greater reduction in illness severity among paroxetine patients as measured by the changes in the CGI-S ratings. At the start of treatment, all patients were judged to be at least moderately ill. At the end of the trial, 40% of paroxetine patients compared with 27% of placebo patients were reported either to be "not ill" or to have only "borderline illness" (CGI-S score of 1 or 2, respectively; $p < .01$).

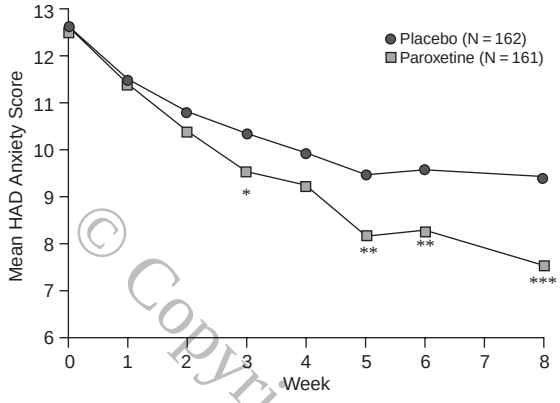
The findings from the clinician-rated HAM-A and CGI-S are complemented by the scores in the patient-rated anxiety subscale of the HAD (Figure 2). At each timepoint, the paroxetine patients reported a greater decrease in anxiety symptoms than that reported by patients

Figure 1. Mean (A) Total, (B) Anxious Mood Item, and (C) Tension Item Scores on the Hamilton Rating Scale for Anxiety[a]



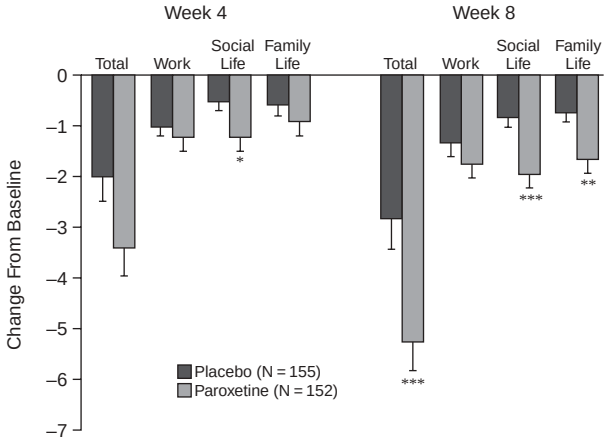
[a]Presented as adjusted least square means. Asterisks represent pairwise comparisons, paroxetine vs. placebo, for difference in mean change from baseline.
*p < .05. **p < .01. ***p < .001.

Figure 2. Mean Scores on the Anxiety Subscale of the Hospital Anxiety and Depression Scale (HAD) During Treatment With Paroxetine or Placebo[a]



[a]Presented as adjusted least square means. Asterisks represent pairwise comparisons, paroxetine vs. placebo, for difference in mean change from baseline.
*p < .05. **p < .01. ***p < .001.

Figure 3. Mean (SEM) Change From Baseline in Sheehan Disability Scale Total and Domain Scores[a]



[a]Adjusted least square mean (SEM) change in total score and on work, social life, and family life domains of the Sheehan Disability Scale. Negative change in score reflects clinical improvement. Asterisks represent pairwise comparisons, paroxetine vs. placebo.
*p < .05. **p < .01. ***p < .001.

Table 2. Response and Remission Rates (LOCF and study-completer data sets)[a]

Rate	Placebo	Paroxetine	Difference (95% CI)	p Value[b]
Response rate, %				
LOCF	47.2	62.1	14.9 (4.0 to 25.7)	.007
Study completers	55.6	72.4	16.8 (5.0 to 28.6)	.005
Remission rate, %				
LOCF	22.7	36.0	13.3 (3.7 to 22.9)	.009
Study completers	26.3	42.5	16.2 (5.1 to 27.3)	.006

[a]Abbreviations: CI = confidence interval, LOCF = last observation carried forward. Response defined as score of 1 ("very much improved") or 2 ("much improved") on the Clinical Global Impressions-Global Improvement scale. Remission defined as total score of ≤ 7 on the Hamilton Rating Scale for Anxiety.
[b]p Value from logistic analysis with treatment effect.

Table 3. Common Adverse Events (> 10% and at least twice placebo rate) During Treatment of Generalized Anxiety Disorder With Paroxetine

	Placebo (N = 163)		Paroxetine (N = 161)	
Adverse Event	N	%	N	%
Asthenia	17	10.4	34	21.0
Constipation	3	1.8	25	15.4
Ejaculation abnormal[a]	2	3.6	22	34.9
Libido decreased	4	2.4	19	11.7
Nausea	10	6.1	41	25.3
Somnolence	11	6.7	27	16.7

[a]Percentages adjusted for gender.

treated with placebo. The difference between the paroxetine and placebo groups was apparent by week 3 ($p < .05$) and was greatest at week 8 endpoint ($p < .001$).

The rates of response and remission were significantly greater for the paroxetine group than for the placebo group (Table 2). Sixty-two percent of the paroxetine-treated patients in the LOCF data set were responders; for those patients completing 8 weeks of treatment, the response rate was over 70%. Remission, i.e., absence or near absence of symptoms, was achieved by 36% of patients in the paroxetine LOCF data set and by over 40% of the patients completing 8 weeks of paroxetine treatment.

At week 8, the paroxetine group demonstrated significantly greater improvement than the placebo group in the total score of the SDS ($p < .001$; Figure 3). This improvement in functional impairment reflects the greater changes seen in paroxetine-treated patients on the social and family life items of the SDS, with significantly greater improvement in social function already evident in the paroxetine group by the first postbaseline assessment (week 4; $p < .05$).

Tolerability

Both groups tolerated the study treatment well. The most frequently reported reason for study discontinuation was lack of efficacy in the placebo group (5.5% vs. 1.9% in the paroxetine group) and adverse events in the paroxetine group (10.5% vs. 3.7% in the placebo group). During the initial 2 weeks of the study, 6.7% of patients in the placebo group and 9.9% in the paroxetine group discontinued treatment, indicating that the initial dosage increase from 10 to 20 mg was well tolerated. The most common events associated with paroxetine treatment (incidence of at least 10% and twice that of placebo) are summarized in Table 3. Most of the adverse events were reported to be mild to moderate in severity and were more likely to occur during the initial weeks of treatment and to diminish with continued treatment. For the 2 most com-

mon adverse events associated with paroxetine treatment, nausea and abnormal ejaculation, treatment was discontinued in only 3 (1.9%) of 161 patients and 2 (3.2%) of 62 men. No substantial effects on laboratory parameters, vital signs, or body weight were observed for paroxetine or placebo.

DISCUSSION

The results of the 8-week study presented here demonstrate that paroxetine is effective in the treatment of GAD. The efficacy of paroxetine was significantly greater than that of placebo for the primary efficacy parameter, the change from baseline in HAM-A total score. This result was confirmed by significant changes in favor of paroxetine on all but one of the secondary clinician- and patient-rated outcome measures, including the HAM-A anxious mood and tension items, the anxiety subscale of the HAD, the HAM-A psychic anxiety subscale, and the CGI-S. Alleviation of core GAD symptoms—"worries" and "fearful anticipation"—appears to occur early in treatment with paroxetine (see Figure 1, panel B). Overall, approximately 70% of paroxetine-treated patients who completed 8 weeks of treatment were responders, and more than 40% of completers satisfied the definition for remission. As has been reported in studies of other disorders,[37] in the present study, the use of more rigorous outcome criteria (i.e., examining rates of remission rather than simply response) tended to increase the discrimination between active treatment and placebo, which serves as a further indication of the specific benefit accruing to patients taking paroxetine after only a relatively short treatment period.

At baseline, the patients in this study were characterized by a long duration of illness and moderately severe levels of GAD symptomatology as measured by the HAM-A and CGI-S (see Table 1). The mean baseline score on the SDS was 14.2, indicating that the patients in this study were moderately to severely impaired. Similar levels of disability have been observed for untreated panic disorder and social phobia.[34] In this study, the paroxetine treatment group demonstrated improvement significantly greater than that of the placebo group in SDS total score. This improvement was due in large part to reductions in impairment of social life and family life domains that were twice as great in the paroxetine group as in the placebo group (see Figure 3). Since GAD has a pernicious effect on the overall functioning of affected individuals, the improvement in social and family functioning observed in the paroxetine-treated patients is particularly noteworthy in relating the significant improvement seen on symptomatic anxiety measures at 8 weeks to a meaningful improvement in the functional capacity of treated patients. That the improvement in the SDS work domain in the paroxetine group was not significantly greater than that of the placebo group may be due in part to the fact that, at baseline and during the study, many of the patients in both treatment groups were still employed despite their disorder.

The study design and the outcome measures used in this trial are similar to those reported for 2 recent studies in which venlafaxine XR was employed as a treatment for GAD.[20,21] It is therefore relevant to compare in a general way the findings presented here for paroxetine with the results of those trials. In both 8-week studies, fixed doses of venlafaxine XR (75 and 150 mg/day in the study by Davidson et al.[20]; 75, 150, and 225 mg/day in the study by Rickels et al.[21]) demonstrated greater effects than placebo on several outcome measures, including the HAM-A anxiety and tension items, the anxiety subscale of the HAD, and the CGI-I. However, only the 225-mg/day regimen showed a statistically significantly greater effect than placebo on the HAM-A total score at the week 8 endpoint.[21] A 6-month, placebo-controlled, flexible-dose trial with venlafaxine XR (75–225 mg/day) also demonstrated efficacy for the active drug, with the majority of the effect occurring by week 8.[22] On all outcome parameters, the magnitude of response reported here for paroxetine is similar to that reported in the 3 venlafaxine studies.

In this study, paroxetine was not significantly more effective than placebo in reducing somatic symptoms of GAD, as measured by the somatic symptom subscale of the HAM-A. This result is consistent with the findings from studies of other nonbenzodiazepine treatments of GAD, including buspirone,[38,39] with mixed results reported from the venlafaxine XR trials,[21,22] and may be related to the lack of muscle-relaxant or other direct somatic effects of these agents, at least in the short term.

Paroxetine was well tolerated. The pattern of commonly reported adverse events shown in Table 3 is similar to that seen during paroxetine use for other indications.[25–27,40,41] The rate of study discontinuation due to an adverse event (10.5%) was also similar to that reported in other anxiety disorders for which paroxetine is indicated [25–27] and lower than that reported for buspirone[20,42] or venlafaxine XR.[20–22] In this study, the mean daily dose of paroxetine was 26.8 mg. A fixed-dosage study[43] comparing 20 and 40 mg/day of paroxetine in the treatment of GAD did not show a clear dose-response relationship with respect to the change from baseline in HAM-A total score, suggesting that paroxetine, 20 mg/day, may be an effective dosage for the majority of GAD patients. However, the fact that a number of patients in this study were taking more than 20 mg/day of paroxetine at week 8 raises the possibility that higher doses of paroxetine may be more effective for some patients, in particular those who do not adequately respond to 20 mg/day. However, further study is required to evaluate this issue systematically.

The response rate in the placebo group was 47% in the LOCF patient sample. This rate is higher than the rates of approximately 40% reported in other GAD

studies using similar definitions of response.[17,20] A post hoc statistical comparison of the placebo and paroxetine responder groups in this study did not reveal significant differences with respect to age, gender distribution, baseline HAM-A total score, or baseline severity of illness; thus, the reason for the higher response rate in the placebo group is not apparent. Nonetheless, despite the higher placebo response rate, the attributable benefit of paroxetine over placebo in reducing the symptoms of GAD (as measured by the HAM-A total and item scores and the anxiety subscale of the HAD) is comparable to that observed for the medications in the studies cited above.

The positive effects of treatment of GAD with paroxetine were demonstrated within the confines of an 8-week study. Although it is reasonable to assume that continuation of paroxetine beyond 8 weeks would lead to further improvement or a larger response rate, this assumption requires confirmation in suitably designed long-term studies. European researchers recently completed a relapse-prevention trial in which GAD patients who responded to open-label treatment with paroxetine were randomly assigned to placebo or paroxetine for 6 months (GlaxoSmithKline, data on file, 2001). The results indicate that the patients on active treatment continued to show symptomatic and functional improvement over time and that patients switched to placebo showed little or no improvement and a significantly greater relapse rate.

Patients with major depression or other anxiety disorders were excluded from participation in this study. As is true in many clinical trials, the study sample may not necessarily reflect a clinically representative group of patients, since it is estimated that 75% of patients with GAD have a comorbid psychiatric disorder.[44] However, substantial clinical trial and clinical practice experience have shown paroxetine to be effective treatment for a number of conditions that are frequently comorbid with GAD, including major depression,[23,24] OCD,[26] panic disorder,[25] and social anxiety disorder.[27] Thus, although further research in clinical settings is warranted to confirm the effectiveness of this agent for the treatment of GAD comorbid with other disorders, the results of this study demonstrate that paroxetine is a useful addition to the therapeutic armamentarium for the treatment of individuals suffering with generalized anxiety disorder.

Drug names: buspirone (BuSpar), nefazodone (Serzone), paroxetine (Paxil), trazodone (Desyrel and others), venlafaxine (Effexor).

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