A Randomized, Double-Blind, Fixed-Dose Comparison of Paroxetine and Placebo in the Treatment of Generalized Social Anxiety Disorder

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Background: This multicenter, double-blind, placebo-controlled study was carried out to determine the effectiveness and safety of various daily dosages of paroxetine for the treatment of generalized social anxiety disorder.

Method: A 1-week, single-blind, placebo run-in was followed by 12 weeks of double-blind treatment. 384 eligible patients meeting DSM-IV criteria for social anxiety disorder were randomly assigned to receive paroxetine, 20 (N = 97), 40 (N = 95), or 60 mg (N = 97), or placebo (N = 95) once daily in a 1:1:1:1 ratio. Primary efficacy variables included mean change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score and proportion of patients exhibiting a therapeutic response (defined as a Clinical Global Impressions-Global Improvement scale [CGI-I] score of 1 or 2).

Results: In the last-observation-carried-forward analyses, patients treated with paroxetine, 20 mg/day, had significantly greater improvement on mean LSAS total scores compared with those receiving placebo ($p < .001$), while the incidence of responders, based on the CGI-I rating, was significantly greater with paroxetine, 40 mg/day, than with placebo ($p = .012$). Patients treated with paroxetine, 20 and 60 mg, also had significantly better responses on the social item of the Sheehan Disability Scale than did patients treated with placebo ($p < .019$). The completer analyses showed a significant difference between the placebo group and the 20-mg and 40-mg paroxetine groups on LSAS total score and rate of response ($p \leq .006$). There were no serious adverse experiences attributed to paroxetine treatment.

Conclusion: Paroxetine, 20 mg/day, is an effective and safe treatment for patients with generalized social anxiety disorder and significantly improves social anxiety, avoidance of social interactions, social disability, and overall clinical condition. Further data analyses are needed to determine whether more specific guidelines for paroxetine dosage escalation in social anxiety disorder can be drawn.

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A complete list of the investigators who participated in this study appears at the end of the article.

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Social anxiety disorder, also known as social phobia, has been formally recognized as a distinct anxiety disorder since the third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) was published. There are 2 distinct subtypes of social anxiety disorder.[1] Persons with the nongeneralized subtype primarily have 1 distinct performance fear, such as public speaking, playing a musical instrument, or eating while being observed. In contrast, individuals with the generalized subtype suffer from fear of a variety of both performance and interactional situations. Some common interactional situations include talking to others, meeting new people, dating, or speaking with people in authority. Two thirds of patients with social anxiety disorder suffer from the generalized subtype and usually are far more impaired than individuals with nongeneralized social anxiety disorder.[2]

Treatment options for social anxiety disorder include the monoamine oxidase inhibitors (MAOIs),[3–5] the selective serotonin reuptake inhibitors (SSRIs),[6–14] the reversible inhibitors of monoamine oxidase A (RIMAs),[15–18] the benzodiazepines,[3,19–22] and gabapentin.[23] The MAOIs are efficacious in the management of this disorder[3–5,15]; however, toxicity concerns have limited the clinical utility of these agents. Although results with RIMAs were initially positive,[15,16] subsequent studies with moclobemide did not confirm efficacy.[17,18] Benzodiazepines, such as clonazepam, also decrease the symptoms associated with social anxiety disorder.[19] Unfortunately, there is a high incidence of relapse following benzodiazepine discontinuation,[20,21] and risks for abuse and psychological dependence are of concern.[22]

Evidence for the efficacy of the SSRIs in the treatment of social anxiety disorder is growing,[6–14] and several studies have demonstrated the efficacy of paroxetine in the treatment of the generalized subtype.[7,8,10,11,14] Promising results with paroxetine in flexible-dose studies[8,11] prompted further evaluation. Because the flexible-dose studies showed that paroxetine doses between 20 and 50 mg were efficacious, a fixed-dose regimen of paroxetine, 20, 40, or 60 mg, was employed to examine the effectiveness and safety of various daily dosages for the treatment of the generalized subtype of social anxiety disorder. In particular, the minimum effective dose cannot be determined from flexible-dose trials because time and dose are confounded, whereas a fixed-dose trial allows determination of how patients will respond over the course of an acute trial to a given dose. With regard to other anxiety disorders, a fixed-dose paroxetine trial[24] in panic disorder found that 40 mg/day was the minimally effective dose, with 10- and 20-mg daily doses demonstrating no significant differences from placebo. A flexible-dose, placebo-controlled trial[25] found paroxetine effective for obsessive-compulsive disorder (OCD), with study patients receiving a mean dose of 37.5 mg/day, but no fixed-dose trial of paroxetine has been reported to date for this disorder. Independent nosologic classification of various anxiety disorders is further supported to the degree that minimum effective doses of particular medications are found to differ across those disorders.

METHOD

Study Design

This multicenter, randomized, double-blind, placebo-controlled study assessed the optimal effective and safe daily dosage of paroxetine in the treatment of the generalized subtype of social anxiety disorder. Investigators at 22 centers in the United States and Canada (see Acknowledgment at end of article) participated in this 12-week study. After an initial screening visit, outpatients with a primary diagnosis of the generalized subtype of social anxiety disorder underwent a 1-week, single-blind, placebo run-in. Eligible patients then began a 12-week double-blind treatment phase and were randomly assigned at baseline to receive paroxetine, 20, 40, or 60 mg, or placebo once daily in a 1:1:1:1 ratio.

All patients randomly assigned to paroxetine began therapy at 20 mg/day. Patients were instructed to take 2 capsules each morning irrespective of treatment assignment. Those randomly assigned to paroxetine, 20 mg, remained at that dose for the duration of the study. At week 1, patients randomly assigned to the 40-mg paroxetine group were titrated to that daily dose. Doses for the 60-mg paroxetine group were titrated to 40 mg at week 1 and to 60 mg at week 2. Other dosage adjustments were not permitted during the study for any reason. However, in the event of an adverse experience, a maximum of 2 consecutive days of dosage interruption was permitted. It was recommended that medications be tapered gradually during a 2-week period in patients completing the study or in those who withdrew prematurely. The concomitant use of other psychotropic medications was prohibited, with the exception of chloral hydrate (up to 1000 mg) for insomnia.

Study Population

A modified version of the Structured Clinical Interview for DSM-IV (SCID)[26] was used to screen for the generalized subtype of social anxiety disorder (available from the authors on request). Patients who endorsed a minimum of 4 interactional and performance phobic situations (of which at least 2 were interactional situations) in the previous 6 months met the operational criteria for the generalized subtype of social anxiety disorder. Adult outpatients (≥ 18 years of age) who met these criteria as their primary diagnosis were enrolled; patients older than 65 years were permitted if they did not have renal or hepatic impairment and could tolerate a paroxetine starting dose of at least 20 mg/day. Patients who scored 1 (very much improved relative to baseline) or 2 (much improved relative to baseline) on the Clinical Global Impressions-Global Improvement (CGI-I)[27] scale at baseline (after the placebo run-in) or who had a score greater than or equal to 15 at baseline on the 17-item Hamilton Rating Scale for Depression (HAM-D)[28] were excluded. Patients with comorbid psychiatric disorders such as major depression, OCD, generalized anxiety disorder, and panic disorder were excluded using the SCID[26] if the comorbid disorder occurred within the past 6 months and was "predominant," which was defined as dominating the clinical picture, bringing the patient to treatment, or being of utmost concern to the patient. Also excluded were patients with substance abuse or dependence within 6 months of baseline, body dysmorphic disorder, schizophrenia, bipolar disorder, homicidal/suicidal tendencies, serious medical illness, or a history of seizures (except febrile seizures), as well as patients who had started psychotherapy within 6 months of baseline or who had been treated with other psychotropic medications or antidepressants (including MAOIs) within 14 days of baseline, fluoxetine within 5 weeks of baseline, depot neuroleptics within 12 weeks of baseline, or electroconvulsive therapy within the past 3 months. Patients requiring concomitant therapy with β-adrenergic blockers, MAOIs, benzodiazepines, other psychoactive medications, warfarin anticoagulants, digitalis glycosides, phenytoin, cimetidine, or sumatriptan were not included. Women who were pregnant, lactating, or of childbearing potential and not practicing a clinically accepted method of contraception were ineligible.

The study protocol and statement of informed consent were approved by the Institutional Review Board or Ethics Committee at all study centers. Written informed consent was obtained from patients prior to study participation.

Efficacy Assessment

Parameters for evaluation of efficacy were the clinician-administered Liebowitz Social Anxiety Scale (LSAS),[29] CGI-Severity of Illness (CGI-S) and CGI-I scales,[27] Social Avoidance and Distress Scale,[30] and Sheehan Disability Scale (SDS).[31] Primary efficacy variables were mean change from baseline in the LSAS total score and percentage of patients with a CGI-I score of 1 or 2. Secondary efficacy variables consisted of mean change from baseline in the fear/anxiety and avoidance subscale scores of the LSAS, CGI-S, Social Avoidance and Distress Scale, and SDS. An additional measure in the study was the 17-item HAM-D, which was administered at baseline and at week 12 (or at the time of discontinuation from the study). After the initial screening visit, all other tests were administered to patients at baseline and weeks 1, 2, 3, 4, 6, 8, and 12 (or at the time of discontinuation).

Safety Assessment

Safety was assessed by monitoring adverse experiences and vital signs at weeks 1, 2, 3, 4, 6, 8, and 12 (or at discontinuation). Reports of adverse experiences were elicited by asking the patients nonleading questions. At week 10, patients were contacted by telephone to assess safety and continued compliance with the study protocol. Physical examination, laboratory evaluation, and a pregnancy test were conducted at the screening visit and at week 12 (or at discontinuation). An additional visit was conducted to assess safety at the end of the 2-week taper phase. For patients who discontinued prematurely because of an adverse experience or who completed the study with an ongoing adverse experience, additional adverse experience monitoring, vital sign and body weight determination, laboratory evaluation, and physical examinations were conducted within 1 month of termination.

Statistical Methods

The mean changes from baseline in LSAS total and subscale scores, CGI-S score, Social Avoidance and Distress Scale scores, and SDS item scores were analyzed using parametric analysis of variance with effects for treatment, investigator, and treatment-by-investigator interaction. The general linear model procedure of the SAS was used to perform these analyses. Type III sums of squares were used. Data are reported as mean values with standard deviations. The proportion of patients achieving a response as defined by a CGI-I score of 1 (very much improved relative to baseline) or 2 (much improved relative to baseline) was analyzed by logistic analysis using the categorical modeling procedure (CATMOD) of the SAS with a model including an effect for treatment.

Orthogonal comparisons were designed to test linear effects of dose. Tests of hypotheses regarding model assumptions were made at the 10% level. All other statistical tests were 2-tailed and performed at the 5% significance level. Because 3 comparisons (each paroxetine dose vs. placebo) are of primary interest, Dunnett's multiple comparison procedure was used to maintain an overall alpha level of p = .05, and the adjusted level of significance was less than .019. The primary efficacy comparison was made by comparing the percentage of responders in each paroxetine treatment group with that in the placebo group as determined by the CGI-I score at endpoint and the mean change from baseline to study endpoint in the LSAS total score; no comparisons between paroxetine dose groups were performed. A post hoc analysis was performed comparing the percentage of patients withdrawing prematurely from each paroxetine dose with the percentage of those taking placebo who withdrew. This analysis employed the chi-square test with an adjusted alpha level of p = .019.

Efficacy and safety analyses were conducted on all patients who received any double-blind medication and for whom at least 1 valid postbaseline efficacy evaluation was obtained. Efficacy data are presented for both the last-observation-carried-forward (LOCF) data set and the completer data set (observed cases). The LOCF data set used the last available on-treatment observation for each patient to estimate missing data points. The primary timepoint of interest was endpoint.

RESULTS

Demographics

Four hundred fifty-one patients were screened for the study, and of these, 67 did not enter, primarily because they did not meet entry criteria at the time of random assignment (Figure 1). A total of 384 patients were randomly assigned to once-daily therapy with paroxetine, 20 mg (N = 97); paroxetine, 40 mg (N = 95); paroxetine, 60 mg (N = 97); or placebo (N = 95) from December 1996 to October 1997. Very few subjects had comorbid major depression (N = 15; 3.9%) or an anxiety disorder (N = 11; 2.9%) other than social anxiety disorder at the time of entry into the study, and few subjects had been treated with an SSRI in the past (N = 26; 6.8%). The demographic characteristics of the 4 treatment groups were well matched with respect to mean age, race, and gender (Table 1). The typical patient was an adult male, white, and relatively young (approximately 37 years old).

The 4 treatment groups were similar with respect to baseline scores on 6 of the 8 primary and secondary efficacy rating scales. The 20-mg paroxetine group exceeded the placebo group on the Social Avoidance and Distress Scale total and the SDS social item scores at baseline. There were no differences between treatment groups with respect to HAM-D total scores, which were low and consistent with the low rate of comorbid depression in this study population (Table 2). Duration of social anxiety disorder, previous treatment, and comorbid psychiatric disorders was comparable among groups (Table 1). The

Figure 1. Patient Disposition

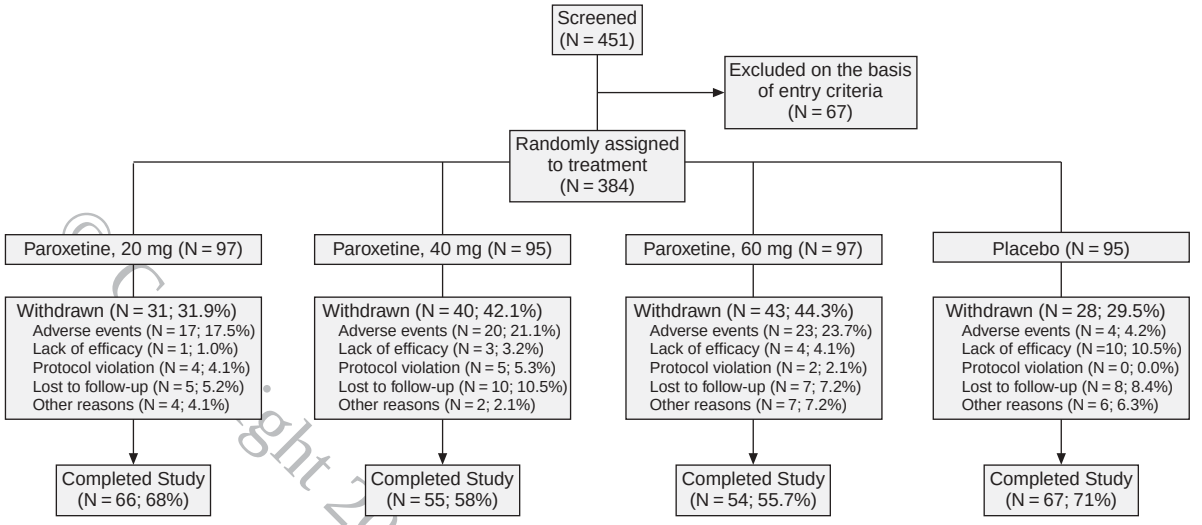


Table 1. Demographic Characteristics[a]

Characteristic	Placebo (N = 95)	Paroxetine 20 mg (N = 97)	Paroxetine 40 mg (N = 95)	Paroxetine 60 mg (N = 97)
Sex				
Male	55 (57.9)	51 (52.6)	63 (66.3)	56 (57.7)
Female	40 (42.1)	46 (47.4)	32 (33.7)	41 (42.3)
Age, y				
Mean (SD)	34.7 (10.4)	39.2 (10.2)	37.9 (9.9)	36.0 (9.7)
Range	18–65	20–70	20–61	20–60
Race				
White	79 (83.2)	79 (81.4)	77 (81.1)	78 (80.4)
African American	10 (10.5)	9 (9.3)	8 (8.4)	8 (8.2)
Asian	1 (1.1)	2 (2.1)	2 (2.1)	2 (2.1)
Other	5 (5.3)	7 (7.2)	8 (8.4)	9 (9.3)
Prior SSRI treatment	5 (5.3)	6 (6.2)	7 (7.4)	8 (8.2)
Psychiatric comorbidity				
Major depression	7 (7.4)	2 (2.1)	1 (1.1)	5 (5.2)
Panic disorder	1 (1.1)	2 (2.1)	2 (2.1)	2 (2.1)
OCD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GAD	2 (2.1)	0 (0.0)	2 (2.1)	0 (0.0)

[a]All values shown as N (%) unless otherwise noted. Abbreviations: GAD = generalized anxiety disorder, OCD = obsessive-compulsive disorder, SSRI = selective serotonin reuptake inhibitor.

mean age at onset of social anxiety symptoms was approximately 14 years.

Approximately 63% of the randomly assigned subjects (242/384) completed the 12-week study. There were no significant differences between the 20-, 40-, or 60-mg paroxetine groups and the placebo group in overall attrition rates. During the first 2 weeks of the study, more patients in the paroxetine treatment groups (20%–23%) withdrew from the study than patients in the placebo group (9%). However, for patients remaining in the study beyond week 2, discontinuation rates were comparable between the paroxetine (8%–23%) and placebo (20%) groups. The primary reason for early discontinuation in any of the paroxetine groups was adverse experiences, ranging from 17.5% for the 20-mg dose to 21.1% for the 40-mg dose to 23.7% for the 60-mg dose, whereas the primary reason for early discontinuation in the placebo group was lack of efficacy (10.5%) (Figure 1). The most common adverse experiences leading to patient withdrawal in the paroxetine groups were asthenia, nausea, insomnia, somnolence, tremor, and abnormal ejaculation. A total of 24 randomly assigned patients (3 placebo, 21 paroxetine) discontinued therapy prior to having any efficacy assessments and were not included in the outcome analyses.

Primary Efficacy Results: LOCF Analyses

Paroxetine, 20 mg, was significantly more effective than placebo on the basis of mean reduction in LSAS total scores ($p < .001$). For patients treated with paroxetine, 20 mg, the mean LSAS total score decreased from 79.8 at baseline to 48.4 at endpoint, compared with a decrease from 73.3 to 58.3 for placebo-treated patients. Mean improvement in the LSAS total score was twice as great for patients treated with paroxetine, 20 mg (–31.4 ± 29.5), compared with placebo-treated patients (–15.0 ± 31.1). The mean improvement in LSAS total score for patients treated with paroxetine, 20 mg, was significantly greater compared with those treated with placebo beginning at week 8 ($p = .002$) and continuing until endpoint ($p < .001$; Figure 2).

Efficacy for paroxetine, 40 and 60 mg, approached statistical significance at study endpoint based on mean LSAS total score compared with placebo. For patients treated with paroxetine, 40 mg, mean LSAS total score decreased from 77.5 at baseline to 53.0 at endpoint. Similarly, mean LSAS total score decreased from 76.9 at baseline to 51.7 at endpoint for patients treated with paroxetine, 60 mg.

Table 2. Primary and Secondary Efficacy Variables at Baseline and at Study Endpoint for Patients With Social Anxiety Disorder Treated With Paroxetine or Placebo[a]

	Paroxetine, 20 mg			Paroxetine, 40 mg			Paroxetine, 60 mg			Placebo	
Measure	Mean (SD)	N	p Value	Mean (SD)	N	p Value	Mean (SD)	N	p Value	Mean (SD)	N
CGI-Severity of Illness											
Baseline	4.4 (0.57)	89	.622	4.4 (0.56)	88	.685	4.3 (0.57)	91	.469	4.4 (0.57)	92
Endpoint	3.3 (1.23)	89	.016[b]	3.3 (1.22)	88	.007[b]	3.3 (1.24)	91	.048	3.8 (1.24)	92
LSAS											
Total											
Baseline	79.8 (22.8)	89	.047	77.5 (22.7)	88	.202	76.9 (23.0)	91	.261	73.3 (23.1)	92
Endpoint	48.4 (29.5)	89	< .001[b]	53.0 (30.3)	88	.039	51.7 (30.0)	91	.024	58.3 (31.1)	92
Fear subscale											
Baseline	41.9 (11.1)	89	.059	40.3 (11.1)	88	.395	40.5 (11.2)	91	.320	38.9 (11.2)	92
Endpoint	26.8 (14.8)	89	.001[b]	27.8 (15.2)	88	.040	27.6 (14.9)	91	.022	31.2 (15.5)	92
Avoidance subscale											
Baseline	37.9 (12.5)	89	.052	37.2 (12.6)	88	.116	36.4 (12.6)	91	.243	34.3 (12.7)	92
Endpoint	21.6 (15.6)	89	< .001	25.2 (15.9)	88	.049	24.1 (15.7)	91	.034	27.1 (16.4)	92
Social Avoidance and Distress Scale											
Baseline	22.6 (5.3)	89	.014[b]	21.2 (5.3)	88	.586	21.7 (5.2)	90	.218	20.8 (5.3)	92
Endpoint	14.8 (8.6)	89	.002[b]	14.7 (8.8)	88	.045	14.3 (8.7)	90	.006[b]	17.0 (9.1)	92
SDS											
Social item											
Baseline	7.1 (2.4)	89	.008[b]	6.5 (2.3)	88	.294	6.6 (2.4)	90	.239	6.2 (2.4)	91
Endpoint	4.4 (2.9)	89	.003[b]	4.4 (3.0)	88	.109	4.2 (2.9)	90	.018[b]	4.9 (3.1)	91
Work item											
Baseline	4.7 (2.4)	86	.354	4.4 (2.4)	87	.893	4.5 (2.5)	90	.672	4.4 (2.5)	91
Endpoint	3.2 (2.8)	86	.059	3.1 (2.9)	87	.150	3.2 (2.8)	90	.161	3.7 (3.0)	91
Family item											
Baseline	3.0 (2.5)	89	.450	2.8 (2.6)	88	.813	2.8 (2.6)	90	.779	2.7 (2.6)	91
Endpoint	2.0 (2.5)	89	.209	2.0 (2.5)	88	.464	2.0 (2.5)	90	.370	2.2 (2.6)	91
HAM-D											
Baseline	6.0 (3.52)	83	…	5.5 (3.65)	81	…	5.0 (3.39)	84	…	5.7 (3.51)	83
Endpoint	4.8 (4.64)	83	…	4.7 (4.22)	81	…	5.3 (4.11)	84	…	5.3 (4.65)	83

[a]The last-observation-carried-forward data set is presented. p Values are from analysis of mean change from baseline compared with placebo. Ns for each drug group vary slightly among the measures due to missing data. Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, LSAS = Liebowitz Social Anxiety Scale, SDS = Sheehan Disability Scale.
[b]Significant difference from placebo using Dunnett's test to maintain overall $\alpha = .05$ ($p < .019$).

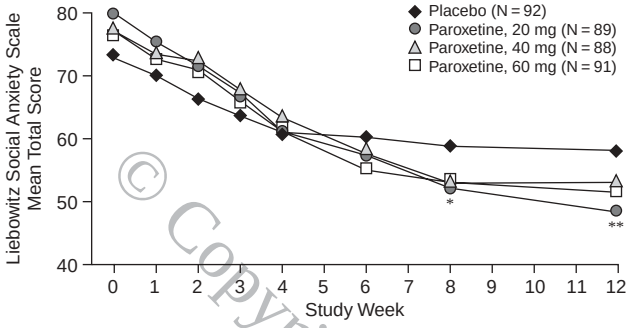
On the basis of a CGI-I score of either 1 (very much improved relative to baseline) or 2 (much improved relative to baseline) at endpoint, the percentage of responders in the 40-mg paroxetine group (46.6%) was significantly greater compared with the placebo group (28.3%) (p = .012; Figure 3). Paroxetine, 40 mg, was also superior to placebo in percentage of responders in the LOCF sample after 6 weeks of treatment (p = .016; see Figure 3). At endpoint, efficacy was suggested for paroxetine, 20 and 60 mg, compared with placebo, although the difference did not reach significance after adjustment for multiple comparisons. In the 20- and 60-mg paroxetine dosage groups, 44.9% and 42.9% of patients, respectively, were rated as responders on the basis of CGI-I score at endpoint. The incidence of responders who were "very much improved" in each of the paroxetine treatment groups (20 mg, 19.1%; 40 mg, 20.5%; 60 mg, 22.0%) was at least twice that in the placebo group (7.6%).

Primary Efficacy Results: Completer Analyses

On the basis of mean reduction in LSAS total scores at week 12, paroxetine, 20 mg (N = 66; p = .006) and 40 mg (N = 55; p = .004), were significantly more effective than placebo. In the 20-mg group, mean baseline LSAS total scores were reduced from 79.8 (N = 87) to 47.3 (N = 66) at week 12. Similarly, mean scores in the 40-mg group decreased from 77.5 (N = 88) at baseline to 43.9 (N = 55) at week 12. Mean scores in the 60-mg group decreased from 76.9 (N = 91) to 47.3 (N = 54) at week 12, which was not a significant reduction compared with that for the placebo group (p = .034). Mean scores in the placebo group decreased from 73.3 (N = 92) at baseline to 55.5 (N = 67) at week 12. Statistically significant differences between the active regimens and placebo in the mean improvement in LSAS total score began at week 6 and continued through week 12.

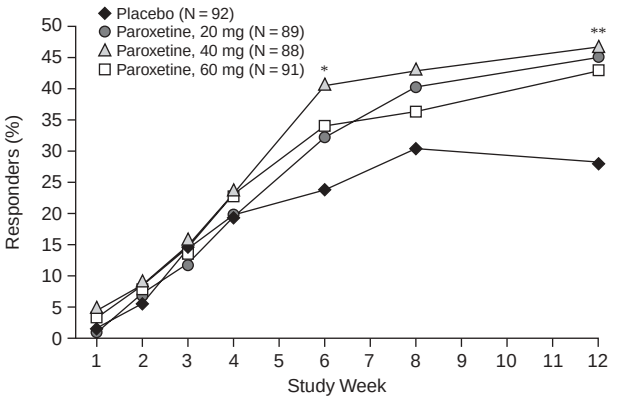
On the basis of CGI-I scores of either 1 or 2 at week 12, differences in the percentage of responders in the 20-mg (57.6%; p = .004), 40-mg (63.6%; p < .001), and 60-mg (63.0%; p < .001) paroxetine groups compared with the placebo group (31.9%) were statistically significant. Similar to the LOCF analyses, the incidence of responders who were "very much improved" in each of the paroxetine treatment groups (20 mg, 24.2%; 40 mg, 30.9%; 60 mg, 35.2%) was at least twice that observed in the placebo group (10.3%).

Figure 2. Liebowitz Social Anxiety Scale Mean Total Score for Patients With Social Anxiety Disorder Treated With Paroxetine or Placebo From the LOCF Data Set at Baseline and Weekly Visits Through Endpoint[a]



[a]p Values are from analysis of mean change from baseline.
Abbreviation: LOCF = last observation carried forward.
*p = .002 vs. placebo.
**p < .001 vs. placebo.

Figure 3. Percentage of Patients With Social Anxiety Disorder Treated With Paroxetine or Placebo From the LOCF Data Set Classified as Therapeutic Responders Based on CGI-Global Improvement Item Score of 1 or 2 at Endpoint[a]



[a]Abbreviations: CGI = Clinical Global Impressions scale, LOCF = last observation carried forward.
*p = .016 vs. placebo.
**p = .012 vs. placebo.

Secondary Efficacy Variable Analyses

At endpoint in the LOCF analyses, paroxetine, 20 mg, was superior to placebo on 5 of the secondary efficacy variables; paroxetine, 40 mg, was superior to placebo on 1 variable; and paroxetine, 60 mg, was superior to placebo on 2 variables (Table 2). At endpoint, paroxetine, 20 mg (p = .016) and 40 mg (p = .007), were more efficacious as assessed by CGI-S score compared with the placebo group. Twice as many patients in the paroxetine treatment groups (20 mg, 11.2%; 40 mg, 8.0%; 60 mg, 6.6%) had a CGI-S score of 1, i.e., not at all ill, compared with patients in the placebo group (3.3%) at endpoint. Similarly, approximately twice as many paroxetine-treated patients (20 mg, 10.1%; 40 mg, 14.8%; 60 mg, 14.3%) had a CGI-S score of 2, i.e., borderline mentally ill, compared with placebo-treated patients (7.6%) at endpoint.

Patients treated with paroxetine, 20 mg, experienced significant improvement compared with the placebo group on the LSAS fear and avoidance subscales at endpoint (p = .001 and p < .001, respectively). Those treated with paroxetine, 20 mg (p = .002) and 60 mg (p = .006), also had greater improvement compared with placebo-treated patients on the Social Avoidance and Distress Scale at endpoint. Patients treated with the 20-mg (p = .003) and 60-mg (p = .018) paroxetine doses had significantly better response on the SDS social item than placebo-treated patients. In terms of the SDS work and family item scores, some improvements were observed in the paroxetine groups, but differences were not statistically significant. The mean change from baseline in the HAM-D score was negligible and similar for all treatment groups.

Safety Results

All randomly assigned patients who received study medication were included in the intent-to-treat population analysis for safety. There were no differences in the overall incidence of reported adverse experiences between the 20-mg (92%), 40-mg (91%), and 60-mg (88%) paroxetine groups and the placebo group (83%). No unexpected or unusual adverse experiences were attributed to paroxetine. The most commonly reported (≥ 10% in any paroxetine group and incidence at least twice that for placebo) adverse experiences are shown in Table 3. Although there was not usually a linear dose–adverse event relationship, such relationships were observed for delayed ejaculation and constipation.

Table 3. Most Commonly Reported Adverse Experiences [N (%)] (≥ 10% in any paroxetine group and incidence at least twice that for placebo) in Patients With Social Anxiety Disorder Treated With Paroxetine or Placebo

Adverse Experience	Paroxetine 20 mg (N = 97)	Paroxetine 40 mg (N = 95)	Paroxetine 60 mg (N = 97)	Placebo (N = 95)
Delayed ejaculation[a]	14 (27.5)	22 (34.9)	30 (53.6)	2 (3.6)
Insomnia	28 (28.9)	22 (23.2)	34 (35.1)	15 (15.8)
Somnolence	32 (33.0)	24 (25.3)	30 (30.9)	5 (5.3)
Asthenia	25 (25.8)	31 (32.6)	21 (21.6)	8 (8.4)
Nausea	30 (30.9)	26 (27.4)	23 (23.7)	7 (7.4)
Dizziness	27 (27.8)	23 (24.2)	22 (22.7)	6 (6.3)
Decreased libido	16 (16.5)	17 (17.9)	11 (11.3)	2 (2.1)
Female genital disorders[a]	7 (15.2)	2 (6.3)	3 (7.3)	0 (0.0)
Nervousness	14 (14.4)	10 (10.5)	14 (14.4)	6 (6.3)
Dry mouth	14 (14.4)	10 (10.5)	10 (10.3)	5 (5.3)
Yawn	7 (7.2)	3 (3.2)	14 (14.4)	0 (0.0)
Tremor	4 (4.1)	13 (13.7)	13 (13.4)	1 (1.1)
Sweating	8 (8.2)	12 (12.6)	11 (11.3)	0 (0.0)
Constipation	7 (7.2)	8 (8.4)	11 (11.3)	3 (3.2)
Impotence[a]	2 (3.9)	7 (11.1)	4 (7.1)	1 (1.8)
Decreased appetite	10 (10.3)	6 (6.3)	9 (9.3)	1 (1.1)

[a]Percentages corrected for gender.

DISCUSSION

This study confirms previous observations that paroxetine is effective for the treatment of generalized social anxiety disorder.[6,7,9,10,13] In terms of primary outcome measures, at endpoint for the LOCF analyses, patients treated with paroxetine, 20 mg, experienced a clinically meaningful response based on a decrease in the mean LSAS total score of more than 30 points, a decrease that was statistically superior compared with placebo. At the conclusion of the study in the LOCF data set, 46.6% of 88 patients who received paroxetine, 40 mg, achieved therapeutic response with a CGI-I score of either 1 or 2 compared with 28.3% of 92 placebo-treated patients ($p = .012$).

Treatment with paroxetine also had favorable effects on many of the secondary efficacy parameters, such as functional impairment, social anxiety, avoidance of social interactions, social disability, and overall clinical condition. This improvement was demonstrated on both clinician- and patient-rated measures. Patients treated with paroxetine, 20 mg, showed significant improvement on 5 of the 7 secondary efficacy variables, i.e., CGI-S score, Social Avoidance and Distress Scale score, LSAS fear subscale score, LSAS avoidance subscale score, and SDS social item score, compared with placebo-treated patients. The CGI-S scores indicated that, on average, patients treated with paroxetine were moderately to markedly ill at baseline and only mildly to moderately ill at endpoint. Among patients who completed the 12-week study, approximately twice as many in each paroxetine treatment group were rated as either not at all ill or borderline ill (1 or 2) compared with the placebo group. Patients treated with paroxetine, 20 and 60 mg, also noted significantly decreased social impairment based on reductions in the SDS social item score. Patients with social anxiety disorder suffer from significant educational, occupational, and social impairment.[31–37] Given the disability associated with this disorder, it is notable that the paroxetine-treated patients in our study experienced marked improvement in functional disability.

The adverse-experience profile of paroxetine observed in this study was similar to that in previous studies of paroxetine and other SSRIs.[7,10,37] The percentage of patients reporting at least 1 adverse experience was comparable across all treatment groups, and no serious adverse experiences were attributed to paroxetine treatment. A greater percentage of patients withdrew because of adverse experiences in the paroxetine groups (17.5%–23.7%) compared with the placebo group (4.2%). However, compared with paroxetine-treated patients (1.0%–4.7%), more placebo-treated patients (10.5%) withdrew because of lack of efficacy. Not surprisingly, in the paroxetine treatment groups, the lowest incidence of withdrawal associated with adverse experiences was in the 20-mg paroxetine group. These findings suggest that paroxetine, 20 mg, is well tolerated and should be the initial target dose in the treatment of social anxiety disorder.

In our experience, fixed-dose studies often do not achieve response rates as high as those observed in flexible-dose studies in which individual doses are titrated to optimal response. We observed that the overall response rate to paroxetine, between 42.9% and 46.6%, was lower than the response rates of 55%[11] and 65.7%[8] noted for patients treated with paroxetine, 20 to 50 mg, in 2 multicenter, double-blind, flexible-dose, randomized studies. Because placebo response rates appear equivalent across the studies, it can be speculated that the flexible-dose regimens achieved better results than the fixed-dose regimen in patients with generalized social anxiety disorder. In our study, patients who did not respond or responded only partially to lower doses may have benefited from a gradual increase in dose. However, it can be argued that dosage escalation should be reserved until after patients with generalized social anxiety disorder have received paroxetine, 20 mg, for 8 to 12 weeks of therapy. In support of this position is the gradual increase in percentage of responders through week 12 in the 20-mg paroxetine dosage group, suggesting that patients not deemed responders earlier in the study were more likely to become responders the longer they received the 20-mg dose.

There are arguments for earlier dose escalation in clinical practice: (1) only slight differences in adverse effects were observed between the 20-mg group and the higher dosage groups in this study, and (2) the flexible-dose studies[8,11] suggest that a higher percentage of patients will become responders during an 8-week period if dosage is increased earlier in the course of treatment. If a patient is interested in receiving the lowest dose possible, it is reasonable to give an 8- to 12-week trial of paroxetine, 20 mg, before increasing the dosage. However, if a patient is interested in maximizing response, it may be prudent to raise the dose of paroxetine above 20 mg when there has been little or no benefit after 4 weeks of treatment. Further analyses of this data set may yield baseline and early outcome guidelines regarding which patients will respond to paroxetine, 20 mg, during an 8- to 12-week trial.

Another limitation to this study was the early dropout rate in the higher paroxetine dosage groups. Although 64% of randomly assigned subjects completed the study and overall attrition rates were comparable between treatment groups, 20% to 23% of patients who received paroxetine withdrew from the study during the first 2 weeks. Although the incidence of premature discontinuation in this study is comparable to the 25%[7] and 34%[10] withdrawal rates observed in the paroxetine flexible-dose studies, the rates of attrition in the higher-dose groups of this study were elevated. The primary reason for early discontinuation in the paroxetine groups was adverse experiences. Rapid titration to the 40-mg and 60-mg dosages was most likely responsible for the initially higher

incidence of adverse experiences. Clinical experience suggests that a more gradual titration to the higher doses may have decreased the early dropout rate and improved our ability to assess efficacy in the higher-dosage treatment groups.

Several other issues need to be considered in relation to this study. First, the inclusion and exclusion criteria used in the study most likely produced a sample with a lower incidence of comorbidity compared with patients in clinical practice. Thus, how the findings of the study generalize to routine clinical care remains to be determined. Second, the superiority of the 20-mg paroxetine group on LSAS total score and the 40-mg paroxetine group on CGI-I score compared with the placebo group in the LOCF sample could be construed to suggest some dissociation of outcome in the 2 dosage groups. However, it appears that this is an artifact of the stringent p value of .019 that was employed. With a conventional p value of .05, these issues disappear. Nevertheless, we felt that the more stringent p value was justified because of the multiple comparisons inherent in a study that compares 3 fixed doses with placebo.

In conclusion, this study confirms the efficacy and safety of paroxetine in the acute treatment of the generalized subtype of social anxiety disorder. Treatment with paroxetine, 20 mg, leads to significant improvement in social anxiety, social interaction, social disability, and overall clinical condition. When data from all the trials of paroxetine in social anxiety disorder are considered, the evidence suggests that patients who do not respond or respond only partially to paroxetine, 20 mg/day, may benefit from gradual dosage increases within the recommended dosing range of 20 to 50 mg/day. However, additional studies are needed to determine the optimal duration of therapy and the effects of concomitant psychotherapy. Furthermore, systematic studies evaluating adjunctive treatments for partial responders and alternative treatments for nonresponders should be undertaken.

Drug names: cimetidine (Tagamet and others), clonazepam (Klonopin and others), fluoxetine (Prozac and others), gabapentin (Neurontin), paroxetine (Paxil), phenytoin (Dilantin), sumatriptan (Imitrex), warfarin (Coumadin).

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