Controlled-Release Paroxetine in the Treatment of Patients With Social Anxiety Disorder

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Background: This double-blind, placebo-controlled, flexible-dose study was conducted to investigate the efficacy and tolerability of the controlled-release (CR) formulation of paroxetine in adults with social anxiety disorder.

Method: Outpatients with a primary diagnosis of social anxiety disorder according to DSM-IV criteria entered a 1-week, single-blind, placebo run-in period. Eligible patients were randomly assigned to receive paroxetine CR (flexible dose of 12.5–37.5 mg/day) or placebo for 12 weeks of treatment. The primary efficacy measures were the change from baseline in Liebowitz Social Anxiety Scale (LSAS) score and the proportion of responders based on Clinical Global Impressions (CGI)-Global Improvement scale score. Data were gathered from September 2001 to July 2002.

Results: The intent-to-treat population consisted of 186 patients randomly assigned to paroxetine CR and 184 patients randomly assigned to placebo. Statistically significant differences in favor of paroxetine CR compared with placebo were observed in the change from baseline to week 12 last-observation-carried-forward (LOCF) dataset in LSAS total score (difference = –13.33, 95% confidence interval [CI] = –18.25 to –8.41, $p < .001$). In the CGI-Global Improvement responder analysis, 57.0% of patients treated with paroxetine CR achieved response (very much improved or much improved), compared with 30.4% of patients treated with placebo at week 12 LOCF (odds ratio = 3.12, 95% CI = 2.01 to 4.83, $p < .001$). Dropout rates due to adverse events were low and comparable in both treatment groups.

Conclusion: Paroxetine CR effectively treated the symptoms associated with social anxiety disorder and was well tolerated, with few patients stopping treatment due to adverse events. This favorable tolerability profile may enable more patients to experience the benefits of effective therapy.

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Social anxiety disorder has been recognized as an Axis I anxiety disorder by the American Psychiatric Association since its introduction as social phobia in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*. Social anxiety disorder is a chronic illness that is characterized by an overwhelming fear of situations in which individuals are exposed to unfamiliar people or to possible scrutiny by others. Those with the disorder fear that they will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing.[1] While many people experience some degree of anxiety in these situations, patients with social anxiety disorder experience marked, persistent, and disabling anxiety that stems from their perception of being scrutinized by strangers, friends, colleagues, or even family members. The anxiety associated with being critically evaluated or humiliated can impair normal function in many facets of life.[1] Specifically, patients with social anxiety disorder have a tendency to avoid social relationships (e.g., friendships, dating, marriage), drop out of school, reject work promotions, and become demoralized.

Epidemiologic surveys conducted in the United States suggest that social anxiety disorder is among the most prevalent of the anxiety disorders in the general population, with a lifetime prevalence of 14%.[2] In addition, social anxiety disorder is the third most common psychiatric disorder in the general population after major depression and alcohol abuse.[3] Comorbidity of other psychiatric disorders with social anxiety disorder is extremely common, with an average of 80% of patients with social anxiety disorder meeting the diagnostic criteria for at least 1 other lifetime disorder.[4] The onset of social anxiety disorder tends to precede that of other psychiatric disorders,[5]

which suggests that social anxiety disorder may precipitate the onset of these latter conditions.[6] Despite the high prevalence of this debilitating condition, social anxiety disorder is believed to be underdiagnosed and undertreated.[2,7,8]

Over the past 2 decades since the introduction of social anxiety disorder in the diagnostic nomenclature, significant gains have been made in the knowledge about effective pharmacologic and psychotherapeutic treatments. Several clinical trials have demonstrated that benzodiazepines and antidepressants, including monoamine oxidase inhibitors, serotonin-norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs), are effective in the treatment of social anxiety disorder.[9–16] The SSRIs are emerging as first-line agents for social anxiety disorder on the basis of their proven efficacy, safety, and tolerability.[2,17]

All SSRIs, however, are associated with a cluster of adverse events, which commonly occur within the first few weeks of therapy and are thought to be serotonin mediated (e.g., nausea, agitation, somnolence, insomnia, sexual dysfunction).[18–20] Early, treatment-emergent adverse events are leading reasons for early discontinuation of SSRI therapy and may therefore jeopardize clinical outcomes.[18,19,21] Previous trials with the controlled-release (CR) formulation of paroxetine in depressed patients suggested that this formulation was associated with lower rates of treatment discontinuation due to adverse events.[22,23]

An extensive database exists for immediate-release (IR) paroxetine, which is effective and well tolerated for short- and long-term treatment of social anxiety disorder.[13–16] This double-blind, placebo-controlled, multicenter study was conducted to investigate the efficacy and tolerability of paroxetine CR in the treatment of adults with social anxiety disorder.

METHOD

We conducted a randomized, double-blind, placebo-controlled, flexible-dose study of outpatients with social anxiety disorder. Investigators at 35 academic centers and private clinics in Europe and South Africa randomized patients in the study. Data were gathered from September 2001 to July 2002.

Study Design

After an initial screening visit, outpatients with a primary diagnosis of social anxiety disorder entered a 1-week, single-blind, placebo run-in period. Eligible patients were then randomly assigned at baseline to receive paroxetine CR (paroxetine hydrochloride) (flexible dose range of 12.5–37.5 mg/day) or placebo once daily in a 1:1 ratio for a treatment duration of 12 weeks.

All patients randomly assigned to paroxetine CR began therapy at 12.5 mg and remained at this daily dose for the first 2 weeks of treatment. Dose elevation was permitted in 12.5-mg/day increments no more frequently than every 7 days to a maximum of 37.5 mg/day. One dose reduction was permitted only when made necessary by the development of an adverse event. Patients completing the study (or withdrawing prematurely) at doses of 37.5 mg/day received 1 week of taper phase medication at a daily dose of 25 mg before stopping treatment. Patients randomly assigned to placebo medication received placebo throughout the study and were dosed in an identical manner to patients randomly assigned to paroxetine CR. All patients were instructed to take 1 capsule each morning irrespective of treatment allocation. The concomitant use of other psychotropic medications was prohibited, with the exception of chloral betaine (up to 828 mg) or chloral hydrate (up to 1000 mg) for insomnia.

Study Population

The Mini-International Neuropsychiatric Interview (Version 5.0; MINI)[24] was used to screen for social anxiety disorder according to DSM-IV criteria (300.23). Outpatients (≥ 18 years of age) who met the criteria as their primary diagnosis were enrolled. Patients older than 65 years were included if they did not have renal or hepatic impairment.

Patients with a Clinical Global Impressions (CGI)-Global Improvement[25] score of 1 or 2 at baseline (following the placebo run-in period) or a score on the 17-item Hamilton Rating Scale for Depression (HAM-D)[26] of ≥ 15 at baseline were excluded. Patients evaluated with the MINI who met DSM-IV criteria for Axis I disorders such as major depressive disorder, obsessive-compulsive disorder, or panic disorder as a primary diagnosis currently or within 6 months prior to the screening visit were excluded. Also excluded were patients with substance abuse within 3 months of screening or substance dependence within 6 months of screening and patients considered a current homicidal or suicidal risk. Patients with a history of seizures (except febrile seizures), schizophrenia, or bipolar disorder or a current diagnosis of body dysmorphic disorder or a serious medical illness were excluded. In addition, patients who had been treated with psychotropic medications or antidepressants within 14 days of screening, monoamine oxidase inhibitors or fluoxetine within 4 weeks of screening, depot neuroleptics within 12 weeks of screening, or electroconvulsive therapy within the past 3 months were excluded. Patients requiring concomitant therapy with β-adrenergic blockers, monoamine oxidase inhibitors, benzodiazepines, or other psychoactive medications were excluded. Women who were pregnant, lactating, or of childbearing potential and not practicing a clinically accepted method of contraception were ineligible.

The study protocol and informed consent procedure were approved by the institutional review board or ethics

committee at all centers. Written informed consent was obtained from all patients prior to study participation.

Efficacy Assessments

Parameters for evaluation of efficacy were the clinician-administered Liebowitz Social Anxiety Scale (LSAS),[27] CGI-Global Improvement, and CGI-Severity of Illness (CGI-S)[25] and the patient-rated Social Avoidance and Distress Scale[28] and Sheehan Disability Scale (SDS).[29] After the initial screening visit, these efficacy assessments were administered at baseline and weeks 1, 2, 3, 4, 6, 8, and 12 (or at the time of early withdrawal from the study). In addition, the 17-item HAM-D was administered by a clinician at baseline and at week 12 (or at the time of early withdrawal).

Safety Assessments

Safety was assessed by monitoring adverse events and vital signs at all postbaseline visits. Reports of adverse events were elicited by asking the patient non-leading questions. Physical examination (including weight), laboratory evaluation, and a pregnancy test were conducted at the screening visit and at week 12 (or at the time of early withdrawal). A follow-up visit was conducted to assess safety 14 days after the last dose of study medication (including taper medication). Patients with an ongoing adverse event or unresolved abnormal laboratory results at the 14-day follow-up visit were also required to attend a further visit to assess safety 28 days after the last dose of study medication (including taper medication).

Statistical Evaluations

All patients who were randomized, received 1 dose of study medication, and had 1 postbaseline assessment were included in the intent-to-treat (ITT) population. There were 2 primary efficacy variables: the mean change from baseline to week 12 last-observation-carried-forward (LOCF) endpoint in the LSAS total score and the proportion of responders at week 12 LOCF endpoint based on CGI-Global Improvement score, with response defined as a score of 1 (very much improved) or 2 (much improved). Secondary efficacy measures included the change from baseline in LSAS fear or anxiety and avoidance subscale scores, CGI-S score, Social Avoidance and Distress Scale total score, and scores on individual family, work, and social life items of the SDS. Statistical inferences concerning the efficacy of paroxetine CR were made using the week 12 LOCF dataset, in which the last available on-therapy observation for each patient was carried forward to all successive timepoints for the ITT population. Statistical testing was performed on the week 12 LOCF and week 12 observed cases (OC) datasets only. Other retrospectively defined analyses included the change from baseline in SDS total score, statistical testing of weekly LSAS and CGI-Global Improvement assessments, and measures of remission as assessed by a CGI-Global Improvement score of 1 (very much improved), a ≥ 70% decrease in LSAS total score from baseline, or an SDS total score < 5. No multiple testing adjustments for these additional analyses were performed.

All hypothesis tests were 2-sided. The effect of interactions was assessed at the 10% level of significance. All other statistical tests were performed at a 5% level of significance. Continuous efficacy variables were analyzed by parametric analysis of covariance techniques with results presented as point estimates, 95% confidence intervals (CIs), and associated p values for the adjusted mean differences between treatments. Binary data were analyzed using logistic regression techniques with results presented as odds ratios (ORs), 95% CIs around the odds ratios, and associated p values. Estimates of treatment difference for all continuous and binary efficacy variables were adjusted for treatment group, center, and appropriate baseline score (baseline score could not be included in the analysis for CGI-Global Improvement).

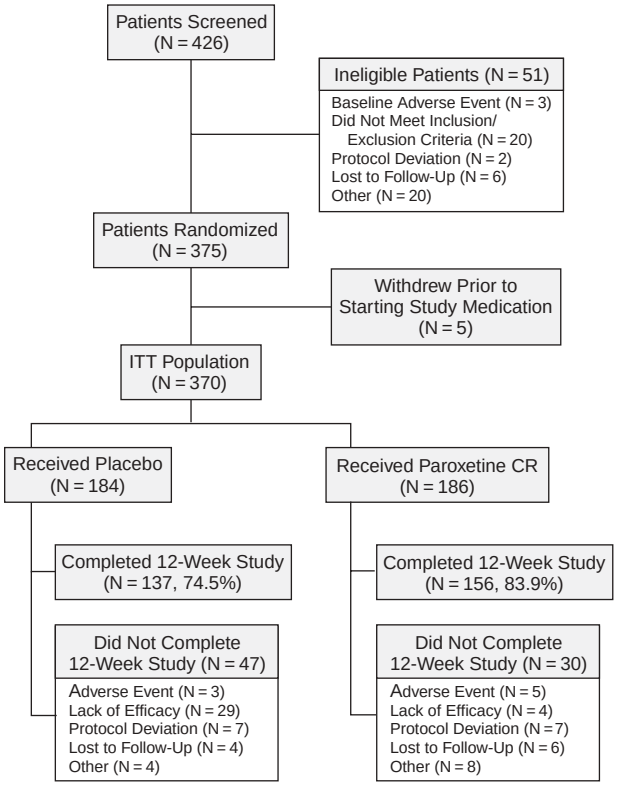
RESULTS

Study Population

A total of 426 patients were screened for study participation; however, 51 patients did not meet the inclusion/exclusion criteria (Figure 1). Of the 375 patients randomly assigned to double-blind study medication, 5 patients, 3 in the paroxetine CR treatment group and 2 in the placebo treatment group, withdrew from the study before starting study medication and were therefore not included in the ITT population. The ITT population consisted of 186 patients randomly assigned to paroxetine CR and 184 patients randomly assigned to placebo. Demographic characteristics of the ITT population are described in Table 1. The treatment groups were generally comparable with respect to age, gender, and race. Investigators reported minimal comorbid psychiatric disorders, and similar percentages of patients used SSRIs prior to study entry. Baseline scores on all efficacy scales were similar between the 2 treatment groups (Table 2). Clinicians rated the patient population as moderately severely ill as represented by mean baseline LSAS scores of approximately 78 and a mean CGI-S score of 4.5 (moderately to markedly ill) for paroxetine CR– and placebo-treated patients. As one would expect in a social anxiety disorder population, functional impairment, measured by the SDS, was greater in the work and social life items. Comorbid depressive symptoms were low as measured by a mean HAM-D total score of 4 in both treatment groups.

A total of 156 patients (83.9%) in the paroxetine CR group and 137 patients (74.5%) in the placebo group completed the 12-week study (Table 3). Dropout rates due to adverse events were low and comparable in the 2 treatment groups (2.7% in the paroxetine CR group and 1.6%

Figure 1. Study Flow



Abbreviations: CR = controlled-release, ITT = intent-to-treat.

in the placebo group). A greater proportion of patients in the placebo group withdrew from the study prematurely due to lack of efficacy (2.2% in the paroxetine CR group and 15.8% in the placebo group).

The mean daily dose of paroxetine CR at study endpoint was 32.3 mg/day. At endpoint, 69% of patients in the paroxetine CR group were taking 37.5 mg/day, 20% were taking 25 mg/day, and 11% remained at the starting dose of 12.5 mg/day.

Efficacy Assessments

Treatment with paroxetine CR resulted in statistically significant and clinically meaningful differences from placebo in both primary efficacy variables. Statistically significant differences were demonstrated in favor of paroxetine CR in the change from baseline to week 12 LOCF in the LSAS total score (adjusted mean difference = –13.33, 95% CI = –18.25 to –8.41, $p < .001$) (Figure 2). The significant difference in LSAS total score in favor of paroxetine CR was maintained from week 6 to the end of the 12-week study. Mean LSAS total scores decreased from 78.3 at the baseline assessment to 47.1 at week 12 LOCF endpoint for patients treated with paroxetine CR. For placebo-treated patients, LSAS total scores decreased from 78.6 at baseline to 60.5 at week 12 LOCF endpoint. The proportion of patients achieving remission, as defined by a ≥ 70% decrease in LSAS total score from baseline to study endpoint, was significantly greater in the paroxetine CR group compared with the placebo group (24.3% [45/185] vs. 8.2% [15/184]; OR = 3.63, 95% CI = 1.92 to 6.85, $p < .001$).

In the CGI-Global Improvement responder analysis, 57.0% (106/186) of patients treated with paroxetine CR

Table 1. Demographic Characteristics of Patients With Social Anxiety Disorder (ITT population)[a]

Characteristic	Paroxetine CR (N = 186)	Placebo (N = 184)
Gender, female	53	47
Age, mean (SD), y	38.7 (10.5)	39.0 (11.5)
Race		
White	93.5	95.1
Black	1.6	1.6
Asian	1.1	0
Other	3.8	3.3
Prior SSRI treatment	10	9
Psychiatric comorbidities[b]		
Major depressive disorder	11	10
Dysthymia	1	4
Panic disorder	3	5

[a]Values shown as percentages unless otherwise specified.
[b]The 3 most common psychiatric conditions reported.
Abbreviations: CR = controlled-release, ITT = intent-to-treat, SSRI = selective serotonin reuptake inhibitor.

Table 2. Baseline Clinical Characteristics of Patients With Social Anxiety Disorder (ITT population)

	Paroxetine CR			Placebo		
Instrument	N	Mean	SD	N	Mean	SD
LSAS total	185	78.3	24.7	184	78.6	23.4
CGI-S	186	4.5	0.8	184	4.5	0.8
Social Avoidance and Distress Scale total	186	21.6	5.7	180	21.8	5.3
SDS						
Work	184	5.6	2.8	180	5.7	2.7
Social life	186	6.6	2.1	182	6.6	2.2
Family life	186	3.4	2.8	182	3.4	2.7
HAM-D total	186	4.1	3.2	183	4.4	3.4

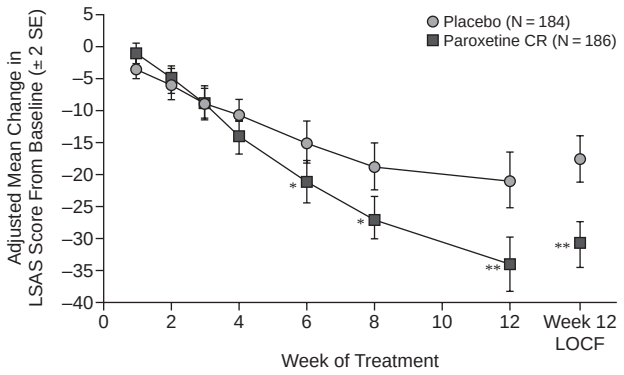
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, CR = controlled-release, HAM-D = Hamilton Rating Scale for Depression, ITT = intent-to-treat, LSAS = Liebowitz Social Anxiety Scale, SDS = Sheehan Disability Scale.

Table 3. Reasons for Study Conclusion in Patients With Social Anxiety Disorder (ITT population)

	Paroxetine CR (N = 186)		Placebo (N = 184)	
Reason	N	%	N	%
Completed study	156	83.9	137	74.5
Dropped out	30	16.1	47	25.5
Adverse event	5	2.7	3	1.6
Lack of efficacy	4	2.2	29	15.8
Protocol deviation	7	3.8	7	3.8
Lost to follow-up	6	3.2	4	2.2
Other	8	4.3	4	2.2

Abbreviations: CR = controlled-release, ITT = intent-to-treat.

Figure 2. Change From Baseline in LSAS Total Score by Week (ITT population)[a]



[a]Represented as adjusted least square means.
*p < .05.
**p < .001.
Abbreviations: CR = controlled-release, ITT = intent-to-treat, LOCF = last observation carried forward, LSAS = Liebowitz Social Anxiety Scale.

achieved response, compared with 30.4% (56/184) of patients treated with placebo at week 12 LOCF (OR = 3.12, 95% CI = 2.01 to 4.83, p < .001) (Figure 3). Statistical significance for the odds of being a CGI-Global Improvement responder for patients in the paroxetine CR group was achieved at week 6 and continued to the end of the 12-week study. In addition, the proportion of patients who were rated as "very much improved" (CGI remission) in the paroxetine CR group (28.0% [52/186] vs. 12.0% [22/184]) was more than twice that in the placebo group (OR = 2.95, 95% CI = 1.67 to 5.20, p < .001).

Paroxetine CR was superior to placebo on all clinician-rated and patient-rated secondary measures of efficacy at week 12 LOCF endpoint (Table 4). Significant improvements for paroxetine CR–treated patients compared with placebo-treated patients were noted on the LSAS fear or anxiety and avoidance subscales (p < .001 for both subscales) and the patient-rated Social Avoidance and Distress Scale (p < .001). Paroxetine CR–treated patients also experienced a statistically significant improvement in overall severity as measured by CGI-S scores (p < .001). Three times as many patients in the paroxetine CR treatment group (13.4% [25/186]) had a CGI-S score of 1 (normal, not at all ill) compared with the placebo treatment group (4.3% [8/184]) at week 12 LOCF.

In a measure of functional impairment, a statistically significant difference was demonstrated in favor of paroxetine CR versus placebo for the week 12 LOCF endpoint for the SDS total score (adjusted mean difference = –2.78, 95% CI = –3.89 to –1.67, p < .001) (Figure 4). Moreover, significant differences were demonstrated in all 3 domains of the SDS (Table 4, p < .001).

Of the 183 paroxetine-treated and 180 placebo-treated patients with a postbaseline SDS assessment, the percentage of patients achieving SDS total scores < 5 at endpoint was significantly greater for patients who received paroxetine CR compared with those who received placebo (32.8% [60/183] and 15.0% [27/180], respectively; OR = 3.51, 95% CI = 1.94 to 6.35, p < .001).

At study endpoint, mean (SD) HAM-D total scores were 3.3 (3.5) for paroxetine CR-treated patients and 4.3 (4.2) for placebo-treated patients, suggesting that the majority of patients had no clinically relevant depressive symptomatology.

Safety Assessments

Treatment-emergent adverse events associated with the use of paroxetine CR (incidence of ≥ 5% in the paroxetine CR treatment group and twice the incidence for placebo) are noted in Table 5. Most treatment-emergent adverse events reported during the 12-week study were mild to moderate in intensity with the incidence greater during the first 14 days of treatment. Of the 5 patients in the paroxetine CR group who stopped treatment due to adverse events, headache, nausea, and diarrhea were the only events reported by more than 1 patient. Frequently reported adverse events reported during the taper phase were abnormal ejaculation, anxiety, headache, and insomnia in paroxetine CR–treated patients and dizziness for placebo-treated patients. Dizziness, paresthesia, vertigo, and additional symptoms reported by investigators as associated with stopping study medication were the adverse events frequently reported during the follow-up phase for patients in the paroxetine CR treatment group. In the majority of patients, the events reported in the taper and follow-up phases were mild to moderate in intensity and required no action or corrective therapy.

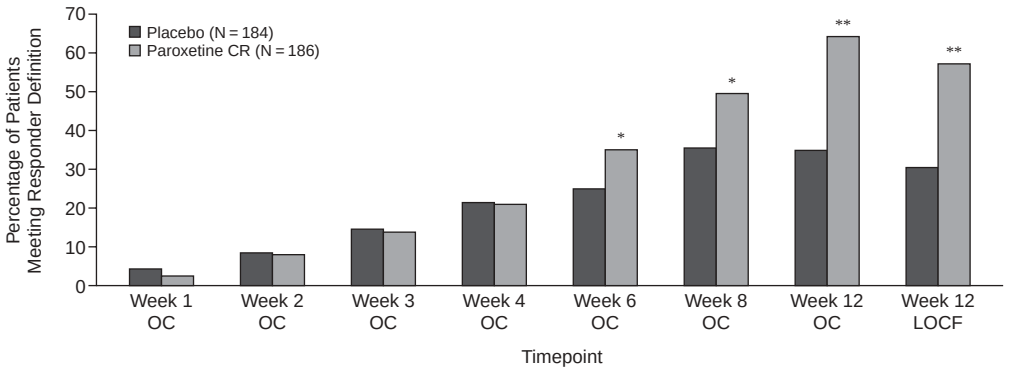
Serious adverse events were reported during the treatment phase in 2 patients (1.1%) in the paroxetine CR group (broken leg and accidental overdose) and 2 patients (1.1%) in the placebo group (depression and meningitis). During the taper and follow-up phases, serious adverse events were reported for 3 patients (1.6%) in the paroxetine CR group (dizziness and symptoms reported by investigators as associated with stopping study medication) and no patients in the placebo group.

There were no significant changes in vital signs or weight from the baseline visit to study endpoint. Changes from baseline to endpoint in laboratory parameters were generally small, of no clinical relevance, and similar between the treatment groups.

DISCUSSION

The IR formulation of paroxetine, as well as other antidepressants, has been proved effective in the treatment of patients with social anxiety disorder.[11–15,30] The current study extends these findings by demonstrating the efficacy of the CR formulation of paroxetine in the treatment

Figure 3. Percentage of Patients Meeting CGI-Global Improvement Scale Responder Definition by Week (ITT population)[a]



[a]Responders defined as those with a CGI-Global Improvement score of 1 (very much improved) or 2 (much improved).
*p < .05.
**p < .001.
Abbreviations: CGI = Clinical Global Impressions scale, CR = controlled-release, ITT = intent-to-treat, LOCF = last observation carried forward, OC = observed cases.

Table 4. Change From Baseline to Week 12 LOCF Endpoint in Secondary Efficacy Variables Among Patients With Social Anxiety Disorder (ITT population)[a]

	Placebo			Paroxetine CR			Paroxetine CR vs Placebo	
Instrument	N	Mean	SE	N	Mean	SE	Difference (95% CI)	p Value
LSAS								
Fear or anxiety	184	–8.9	0.94	185	–15.7	0.94	–6.86 (–9.42 to –4.30)	< .001
Avoidance	184	–8.7	0.92	185	–15.2	0.92	–6.47 (–8.98 to –3.96)	< .001
Social Avoidance and Distress Scale total	180	–4.1	0.52	185	–6.6	0.52	–2.43 (–3.84 to –1.01)	< .001
CGI-S	184	–0.7	0.08	186	–1.4	0.08	–0.63 (–0.85 to –0.40)	< .001
SDS								
Family life	182	–0.7	0.13	185	–1.3	0.13	–0.64 (–0.99 to –0.29)	< .001
Work	180	–1.0	0.17	183	–2.1	0.17	–1.10 (–1.56 to –0.65)	< .001
Social life	182	–1.6	0.17	185	–2.7	0.17	–1.10 (–1.57 to –0.63)	< .001

[a]Differences are represented in adjusted least square means (paroxetine CR – placebo).
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, CI = confidence interval, CR = controlled-release, ITT = intent-to-treat, LOCF = last observation carried forward, LSAS = Liebowitz Social Anxiety Scale, SDS = Sheehan Disability Scale.

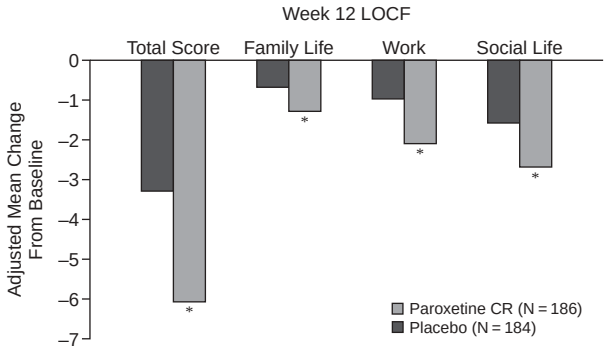
of patients suffering from social anxiety disorder. The principal evidence to support the benefit of paroxetine CR is based on positive findings versus placebo on both of the protocol-defined primary measures of efficacy, which were the change from baseline in LSAS total score and the proportion of responders based on the CGI-Global Improvement score. The reduction in the LSAS total score included significant reduction in both the fear or anxiety subscale and the avoidance subscale of the LSAS. Furthermore, a greater proportion of patients treated with paroxetine CR achieved clinical remission, defined as a decrease of at least 70% in LSAS total score or a CGI-Global Improvement score of "very much improved," compared with patients treated with placebo.

The results of the primary efficacy measures were corroborated by all of the secondary efficacy measures. Positive benefit for paroxetine CR was demonstrated by scores on the patient-rated Social Avoidance and Distress Scale and the clinician-rated CGI-S, a measure of the overall severity of patients' illness. Taken together, these results provide strong evidence that paroxetine CR is effective in treating social anxiety disorder.

The magnitude of clinical response observed in this study is similar to results reported with the IR formulation of paroxetine,[13–15] which is noteworthy since the improvement in disease symptomatology in the current study was observed at a lower dose range. The flexible dose range in the IR studies was 20 to 50 mg/day, and the current study employed a flexible dose range of 12.5 to 37.5 mg/day, which is equivalent to 10 to 30 mg of the IR formulation. Thus, patients were exposed to less medication and obtained a similar clinical response.

Social anxiety disorder imposes persistent functional impairment and disability.[17] In the present study, functional impairment of patients before treatment, as measured by a baseline score of 16 on the SDS, suggests that the impairment was on the order of that seen in patients suffering from other anxiety disorders such as panic disorder.[31] With paroxetine CR treatment, however, there was significant improvement in patient functionality. By study

Figure 4. Change From Baseline in Sheehan Disability Scale Total Score and Individual Item Scores (ITT population)[a]



[a]Represented as least square means.
*p < .001.
Abbreviations: CR = controlled-release, ITT = intent-to-treat, LOCF = last observation carried forward.

Table 5. Most Commonly Reported Treatment-Emergent Adverse Events Associated With the Use of Paroxetine CR in Patients With Social Anxiety Disorder (ITT population)[a]

	Paroxetine CR (N = 186)		Placebo (N = 184)	
Adverse Event	N	%	N	%
Nausea	40	21.5	11	6.0
Asthenia	33	17.7	13	7.1
Abnormal ejaculation[b]	13	14.8	1	1.0
Sweating	26	14.0	5	2.7
Impotence[b]	8	9.1	0	0
Somnolence	17	9.1	7	3.8
Insomnia	16	8.6	8	4.3
Libido decreased	15	8.1	2	1.1

[a]Events with ≥ 5% incidence rate in the paroxetine CR treatment group and at least twice that of placebo.
[b]Percentages based on male patients only; N = 88 for paroxetine CR group and N = 97 for placebo group.
Abbreviations: CR = controlled-release, ITT = intent-to-treat.

endpoint, a mean decrease of 40% in SDS total scores were observed for patients treated with paroxetine CR. Given the debilitating social and occupational impairment in this population, the majority of benefit was observed in the social and work items for patients treated with paroxetine CR. As the goal of treatment is to restore functional normality, we examined the proportion of patients who achieved an SDS total score of less than 5. Remission was operationally defined by Leon et al.[32] as a level at which there is no perceivable impairment in work or psychosocial functioning. On the basis of this definition, twice as many patients treated with paroxetine CR compared with placebo achieved functional normality, indicating that a significant proportion of patients achieved remission of functional impairment.

In addition to its ability to effectively treat patients with social anxiety disorder, paroxetine CR was well tolerated in this study. The adverse events reported throughout this study and the events causing patients to stop treatment were similar in nature and incidence to those reported in the prescribing information of paroxetine CR.[33] However, the dropout rates due to adverse events were low and similar to placebo (2.7%, N = 5 in the paroxetine CR group vs. 1.6%, N = 3 in the placebo group). In trials assessing the safety and efficacy of immediate-release SSRIs (escitalopram, paroxetine, and sertraline) and the SNRI, venlafaxine extended release, in the treatment of social anxiety disorder, the dropout rates due to adverse events were between 7% and 21% for active treatments and 3% to 6% for placebo.[11–15,24,34] This pattern of results is consistent with previously reported trials with paroxetine CR and an immediate-release SSRI comparator.[22,23] Better tolerability may increase medication compliance and the opportunity for patients to continue therapy and respond to treatment.

It must be emphasized that this study did not include a comparison of paroxetine CR and paroxetine IR. Moreover, the dose ranges studied in the current study were not identical to the dose ranges employed in prior studies, hence conclusions regarding their relative tolerability and efficacy profiles cannot be drawn from these trials. Another limitation of this study is the uniform clinical profile of its patients, as the patients had few comorbid psychiatric conditions and the majority were receiving SSRI treatment for the first time. This cohort may represent only a minority of the patients presenting for treatment in clinical practice.

This study demonstrated that paroxetine CR effectively treated the symptoms and disability associated with social anxiety disorder. In addition, paroxetine CR was well tolerated with few patients stopping treatment due to adverse events. This favorable tolerability profile may enable more patients to experience the benefits of effective therapy.

Drug names: escitalopram (Lexapro), fluoxetine (Prozac and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

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