A Multicenter, Randomized, Double-blind, Placebo-Controlled Trial of Paroxetine in Children and Adolescents With Social Anxiety Disorder

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Background: Social anxiety disorder is a debilitating, highly prevalent disorder in children and adolescents. If left untreated, it can interfere with emotional, social, and school functioning.

Objective: To evaluate the efficacy and tolerability of paroxetine in children and adolescents with social anxiety disorder.

Design and Setting: Multicenter, 16-week, randomized, double-blind, placebo-controlled, flexible-dose, parallel-group, outpatient study.

Patients: A total of 322 children (8-11 years of age) and adolescents (12-17 years of age) with social anxiety disorder as their predominant psychiatric illness.

Intervention: Eligible patients were randomized (1:1) to receive paroxetine (10-50 mg/d) or placebo.

Results: Four hundred twenty-five patients were screened, and 322 were randomized to treatment. Of these, 319 were included in the intention-to-treat population (paroxetine, n=163; placebo, n=156). At the week 16 last observation carried forward end point, the odds of responding (Clinical Global Impression-Improvement score of 1 or 2) were statistically significantly greater for paroxetine (77.6% response [125/161]) than for placebo (38.3% response [59/154]) (adjusted odds ratio, 7.02; 95% confidence interval, 4.07 to 12.11; $P<.001$). The proportion of patients who were "very much" improved (Clinical Global Impression-Improvement score of 1) was 47.8% (77/161) for paroxetine compared with 14.9% (23/154) for placebo. Adverse events occurring at an incidence of 5% or greater for paroxetine and twice that for placebo were insomnia (14.1% vs 5.8%), decreased appetite (8.0% vs 3.2%), and vomiting (6.7% vs 1.9%). Withdrawals due to adverse events were infrequent (5.5% [9/163] for paroxetine and 1.3% [2/156] for placebo).

Conclusion: Paroxetine is an effective, generally well-tolerated treatment for pediatric social anxiety disorder.

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OCIAL ANXIETY DISORDER IS A common condition in children and adolescents, with prevalence rates ranging from 0.9% to 7% in youths.[1,2] Children with social anxiety disorder, as defined by the *DSM-IV*,[3] have a fear of social and performance situations in which embarrassment or humiliation may occur. When exposed to these situations, they experience intense anxiety that substantially interferes with normal childhood activities. Ordinary social interactions, such as starting or joining a conversation, and performances, such as playing sports or participating in dance recitals, cause significant distress for these children. Their fears and avoidance result in loneliness, dysphoria, and inadequate social skills.[4,5] The detrimental effects of social anxiety disorder

are not limited to childhood. Adolescents with social anxiety disorder may be at increased risk for depression,[6] substance abuse, nicotine use, suicidal behavior, and educational underachievement in young adulthood.[7] Moreover, social anxiety disorder in adolescents can persist to adulthood.[8] As adults, these individuals frequently have substantial impairment in work and social functioning[9] and reduced quality of life.[10]

Given the significant morbidity and chronicity of childhood social anxiety disorder, it is essential to identify efficacious treatments. Unfortunately, little attention has been directed at the pharmacological treatment of this disorder in the pediatric population. Most pharmacological studies have been aimed at the treatment of adults. The selective seroto-

nin reuptake inhibitors (SSRIs) paroxetine and sertraline and the serotonin norepinephrine reuptake inhibitor venlafaxine have been shown in multicenter controlled trials to be effective for the treatment of social anxiety disorder in adults.[11-14]

Open-label studies with SSRIs for the treatment of childhood social anxiety disorder have shown some promising results. Sertraline treatment for social anxiety disorder,[15] citalopram combined with psychoeducation for social anxiety disorder,[16] and fluoxetine for mixed anxiety disorders[17,18] demonstrated some improvement in anxiety symptoms. A small, controlled, randomized trial showed efficacy of fluoxetine treatment of child anxiety disorders.[19] In a multicenter, double-blind, placebo-controlled trial of fluvoxamine treatment for children and adolescents with anxiety disorders, fluvoxamine was superior to placebo in the reduction of anxiety.[20]

This study is the first multicenter, double-blind, randomized pharmacological trial directed specifically at the treatment of social anxiety disorder in children and adolescents. Given the established efficacy of paroxetine in adults with this disorder, this study was designed to examine the efficacy and safety of paroxetine for the treatment of social anxiety disorder in children and adolescents.

METHODS

PATIENTS

Male and female children (8-11 years of age) and adolescents (12-17 years of age) who met *DSM-IV* diagnostic criteria for social anxiety disorder, according to the Anxiety Disorders Interview Schedule for *DSM-IV* (child and parent versions, present disorders),[21] were eligible. Patients were enrolled from 38 centers (22 in the United States, 10 in South Africa, 4 in Canada, and 2 in Belgium) from November 30, 1999, to October 19, 2001. Centers in the United States and South Africa enrolled the majority of patients, 182 (57.1%) and 100 (31.3%), respectively.

The study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki (amended in Somerset West, Republic of South Africa, October 1996), with the protocol and statement of informed consent approved by the institutional review boards/ethics committees prior to each center's initiation. Written informed consent/assent was obtained from all patients and their parents/guardians prior to study entry.

ELIGIBILITY CRITERIA

Patients were evaluated at the screening and baseline visits and were excluded if they had a clinically predominant Axis I disorder (based on the investigator's judgment) other than social anxiety disorder (eg, dysthymia, simple phobia, obsessive-compulsive disorder, panic disorder, body dysmorphic disorder, attention-deficit/hyperactivity disorder, generalized anxiety disorder, or separation anxiety disorder) or if they had a concurrent major depressive episode. Patients were also excluded if they had any history of a psychotic episode (including schizophrenia), bipolar disorder, or a pervasive developmental disorder. Other grounds for exclusion were concurrent psychotherapy, concurrent psychoactive medication use, substance abuse/dependence, hypersensitivity (defined as previous intolerance) to SSRIs, pregnancy/lactation, recent electro-convulsive therapy, serious suicidal/homicidal risk, clinically significant abnormal laboratory or electrocardiogram findings, and a positive test result for illicit drug use. In addition, patients were excluded if they had a serious medical condition that would preclude the administration of paroxetine.

DESIGN AND PROCEDURES

This was a prospective, multicenter, randomized, double-blind, placebo-controlled, flexible-dose, parallel-group, outpatient study. A 1-week screening phase was used to determine eligibility and to conduct baseline efficacy and safety assessments. Patients meeting eligibility criteria were randomized (1:1) to receive paroxetine (10-50 mg/d) or placebo for 16 weeks. Study assessments were scheduled at the end of weeks 1, 2, 3, 4, 6, 8, 10, 12, and 16 or on early withdrawal. Disorder-specific and global assessment scales were administered at each visit, and adverse events (AEs) and vital signs were monitored.

In light of the recognized importance of patient and family education in the management of any chronic disease, particularly one that affects children and adolescents in the context of their families, this study incorporated age-appropriate psychoeducational pamphlets (1 each for children, adolescents, and parents/guardians). These pamphlets were provided at baseline and included information on the nature and course of the disorder and suggestions for self-help.[22-24] The pamphlet for parents/guardians also included reasons for children/adolescents' developing social anxiety disorder, symptoms, types of treatment, and what parents can do to help. Extended discussions or more specific cognitive or behavioral interventions were not permitted.

STUDY MEDICATION AND DOSING REGIMEN

A computer-generated randomization list was used to assign patients to each treatment group. The randomization code was not stratified by age or sex. Placebo and paroxetine capsules were identical in appearance, so that all study personnel and patients were blinded to treatment.

During the first week of the double-blind treatment phase, patients received 10 mg/d of paroxetine or matching placebo. The dose could then be up-titrated (10 mg/d) no more frequently than every 7 days to a maximum dose of 50 mg/d. A dose reduction to the next lower dose consequent to an AE was permitted after week 2. At the conclusion of the treatment phase or upon early withdrawal, patients ending treatment at 20 mg/d or higher were required to gradually reduce study medication by 10 mg/d each week up to a maximum of 4 weeks prior to stopping therapy. Following completion of this taper phase, patients returned to the clinic for a taper end visit. A follow-up visit was required (14±3 days) after the last dose including taper medication.

OUTCOME MEASURES

A psychiatrist, clinical psychologist, or psychometrician with at least 2 to 3 years' experience with pediatric patients conducted all diagnostic and efficacy assessments. For consistency, detailed instruction on the use of the Anxiety Disorders Interview Schedule instrument and on the efficacy rating scales (Liebowitz Social Anxiety Scale for Children and Adolescents [LSAS-CA],[25] Social Phobia and Anxiety Inventory/Social Phobia and Anxiety Inventory for Children,[26] and Kutcher Generalized Social Anxiety Disorder Scale for Adolescents[27]) was provided at the prestudy investigator's meeting. Additionally, the

same rater performed assessments on individuals throughout the study when possible.

EFFICACY END POINTS

Social anxiety disorder in children and adolescents has only recently received recognition. Consequently, at the time this study was conducted, there were no validated, clinician-rated pediatric social anxiety scales available for use. As a result, the Clinical Global Impression-Improvement (CGI-I) scale[28] was used as the primary efficacy end point (proportion of responders based on a score of 1 ["very much improved"] or 2 ["much improved"] at the week 16 last observation carried forward [LOCF] end point). In addition, several disorder-specific and global scales were included as secondary efficacy end points and summarized as the change from baseline at the week 16 LOCF end point. Secondary efficacy measures were LSAS-CA, Clinical Global Impression-Severity of Illness (CGI-S),[28] Kutcher Generalized Social Anxiety Disorder Scale for Adolescents (≥11 years of age), Social Phobia and Anxiety Inventory for Children (<14 years of age), Social Phobia and Anxiety Inventory for Adolescents (≥14 years of age),[29] and Global Assessment of Functioning scale. Age subgroup analyses were conducted post hoc for CGI-I and LSAS-CA.

SAFETY END POINTS

Safety was assessed at every visit through AE monitoring and vital sign determination (eg, blood pressure and pulse). A serious AE was defined as any event that was fatal, life threatening, disabling/incapacitating or resulted in hospitalization, prolonged a hospital stay, or was associated with congenital abnormality, cancer, or overdose (either accidental or intentional). In addition, any experience that the investigator regarded as serious or that suggested any significant hazard, contraindication, adverse effect, or precaution that may have been associated with the use of the drug was documented as a serious event. Clinical laboratory evaluations (eg, hematology and serum chemistry) and physical examinations (including weight) were performed at baseline and week 16 or upon early withdrawal.

STATISTICAL ANALYSES

It was estimated that 130 patients per treatment group who could be evaluated would be sufficient to detect a 20% difference between paroxetine and placebo in the proportion of patients with a CGI-I score of 1 or 2 at the week 16 LOCF end point. The number of patients who could be evaluated was based on a placebo response rate of 40%. This difference is detectable with a power of 90%, given a significance level of 5% and using a 2-sided significance test.

All patients who were randomized into the treatment phase, who received at least 1 dose of study medication, and who had at least 1 postbaseline safety or efficacy assessment were included in the intention-to-treat (ITT) population.

Statistical conclusions concerning the efficacy of paroxetine were made using the week 16 LOCF and the week 16 observed cases data sets, based on the ITT population. Primary inference was based on week 16 LOCF, with week 16 observed cases used to assess the robustness of the conclusions. All hypothesis tests were 2-sided, and the effect of interactions was assessed at the 10% level of significance (primary end point at week 16 LOCF only). All other statistical tests were performed at the 5% level of significance. Binary data (proportion of responders based on CGI-I) were analyzed using logistic regression with results presented as adjusted odds ratios, 95% confidence intervals (CI) around the odds ratios, and associated P values. Continuous efficacy variables were analyzed by analysis of variance techniques with results presented as the difference in adjusted means for change from baseline, 95% CI for the differences, and associated P values. Estimates of treatment difference for binary and continuous efficacy variables were adjusted for age group, sex, applicable baseline score, and country group (United States, Canada, or South Africa/Belgium combined). Baseline CGI-S was used as baseline score for CGI-I analysis. The change from baseline in CGI-S was analyzed using the Wilcoxon rank sum test with results presented as the median difference and P value for the Wilcoxon rank sum test. The incidence of AEs of interest was compared between treatment groups post hoc using the continuity adjusted χ^2 test or Fisher exact test where there were small expected frequencies (<5).

POST HOC ANALYSIS OF REMISSION STATUS

The rigorous criterion for remission of a 70% or greater reduction in the LSAS has been recommended for social anxiety disorder in adults.[30] Post hoc remission analysis was performed following the current study to provide a thorough assessment of remission in this group of patients. Here, a 70% or greater reduction from baseline in LSAS-CA (reduction in symptomatology) was utilized in retrospective analyses. The other remission criterion that was analyzed was the CGI-I, where a CGI-I score of 1 ("very much improved") indicated improvement in well-being/overall CGI disease severity. Estimates of treatment difference were adjusted for age group (age subgroups, combined analysis only), sex, baseline score (LSAS-CA or CGI-S), and country group. Additionally, the proportion of patients meeting both remission criteria was summarized.

RESULTS

A total of 425 patients were screened, and 322 were randomized to double-blind treatment. The ITT population consisted of 319 patients (163 paroxetine and 156 placebo). Of the 319 patients in the ITT population, 91 (28.5%) were children, and 228 (71.5%) were adolescents; 160 (50.2%) were male, and 159 (49.8%) were female.

There were no marked imbalances between treatment groups in demographic characteristics except for sex (**Table 1**). The percentage of males in the paroxetine group overall (43.6% [71/163]) was lower than in the placebo group (57.1% [89/156]). This was also the case in the adolescent subgroup.

At baseline, the vast majority of patients (95.6%) were given a CGI-S rating of "moderately ill" (45.1%), "markedly ill" (38.5%), or "severely ill" (12.0%). The 2 treatment groups were similar with respect to their mean baseline scores on all symptom-severity rating scales, indicating comparable levels of social anxiety disorder severity (**Table 2**, **Table 3**).

The percentage of patients with a current comorbid psychiatric illness was slightly greater in the paroxetine group (56.4% [92/163]) than in the placebo group (48.7% [76/156]). The most common (>10%) comorbid psychiatric conditions in the overall population were specific phobia (24.8% [79/319]), generalized anxiety disorder (23.5% [75/319]), and separation anxiety disorder (16.3% [52/319]).

Table 1. Demographic Characteristics (Intention-to-Treat Population)

| | Age Group | | | | | | | | |
| | Children | | | Adolescents | | | Total | | |
Demographic Characteristic	Paroxetine (n = 46)	Placebo (n = 45)	Total (n = 91)	Paroxetine (n = 117)	Placebo (n = 111)	Total (n = 228)	Paroxetine (n = 163)	Placebo (n = 156)	Total (N = 319)
Sex, No. (%)									
Male	25 (54.3)	23 (51.1)	48 (52.7)	46 (39.3)	66 (59.5)	112 (49.1)	71 (43.6)	89 (57.1)	160 (50.2)
Female	21 (45.7)	22 (48.9)	43 (47.3)	71 (60.7)	45 (40.5)	116 (50.9)	92 (56.4)	67 (42.9)	159 (49.8)
Age, y*									
Mean (SD)	9.3 (1.26)	9.8 (1.15)	9.5 (1.22)	14.5 (1.67)	14.7 (1.71)	14.6 (1.69)	13.0 (2.81)	13.3 (2.73)	13.1 (2.77)
Race, No. (%)									
White	38 (82.6)	41 (91.1)	79 (86.8)	101 (86.3)	90 (81.1)	191 (83.8)	139 (85.3)	131 (84.0)	270 (84.6)
Other	8 (17.4)	4 (8.9)	12 (13.2)	16 (13.7)	21 (18.9)	37 (16.2)	24 (14.7)	25 (16.0)	49 (15.4)
Weight, kg†									
Mean (SD)	37.95 (11.6)	42.44 (14.5)	40.17 (13.2)	61.87 (18.8)	65.48 (18.4)	63.62 (18.6)	55.12 (20.1)	58.79 (20.2)	56.91 (20.2)
Range	20.5-64.5	24.1-90.5	20.5-90.5	27.2-115.5	30.6-140.7	27.2-140.7	20.5-115.5	24.1-140.7	20.5-140.7

*Five patients were younger than 8 years old (3 paroxetine-treated and 2 placebo patients). All were older than 7 years 6 months at study entry.
†One value for weight is missing (an adolescent in the placebo group).

Table 2. Baseline Efficacy Parameter Scores (Intention-to-Treat Population)

| | | Treatment Group | | | | | | | | |
| | | Paroxetine (n = 163) | | | Placebo (n = 156) | | | Total (N=319) | | |
Instrument	Age Group	No. of Patients	Mean	SD	No. of Patients	Mean	SD	No. of Patients	Mean	SD
LSAS-CA total score	Total	161	77.6	28.72	155	77.7	27.05	316	77.6	27.87
	Children	44	70.7	31.00	45	71.2	28.65	89	70.9	29.66
	Adolescents	117	80.3	27.49	110	80.3	26.04	227	80.3	26.74
K-GSADS-A total score*	Adolescents	126	84.4	25.42	125	81.9	26.25	251	83.2	25.82
SPAI-C total score*	Children	71	28.1	11.71	66	29.5	11.06	137	28.8	11.39
SPAI difference score*	Adolescents	81	98.7	31.56	84	90.9	32.23	165	94.8	32.04
GAF score	Total	162	53.0	6.85	155	53.5	7.51	317	53.2	7.17
	Children	45	53.0	6.30	45	55.0	7.70	90	54.0	7.07
	Adolescents	117	52.9	7.07	110	52.8	7.38	227	52.9	7.20

Abbreviations: GAF, Global Assessment of Functioning; K-GSADS-A, Kutcher Generalized Social Anxiety Disorder Scale for Adolescents; LSAS-CA, Liebowitz Social Anxiety Scale for Children and Adolescents; SPAI, Social Phobia and Anxiety Inventory; SPAI-C, Social Phobia and Anxiety Inventory for Children.

*Adolescents were 12 years of age or older per protocol except for the following: K-GSADS-A was administered to patients aged 11 years or older; SPAI was to be assessed in patients 14 years of age or older; however, it also included some patients aged 13 years; and SPAI-C was to be assessed in patients 13 years of age or younger; however, it also included some patients aged 14 and 15 years.

Table 3. Clinical Global Impression-Severity of Illness Score at Baseline (Intention-to-Treat Population)*

| | Age Group | | | | | | | | |
| | Children | | | Adolescents | | | Total | | |
Instrument	Paroxetine (n = 45)	Placebo (n = 45)	Total (n = 90)	Paroxetine (n = 117)	Placebo (n = 110)	Total (n = 227)	Paroxetine (n = 162)	Placebo (n = 155)	Total (N = 317)
Clinical Global Impression-Severity baseline (score)†									
Mildly ill (3)	1 (2.2)	3 (6.7)	4 (4.4)	3 (2.6)	3 (2.7)	6 (2.6)	4 (2.5)	6 (3.9)	10 (3.2)
Moderately ill (4)	25 (55.6)	20 (44.4)	45 (50.0)	49 (41.9)	49 (44.5)	98 (43.2)	74 (45.7)	69 (44.5)	143 (45.1)
Markedly ill (5)	16 (35.6)	20 (44.4)	36 (40.0)	45 (38.5)	41 (37.3)	86 (37.9)	61 (37.7)	61 (39.4)	122 (38.5)
Severely ill (6)	3 (6.7)	2 (4.4)	5 (5.6)	18 (15.4)	15 (13.6)	33 (14.5)	21 (13.0)	17 (11.0)	38 (12.0)
Among the most extremely ill (7)	0	0	0	2 (1.7)	2 (1.8)	4 (1.8)	2 (1.2)	2 (1.3)	4 (1.3)

*Data are presented as number (percentage).
†No patients had a baseline Clinical Global Impression-Severity of Illness score of 0 (not assessed), 1 (normal, not at all ill), or 2 (borderline mentally ill) in any group.
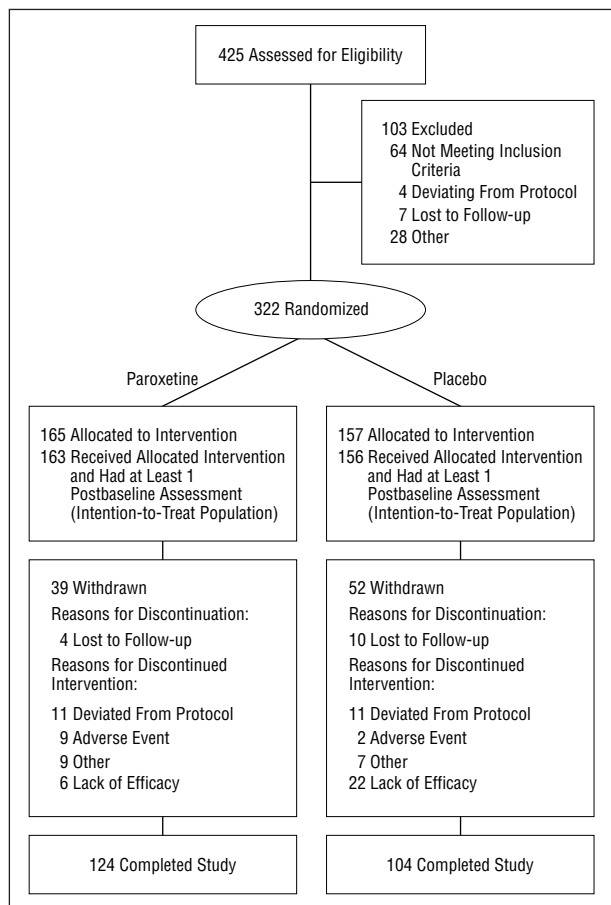
Figure 1. Flow of subjects through the study, showing progress through the different stages, including withdrawals.

Figure 2. Proportion of Clinical Global Impression-Improvement (CGI-I) responders (intention-to-treat population) for children and adolescent subgroups and total (week 16 last observation carried forward). Children: adjusted odds ratio, 6.40; 95% confidence interval, 2.20 to 18.63; *P*<.001. Adolescents: adjusted odds ratio, 7.81; 95% confidence interval, 4.05 to 15.03; *P*<.001. Total: adjusted odds ratio, 7.02; 95% confidence interval, 4.07 to 12.11; *P*<.001.

Figure 3. Proportion of Clinical Global Impression-Improvement responders (intention-to-treat population) by treatment and by week for the total population. LOCF indicates last observation carried forward; OC; observed cases.

PREMATURE DISCONTINUATION

The progress of patients through the study and details of reasons for withdrawal are shown in **Figure 1**. A total of 228 (71.5%) of 319 patients completed the 16-week double-blind phase (ITT population). Overall, the percentage of patients who withdrew was higher in the placebo group (33.3% [52/156]) than in the paroxetine group (23.9% [39/163]). Rates of withdrawal due to AEs were low in both groups (5.5% paroxetine vs 1.3% placebo). Withdrawals due to a lack of efficacy were higher in the placebo group (14.1% placebo vs 3.7% paroxetine).

DOSAGE TITRATION

A total of 72.2% (117/162) of patients in the paroxetine group received a dose higher than 20 mg/d. Slightly more than half the children (56.5% [26/46]) received a dose higher than 20 mg/d, compared with 78.4% (91/116) of the adolescents. The number of patients in the paroxetine group who received a maximum dose of 50 mg/d (26.5% [43/162]) was approximately half that for placebo (49.4% [77/156]). At end point (week 16 LOCF), the mean dose for paroxetine was 32.6 mg/d for all patients (26.5 mg/d for children and 35.0 mg/d for adolescents), whereas the overall mean dose for paroxetine-treated patients was slightly lower (24.8 mg/d for all patients, 21.7 mg/d for children, and 26.1 mg/d for adolescents).
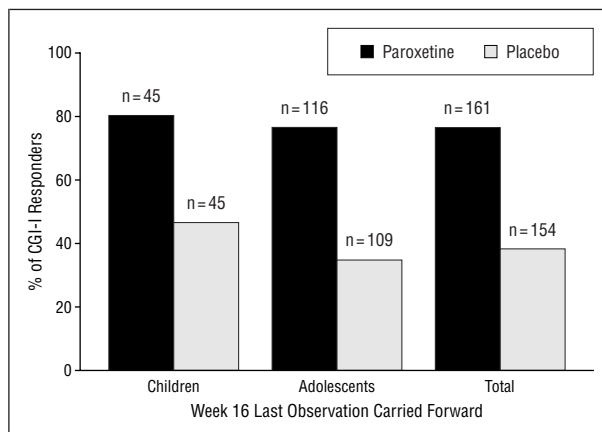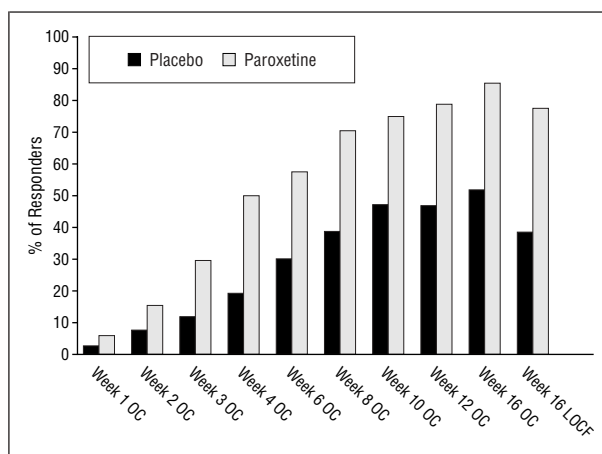
EFFICACY END POINTS

Overall, 77.6% (125/161) of patients randomized to receive paroxetine were defined as CGI-I responders at week 16 LOCF end point compared with 38.3% (59/154) for placebo (adjusted odds ratio, 7.02; 95% CI, 4.07 to 12.11; *P*<.001) (**Figure 2**). This result was supported by the week 16 observed cases analysis. The benefit of paroxetine was apparent within the first 4 weeks of treatment (**Figure 3**). The CGI-I responder data demonstrated a statistically significant benefit of paroxetine over placebo in both age subgroups, again, for both the week 16 LOCF results and the week 16 observed cases data (post hoc analysis). There was no evidence of any statistically significant treatment by covariate interactions, indicating that the treatment effect was consistent across age group, sex, baseline score, and country grouping.

Results for the treatment effect of paroxetine compared with placebo at the week 16 LOCF end point for the secondary efficacy parameters are shown in **Table 4**

Table 4. Change From Baseline in Secondary Efficacy Parameters at Week 16 LOCF End Point (Intention-to-Treat Population)

| Instrument | Adjusted Mean Change From Baseline (SE) | | | | Adjusted Mean Difference* (95% Confidence Interval) | P Value |
	No. of Patients	Paroxetine	No. of Patients	Placebo		
LSAS-CA total score	159	−48.01 (2.64)	150	−24.25 (2.67)	−23.75 (−29.77 to −17.74)	<.001
K-GSADS-A total score	124	−42.94 (2.66)	120	−21.08 (2.71)	−21.86 (−28.56 to −15.16)	<.001
SPAI-C total score	69	−17.55 (1.59)	66	−8.11 (1.62)	−9.44 (−13.19 to −5.69)	<.001
SPAI difference score	77	−51.85 (4.53)	81	−19.05 (4.40)	−32.80 (−43.57 to −22.03)	<.001
GAF score	159	17.11 (1.14)	151	8.37 (1.15)	8.74 (6.15 to 11.34)	<.001
	Mean Change From Baseline (Range)					
	No. of Patients	Paroxetine	No. of Patients	Placebo	Median Difference*	P Value
CGI-S score						
Child subgroup	45	−2.0 (−5 to 0)	45	−1.0 (−4 to 1)	−1.0	<.001
Adolescent subgroup	116	−2.0 (−5 to 1)	109	−1.0 (−5 to 0)	−1.0	<.001

Abbreviations: CGI-S, Clinical Global Impression-Severity; GAF, Global Assessment of Functioning; K-GSADS-A, Kutcher Generalized Social Anxiety Disorder Scale for Adolescents; LOCF, last observation carried forward; LSAS-CA, Liebowitz Social Anxiety Scale for Children and Adolescents; SPAI, Social Phobia and Anxiety Inventory; SPAI-C, Social Phobia and Anxiety Inventory for Children.
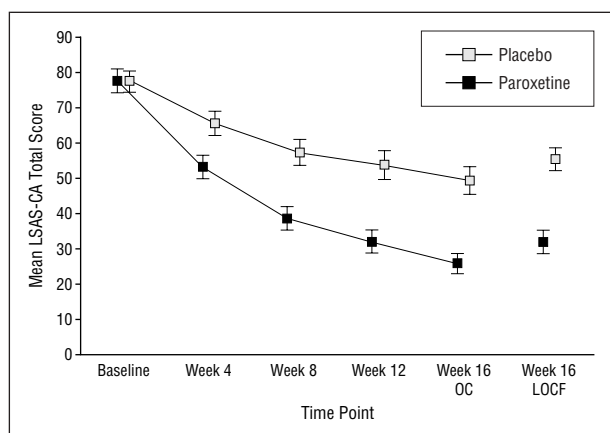*Paroxetine minus placebo.

Figure 4. Mean Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA) total score (±1.96 SE) at each visit (intention-to-treat population). LOCF indicates last observation carried forward; OC; observed cases.
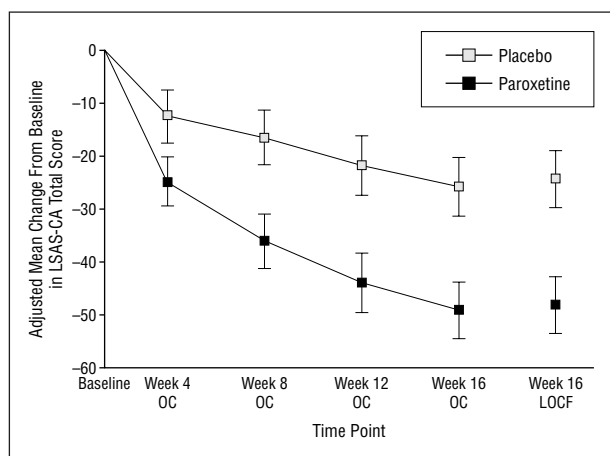

Figure 5. Adjusted mean change from baseline (±1.96 SE) in Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA) total score at each visit (intention-to-treat population). Week 16 observed cases (OC): adjusted treatment difference, −23.31; 95% confidence interval, −29.59 to −17.03; P<.001. Week 16 last observation carried forward (LOCF): adjusted treatment difference, −23.75; 95% confidence interval, −29.77 to −17.74; P<.001.

and demonstrate a statistically significant benefit of paroxetine over placebo for all 5 parameters.

Patients in the paroxetine group had greater reductions in LSAS-CA total score at all time points (**Figure 4**). The adjusted mean difference in LSAS-CA total score between paroxetine and placebo at week 16 LOCF for the ITT population was −23.75 points in favor of paroxetine (95% CI, −29.77 to −17.74; P<.001), indicating a statistically significant benefit of paroxetine over placebo (Table 4, **Figure 5**). The treatment effect shown for LSAS-CA was consistent across age subgroups (post hoc analysis). The adjusted mean difference in change from baseline in LSAS-CA total score between paroxetine and placebo at week 16 LOCF for the ITT population in the child subgroup was −28.82 points in favor of paroxetine (95% CI, −38.71 to −18.92; P<.001), and in the adolescent subgroup it was −20.62 points in favor of paroxetine (95% CI, −28.10 to −13.14; P<.001).

The analysis for CGI-S was performed separately for each age group. For both children and adolescents, the median difference between paroxetine and placebo at week 16 LOCF end point in change from baseline in CGI-S score was −1.0 (P<.001), indicating a statistically significant benefit in terms of the severity of illness of paroxetine over placebo (Table 4). Similar results were observed for the week 16 observed cases analysis. At week 16 LOCF based on the CGI-S, 47.5% (77/162) of paroxetine-treated patients vs 20.7% (32/154) of placebo patients were rated normal ("not at all ill") or borderline mentally ill (**Figure 6**).

POST HOC ANALYSIS OF REMISSION STATUS

At the week 16 LOCF end point, the odds of being in remission according to the criterion of a 70% or greater reduction (from baseline) in LSAS-CA total score were statistically significantly greater for patients receiving paroxetine (remission proportion, 47.2% [75/159]) than for those receiving placebo (remission proportion, 13.3%

[20/150]) (adjusted odds ratio, 6.05; 95% CI, 3.38 to 10.82; $P<.001$) (**Table 5**).

At the week 16 LOCF end point, the odds of being in remission according to the criterion of a CGI-I score of 1 were statistically significantly greater for patients receiving paroxetine (remission proportion, 47.8% [77/161]) than for those receiving placebo (remission proportion, 14.9% [23/154]) (adjusted odds ratio, 5.44; 95% CI, 3.09 to 9.57; $P<.001$) (Table 5). The remission analyses in both age subgroups were consistent with the results in the total population (Table 5).

More than 4 times as many patients randomized to paroxetine met both remission criteria ($\geq70\%$ reduction in LSAS-CA and CGI-I of 1) at week 16 LOCF end point compared with those receiving placebo (34.6% [55/159] vs 8.0% [12/150], respectively). This was also the case in both age subgroups at week 16 LOCF end point: children, 38.6% (17/44) vs 8.9% (4/45), respectively; adolescents, 33.0% (38/115) vs 7.6% (8/105), respectively.
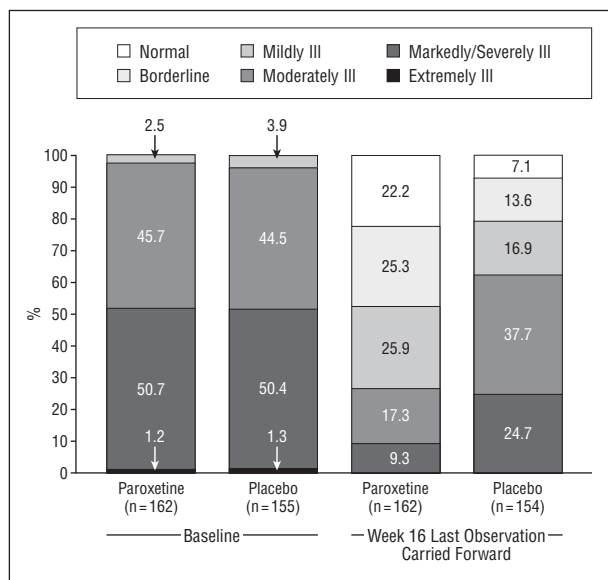

Figure 6. Percentage of patients in each category of the Clinical Global Impression-Severity of Illness item score at week 16 last observation carried forward (intention-to-treat population).

TOLERABILITY

Adverse events considered possibly treatment emergent (incidence $\geq5\%$ for paroxetine and at least twice that for placebo in both age groups combined) were insomnia (14.1% [23/163] vs 5.8% [9/156]; $\chi^2_1=5.26$; $P=.02$), decreased appetite (8.0% [13/163] vs 3.2% [5/156]; $\chi^2_1=2.57$; $P=.11$), and vomiting (6.7% [11/163] vs 1.9% [3/156]; $\chi^2_1=3.35$; $P=.07$) (**Table 6**). Most AEs were mild to moderate in intensity.

The behavior-related AEs with an incidence of 5% or greater for paroxetine and at least twice that for placebo were somewhat different between children and adolescents. Nervousness, hyperkinesia, asthenia, and hostility met these criteria in children who had received paroxetine, and somnolence and insomnia met these criteria in adolescents who had received paroxetine. Other behavioral AEs of interest not included in Table 6 were agitation (1.8% [3/163] vs 1.3% [2/156] for paroxetine and placebo, respectively), manic reaction (1.8% [3/163] vs 0% for paroxetine and placebo, respectively), and emotional lability (2.5% [4/163] vs 1.3% [2/156] for paroxetine and placebo, respectively).

The 4 paroxetine-treated patients who had an AE of emotional lability had expressed suicidal ideation or had threatened suicide (vs no patients in the placebo group with a similar AE; $P=.12$ using Fisher exact test). One of these patients, in addition to experiencing suicidal thoughts, also exhibited self-harm behavior. For 3 of these patients the event occurred while receiving treatment, whereas for the fourth patient the event occurred during the follow-up phase. A second instance of self harm (superficial cuts to the arms to get parents' attention) was reported in a fifth patient in the paroxetine group. This event was categorized as an AE of neurosis because the investigator indicated that the event was due to impulsive behavior. If this event is combined with the 4 cases mentioned above, the P value becomes .06 for paroxetine vs placebo. None of these 5 cases were considered serious, none involved clear evidence of a suicide attempt, and none of the events were attributed to the study medication by the investigator.

Table 5. Percentage Remission and Adjusted Odds Ratio for Paroxetine vs Placebo (Week 16 LOCF, Intention-to-Treat Population)

	$\geq70\%$ Reduction in LSAS-CA Score	CGI-I Score of 1
Age subgroups combined		
Paroxetine	75/159 (47.2%)	77/161 (47.8%)
Placebo	20/150 (13.3%)	23/154 (14.9%)
Adjusted odds ratio (95% CI; P value)	6.05 (3.38 to 10.82; $P<.001$)	5.44 (3.09 to 9.57; $P<.001$)
Child subgroup*		
Paroxetine	26/44 (59.1%)	24/45 (53.3%)
Placebo	7/45 (15.6%)	6/45 (13.3%)
Adjusted odds ratio (95% CI; P value)	7.80 (2.84 to 21.42; $P<.001$)	8.68 (2.88 to 26.19; $P<.001$)
Adolescent subgroup		
Paroxetine	49/115 (42.6%)	53/116 (45.7%)
Placebo	13/105 (12.4%)	17/109 (15.6%)
Adjusted odds ratio (95% CI; P value)	4.95 (2.43 to 10.10; $P<.001$)	4.31 (2.21 to 8.43; $P<.001$)

Abbreviations: CGI-I, Clinical Global Impression-Improvement; CI, confidence interval; LOCF, last observation carried forward; LSAS-CA, Liebowitz Social Anxiety Scale for Children and Adolescents.
*For the country grouping adjustment, the United States and Canada were further combined for the children subgroup analyses.

Table 6. Treatment-Emergent Adverse Events Occurring in 5% or More of Paroxetine-Treated Patients and With an Incidence at Least Twice That for Placebo (in Any Age Group)*

| | Age Group | | | | | |
| | Children | | Adolescents | | Total† | |
Characteristic	Paroxetine (n = 46)	Placebo (n = 45)	Paroxetine (n = 117)	Placebo (n = 111)	Paroxetine (n = 163)	Placebo (n = 156)
≥1 Adverse event	41 (89.1)	35 (77.8)	103 (88.0)	90 (81.1)	144 (88.3)	125 (80.1)
Adverse event leading to withdrawal	2 (4.3)	2 (4.4)	7 (6.0)	0	9 (5.5)	2 (1.3)
Adverse event leading to dose reduction	12 (26.1)	2 (4.4)	16 (13.7)	4 (3.6)	28 (17.2)	6 (3.8)
Respiratory disorder	7 (15.2)	3 (6.7)	18 (15.4)	17 (15.3)	25 (15.3)	20 (12.8)
Asthenia	3 (6.5)	1 (2.2)	21 (17.9)	11 (9.9)	24 (14.7)	12 (7.7)
Insomnia	6 (13.0)	3 (6.7)	17 (14.5)	6 (5.4)	23 (14.1)	9 (5.8)
Somnolence	4 (8.7)	5 (11.1)	17 (14.5)	8 (7.2)	21 (12.9)	13 (8.3)
Nervousness	7 (15.2)	2 (4.4)	7 (6.0)	7 (6.3)	14 (8.6)	9 (5.8)
Decreased appetite	3 (6.5)	2 (4.4)	10 (8.5)	3 (2.7)	13 (8.0)	5 (3.2)
Dyspepsia	2 (4.3)	2 (4.4)	10 (8.5)	4 (3.6)	12 (7.4)	6 (3.8)
Vomiting	3 (6.5)	2 (4.4)	8 (6.8)	1 (0.9)	11 (6.7)	3 (1.9)
Rash	5 (10.9)	2 (4.4)	3 (2.6)	2 (1.8)	8 (4.9)	4 (2.6)
Otitis media	5 (10.9)	1 (2.2)	1 (0.9)	1 (0.9)	6 (3.7)	2 (1.3)
Conjunctivitis	3 (6.5)	0	3 (2.6)	1 (0.9)	6 (3.7)	1 (0.6)
Hyperkinesia	4 (8.7)	0	2 (1.7)	0	6 (3.7)	0
Hostility	3 (6.5)	0	2 (1.7)	2 (1.8)	5 (3.1)	2 (1.3)
Urinary incontinence	5 (10.9)	0	0	0	5 (3.1)	0

*Data are presented as number (percentage) of total patients.
†Sorted by decreasing frequency in the paroxetine group, age group = total.

Serious AEs were reported in 3 patients in the paroxetine group (anemia, fear and depression related to social anxiety disorder, and broken arm) and 1 in the placebo group (unintentional overdose). All except the unintentional overdose were considered unrelated to study medication.

The proportion of patients withdrawing from the study because of an AE was low in both groups (5.5% and 1.3% for paroxetine and placebo, respectively). Two patients in the paroxetine group were withdrawn because of manic reaction; this was the only AE that led to the withdrawal of more than 1 paroxetine-treated patient from the study. Dose reduction consequent to an AE was permitted once a patient had reached 20 mg/d of paroxetine or matching placebo. In the paroxetine group, the proportion of patients who had dose reductions because of an AE was statistically significantly greater than for placebo (17.2% [28/163] compared with 3.8% [6/156], respectively; $\chi^2_1 = 13.51$; $P < .001$).

The proportion of patients with an AE emerging upon treatment discontinuation (ie, with an onset either during taper dosing or during the follow-up phase) was significantly greater in the paroxetine group (47.2% [68/144]) than in the placebo group (32.6% [42/129]; $\chi^2_1 = 5.49$; $P = .02$). Discontinuation-emergent AEs, which occurred at an incidence of 5% or greater in the paroxetine group and also at twice that incidence for the placebo group, were nausea (11.1% [16/144] vs 2.3% [3/129]; $\chi^2_1 = 6.81$; $P < .01$), dizziness (11.1% [16/144] vs 1.6% [2/129]; $\chi^2_1 = 8.61$; $P < .01$), and abdominal pain (6.9% [10/144] vs 1.6% [2/129]; $\chi^2_1 = 3.52$; $P = .06$).

No clinically significant changes in blood pressure, pulse, weight, or laboratory values were found.

COMMENT

Paroxetine was significantly superior to placebo on the primary efficacy measure and all 5 secondary efficacy measures. Seventy-seven percent of the paroxetine-treated group were "much improved" or "very much improved" at week 16 LOCF end point compared with 38% of the placebo group. Response rates were comparable for children and adolescents.

Beyond response, a major goal of clinical treatment is remission.[30] Significantly more paroxetine-treated patients (almost 50%) achieved remission, defined as either a 70% or greater reduction in symptoms of anxiety (LSAS-CA) or a CGI-I score of "very much" improved. The proportion of patients meeting both remission criteria was 34.6% for the paroxetine group and 8% for the placebo group. This finding is particularly striking because more than 50% of the study population at baseline was rated as "markedly ill" to "among the most extremely ill" based on CGI-S.

It is interesting to note that the response rate to paroxetine in this group of children and adolescents (77.6%) was higher than that reported for adults treated with paroxetine for social anxiety disorder (55%).[11] The mean dose of paroxetine treatment in this study was 24.8 mg/d, whereas for adults the mean dose was 36.6 mg/d. Because most adults report having symptoms of social anxiety disorder in childhood,[31] it may be the case that this disorder is less treatment responsive in adulthood.

The majority of AEs ranged from mild to moderate in intensity. Adverse effects considered possibly treatment emergent (incidence ≥5% for the paroxetine group and at least twice that for the placebo group) were insomnia, decreased appetite, and vomiting. When compar-

ing AEs between age subgroups, there was some indication that the AE profile in children may differ slightly from that in adolescents. Withdrawal due to AEs was low in the paroxetine group. There were no clinically significant changes in vital signs, weight, or laboratory values in the paroxetine-treated group.

The use of antidepressants, including paroxetine, in patients younger than 18 years of age has recently come under scrutiny by regulatory authorities (and the media) because of concerns of a possible increased risk of suicidal thinking, suicide attempts, or self-harm. The Food and Drug Administration has initiated analyses of the pertinent safety data from all placebo-controlled trials of antidepressants in pediatric patients. In addition, the Food and Drug Administration has requested that all antidepressant manufacturers include a warning statement in product labeling that recommends close observation of patients with major depressive disorder or other indications for the emergence of suicidality when treated with antidepressants.

There are a number of limitations to this study. At the time it was conducted, no validated instruments were available specifically to measure symptoms of childhood social anxiety disorder; therefore, this study relied on CGI-I as the primary outcome measure. However, the LSAS-CA and the Kutcher Generalized Social Anxiety Disorder Scale for Adolescents, which produced results consistent with the CGI-I in this study, have since been validated.[25,27] Some commonly occurring comorbid conditions in adolescents with social anxiety, such as major depression and substance abuse,[32,33] were exclusion criteria for this study. Furthermore, the diagnostic instrument (Anxiety Disorders Interview Schedule) was designed primarily to assess current anxiety disorders and therefore by design did not assess the presence of some psychiatric disorders (eg, bipolar disorder) or any past disorders. The duration of the treatment period was relatively short, given the chronicity of childhood social anxiety. Although further improvement may have been possible with a longer treatment trial, the long-term maintenance of effect is best addressed via a relapse-prevention design trial. No other concomitant psychotherapy was permissible, other than the psychoeducation of patients about their illness. Lastly, some clinicians may have conducted both the efficacy and the safety assessments, which could have led to unblinding and potential bias. These limitations may impact the generalizability of the findings (efficacy and safety) to a broader population.

Psychotropic prescription for children has almost reached adult-use rates, although the evidence base for their use in children is not nearly as strong as in adults.[34,35] This study is therefore a welcome addition to the growing evidence base for the utility of SSRIs in the treatment of anxiety disorders in children.[15,18,19] While specialized individual and group behavioral therapies have also shown benefit in the treatment of childhood social anxiety disorder,[36-40] a paucity of skilled therapists limits accessibility to such treatments. It is important that clinicians determine the need for pharmacological intervention in each case of social anxiety disorder, particularly when parental education and supportive counseling prove ineffective. Paroxetine is not currently approved for use in pediatric patients.

For the purpose of demonstrating a pharmacological effect, our study design was constrained in the use of other nonpharmacological techniques that might enhance effectiveness outside of research settings. Yet there is reason to expect that the provision of simple instructions about exposure in the context of the provision of pharmacotherapy (eg, "As the medication begins to work, encourage your child to do new things; reward your child for speaking to peers") might enhance response.[16] If nothing else, such instructions are likely to enhance compliance by providing parents (and children) with a model for how they can help themselves while the children take the medication. These instructions should be shared (either by the health care provider or by the parent) with teachers and school counselors, all of whom will play an integral role in promoting socialization, increasing confidence, and helping the child to build and maintain enriching peer networks. Future research should be conducted to demonstrate the merits of combined pharmacotherapy and basic psychoeducation and/or behavioral therapy for childhood anxiety disorders.

In conclusion, this is the first multicenter, well-controlled trial to demonstrate the efficacy of paroxetine in the treatment of social anxiety disorder in children and adolescents. This finding is important and clinically meaningful given the chronicity and substantial functional and social impairment of untreated childhood social anxiety disorder.

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