Acute and Long-Term Treatment and Prevention of Relapse of Obsessive-Compulsive Disorder With Paroxetine

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Background: Limited information is available regarding optimal dosing or long-term pharmacotherapy with serotonin reuptake inhibitors in obsessive-compulsive disorder. This study evaluated the acute safety and efficacy and long-term efficacy, safety, and impact on relapse prevention of paroxetine in obsessive-compulsive disorder.

Method: We enrolled 348 outpatients with DSM-III-R obsessive-compulsive disorder in phase 1, a 12-week randomized, double-blind, parallel study of fixed doses of paroxetine (20 mg/day, 40 mg/day, or 60 mg/day) and placebo. In phase 2, 263 phase 1 completers were enrolled in 6 months of flexibly dosed open-label paroxetine treatment. In phase 3, 105 responders to open-label paroxetine were randomized to 6-month double-blind, fixed-dose, parallel paroxetine/placebo treatment to evaluate long-term efficacy, safety, and impact on relapse prevention. The study was conducted from July 1991 to February 1994.

Results: Patients in phase 1 acute treatment receiving 40 mg/day or 60 mg/day of paroxetine improved significantly ($p < .05$) more than those receiving placebo; the mean reduction in Yale-Brown Obsessive-Compulsive Scale score was 25% on 40 mg/day of paroxetine and 29% on 60 mg/day compared with 13% on placebo. During phase 3, long-term treatment, a greater proportion of placebo- (59%) than paroxetine-treated (38%) patients relapsed. Paroxetine was well tolerated at all doses, with no significant increase in frequency of adverse events during long-term compared with short-term therapy. Greater adverse events in the placebo than in the paroxetine group in phase 3 probably represent a discontinuation effect.

Conclusion: Paroxetine doses of 40 mg/day and 60 mg/day (but not 20 mg/day) are effective in treating acute obsessive-compulsive disorder. Long-term treatment with paroxetine is effective and safe, decreases the rate of relapse, and lengthens the time to relapse.

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Obsessive-compulsive disorder (OCD) is characterized by recurrent and excessive obsessions and/or compulsions, which are time consuming, cause considerable distress to the sufferer, and/or interfere with daily living. In clinical samples, the disorder is generally chronic in nature, but in some patients, symptoms may wax and wane over time. Serotonin reuptake inhibitors (SRIs), including both the selective serotonin reuptake inhibitors (SSRIs) and clomipramine, are effective treatments for patients with OCD.[1–11] These medications are also proven to be effective antidepressants, but research on fluoxetine suggests that higher doses tend to be more effective than lower doses for OCD.[4,6,12]

Although SRIs have been proven effective in acute treatment of OCD, double-blind substitution trials have shown that symptoms frequently recur within 2 to 8 weeks after discontinuation of treatment.[13–15] Thus, long-term therapy with effective agents that also have favorable tolerability and safety profiles is necessary for the successful treatment of OCD.

Research suggests that SRIs are effective as long-term treatment for OCD. A retrospective follow-up study of 85

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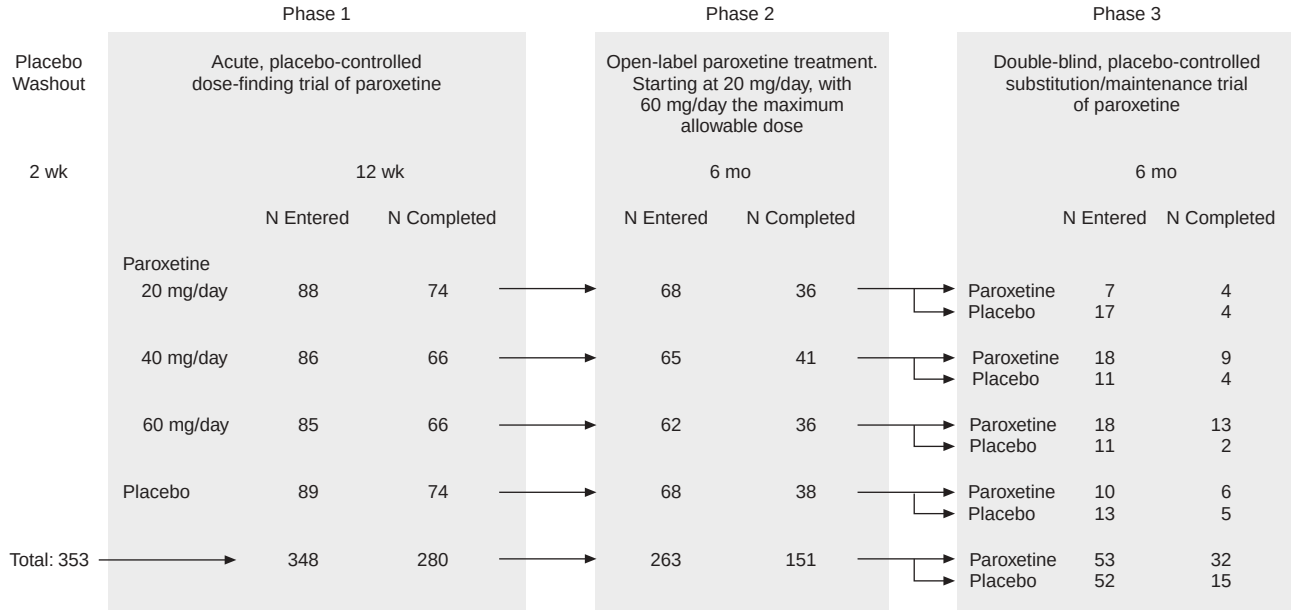
Figure 1. Design Overview and Subject Accrual in a Study of Acute and Long-Term Paroxetine Treatment of OCD



Abbreviation: OCD = obsessive-compulsive disorder.

patients with OCD reported that most of the patients treated with SSRIs for 1 to 3 years had maintained or increased symptom improvement.[16] A study of sertraline in which half the patients were on active medication for as long as 2 years (half were on placebo for the first year) showed continued efficacy.[17] Two double-blind, placebo-controlled, long-term SSRI continuation studies have reported continued efficacy and tolerability.[18,19] While valuable, these studies have inherent design limitations: since only responders to an acute trial continued into long-term maintenance, there were only a handful of placebo patients in maintenance, and there was no other control group. To date, no long-term, double-blind, placebo-controlled substitution trials have been reported. An open-label discontinuation trial followed 130 responders to 6 months of acute treatment with an SRI (clomipramine, fluoxetine, or fluvoxamine) for 2 years of treatment (or until they experienced a recurrence) with the same medication at the same dose, the same medication at half the dose, or no treatment. The study showed a superior therapeutic effect for both medication conditions compared with discontinuation of pharmacotherapy.[20]

Paroxetine, an SSRI with demonstrated effectiveness in the treatment of depression,[21] panic disorder,[22] and social phobia,[23] was also reported to be effective in a small study of OCD.[24] The current study has 2 objectives: to assess the efficacy and safety of 3 dose levels of paroxetine in the treatment of acute OCD and to assess the long-term efficacy and tolerability of paroxetine in preventing OCD recurrence.

METHOD

Overview

From July 1991 to February 1994, we conducted a 3-phase study of the SSRI paroxetine in OCD preceded by a 2-week placebo run in. The study was approved by the Institutional Review Board of each study site. Phase 1 consisted of a 12-week randomized, double-blind, placebo-controlled study of paroxetine at 3 fixed doses (20 mg, 40 mg, and 60 mg per day) designed to assess acute treatment of OCD. Unless clinically contraindicated, all patients who completed phase 1 (either paroxetine or placebo) were eligible to continue into phase 2, 6 months of open-label, flexible-dose (20–60 mg/day) paroxetine treatment designed to provide a realistic period in which to establish clinical treatment response. Patients who achieved a therapeutic response during phase 2 (compared with their post-placebo baseline prior to phase 1) were permitted to continue to phase 3, a 6-month double-blind, randomized, placebo-controlled substitution/maintenance trial of paroxetine designed to assess relapse prevention and tolerability (Figure 1).

Subjects

Outpatients, aged 16 years and older, who met *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) criteria for OCD of at least 6 months' duration were eligible to participate in this study. Additionally, total scores ≥ 7 on the National Institute of Mental Health Obsessive-Compulsive Scale

Table 1. Demographic and Clinical Characteristics of OCD Study Participants in 3 Study Phases

Characteristic	Phase 1				Phase 2	Phase 3	
		Paroxetine					
	Placebo (N = 89)	20 mg (N = 88)	40 mg (N = 86)	60 mg (N = 85)	Open Label (N = 263)	Placebo (N = 52)	Paroxetine (N = 53)
Age,[a] y							
Mean (SD)	43.1 (12.3)	40.2 (13.4)	42.1 (12.7)	40.0 (15.4)	41.5 (13.1)	40.1 (13.0)	45.1 (11.7)
Range	20–73	17–78	19–73	16–73	17–75	18–67	20–75
Gender, % (N)							
Male	67 (60)	73 (64)	72 (62)	82 (70)	72 (190)	70 (37)	64 (33)
Female	33 (29)	27 (24)	28 (24)	18 (15)	28 (73)	30 (16)	37 (19)
Race, % (N)							
White	96 (85)	98 (86)	95 (82)	94 (80)	97 (255)	98 (52)	96 (50)
Black	1 (1)	2 (2)	3 (3)	4 (3)	2 (6)	2 (1)	2 (1)
Hispanic	2 (2)	0 (0)	1 (1)	1 (1)	0 (1)	0 (0)	0 (1)
Other	1 (1)	0 (0)	0 (0)	1 (1)	0 (1)	0 (0)	0 (0)
YBOCS total score, mean (SE)[a,b]	25.6 (0.55)[a]	25.9 (0.57)[a]	25.4 (0.57)[a]	25.3 (0.57)[a]	25.5 (0.32)[a]	11.4 (0.99)[b]	11.3 (0.97)[b]
CGI-Severity score, mean (SE)[a,b]	4.7 (0.08)[a]	4.8 (0.09)[a]	4.8 (0.09)[a]	4.7 (0.09)[a]	4.8 (0.05)[a]	2.8 (0.15)[b]	2.8 (0.15)[b]

[a]Baseline of phase 1.
[b]Last phase 2 (open-label) value prior to entering phase 3.
Abbreviations: CGI = Clinical Global Impressions scale, YBOCS = Yale-Brown Obsessive-Compulsive Scale.

(NIMH-OCS)[25] and ≥ 16 on the Yale-Brown Obsessive-Compulsive Scale (YBOCS)[26,27] were required at baseline.

Participants were required to be relatively free of depressive symptomatology and to obtain a total Hamilton Rating Scale for Depression[28] score ≤ 16 on the first 17 items of the 21-item scale, and ≤ 2 on item 1. Patients who had experienced an episode of major depressive disorder within the previous 3 months or whose primary Axis I disorder was not OCD, and those with serious concomitant medical conditions, a history of seizure disorder, or a history of substance abuse were also excluded, as were all women of childbearing potential. Subjects with tics or Tourette's disorder were excluded. The diagnostic interview was conducted by a psychiatrist using DSM-III-R criteria; ratings were conducted by either a master's level psychologist or a psychiatric nurse experienced in research. Behavioral therapy during the study was prohibited, as was use of concomitant psychotropic medications, with the exception of chloral hydrate needed for sleep (up to 1000 mg). Patients who had received other investigational drugs within 30 days of baseline, any psychotropic drug within 14 days of baseline, fluoxetine within 6 weeks of baseline, or paroxetine at any time previously were not eligible to enter the study. Patients were recruited at 15 sites nationwide from clinic populations and from physician and self-referrals, some of which resulted from media coverage or advertising.

Following a full explanation of the study, including procedures and possible side effects, all subjects provided written informed consent prior to participation in the study. For phase 1, 348 patients completed the 2-week placebo washout, continued to meet all entry criteria, and were randomized to 1 of 4 treatment groups: paroxetine 20 mg/day (N = 88), 40 mg/day (N = 86), 60 mg/day (N = 85), or placebo (N = 89). The participants were predominantly white (95.7%) and had a mean age of 41.3 ± 12.3 years (range, 16 to 78 years). Because all women of childbearing potential were excluded, the sample was almost three fourths male (72.2%). The mean age at the time of OCD diagnosis was 31.8 ± 15.6 years; more than half of the patients (56.0%) reported having received previous drug treatment for OCD, most frequently with clomipramine or fluoxetine.

A computer randomization was conducted by SmithKline Beecham. Randomization for both phase 1 and phase 3 was done at the time of study entry. For phase 1, the randomization was done in groups of 4 such that assignment to the 4 treatment groups was balanced across sites. Randomization for phase 3 was independent of randomization for phase 1. Except for emergency situations, the blind was not broken for the investigational sites until the end of phase 3. Both paroxetine and placebo were provided in identical tablets and identical coded bottles. Throughout, compliance was monitored by tablet count.

Two hundred sixty-three patients who completed phase 1 entered phase 2, the open-label extension phase, and 257 of them had efficacy data while receiving study treatment. One hundred fifty-one patients completed phase 2; 105 of them met response criteria and entered phase 3, with 53 receiving paroxetine and 52 receiving placebo. There were no significant differences between participants in the 3 study phases or in the different treatment groups in either phase 1 or phase 3 in demographic or clinical characteristics at study entry (see Table 1).

Study Design

Phase 1. Following a 2-week single-blind placebo washout period, patients entered double-blind treatment.

They were randomized to receive placebo or paroxetine at a dose of 20 mg, 40 mg, or 60 mg per day. Patients assigned to 40 mg or 60 mg per day were titrated upward in 20-mg increments at weekly intervals.

Efficacy and safety were assessed at baseline, at weekly intervals during the first 4 weeks of the study, and at 2-week intervals during the remaining 8 weeks of phase 1. The primary measure of efficacy was the change from baseline in the YBOCS total score. Secondary efficacy variables included the NIMH-OCS and the Clinical Global Impressions-Severity of Illness scale (CGI-S).[29] Safety was assessed by physical examination, vital signs, laboratory evaluations, and reports of adverse effects.

Patients who completed phase 1, and for whom ongoing paroxetine therapy was not contraindicated, were eligible to continue into phase 2. Patients were not required to have responded to phase 1 treatment in order to participate in phase 2.

Phase 2. In this 6-month open-label, flexible-dosing phase, patients were treated with paroxetine to provide a population of responders, based on regular clinical practice, that would be suitable for double-blind placebo substitution/paroxetine maintenance in phase 3. Patients were administered paroxetine at a starting dosage of 20 mg/day regardless of their dose for phase 1 treatment. The dose could be escalated in 10-mg increments every 3 days until a satisfactory response (as determined by the investigator) was achieved; the maximum allowable paroxetine dosage was 60 mg/day. The mean paroxetine dosage at the end of phase 2 was 52.5 mg/day (median = 60 mg/day).

Safety variables were assessed at weekly intervals and efficacy variables at 2-week intervals during the first month of phase 2. Efficacy and safety variables were assessed at monthly intervals during the remainder of phase 2. The YBOCS and the CGI-S scores were used to assess efficacy and to determine whether a patient was a responder (see Data Analyses section below) in comparison with the patient's own baseline (at the end of the placebo washout period for phase 1). Only responders to phase 2 could proceed to phase 3.

Phase 3. The final phase was a 6-month double-blind, fixed-dose study in which patients who had responded to paroxetine in phase 2 were randomly assigned to either continue with paroxetine or switch to placebo in order to assess relapse prevention and tolerability. Those patients who were randomized to paroxetine were continued on their final phase 2 paroxetine dosages during phase 3. Patients who were randomized to placebo were switched immediately and received the placebo in pills indistinguishable from the paroxetine they had been receiving. Dosages of study medication could be decreased due to adverse events or intolerability, but not increased. Pharmacotherapy was administered in a double-blind fashion for 6 months during this phase.

Safety variables were assessed at weekly intervals and efficacy variables at 2-week intervals during the first month of phase 3. Safety and efficacy variables were assessed at monthly intervals during the remainder of the study. The efficacy variables for phase 3 were time to relapse, proportion of patients who relapsed, and the YBOCS total score. Relapse was defined as a return of the YBOCS score to baseline (the rating at the end of the placebo washout period prior to phase 1) or an increase of at least 1 point in the CGI-S score on any 1 assessment compared with the beginning of phase 3.

Data Analyses

For all phases, response to treatment was defined as a 25% or greater reduction in the YBOCS total score or a decrease of 2 points or more in the CGI-S score from the post-placebo baseline.

For phases 1 and 3, efficacy analyses are based on the intent-to-treat populations, which include all patients who received study medication for the phase and had at least 1 efficacy evaluation. Except for the analysis of relapse in phase 3, the focus of data analysis was on the final efficacy data available for each patient in each phase (last observation carried forward).

For phase 1, analysis of variance was used for continuous variables. Paired comparisons were performed between each dosage group and the placebo group only when the overall treatment effect was statistically significant; $p < .0172$ was used for each paired comparison based on Dunnett's test, which corrects for multiple comparisons in situations where multiple treatment groups will be compared with 1 control. In phase 1, tests of overall treatment effects and of linearity were significant if $p < .04588$. This alpha was adjusted from .05 as a result of an interim analysis. For phase 3, the time to relapse was analyzed via survival analysis using Cox proportional hazards model. Logistic analysis was used to evaluate the proportion of patients relapsing. Tests of hypotheses regarding treatment effects were considered significant if $p < .05$. (All tests are 2-tailed.)

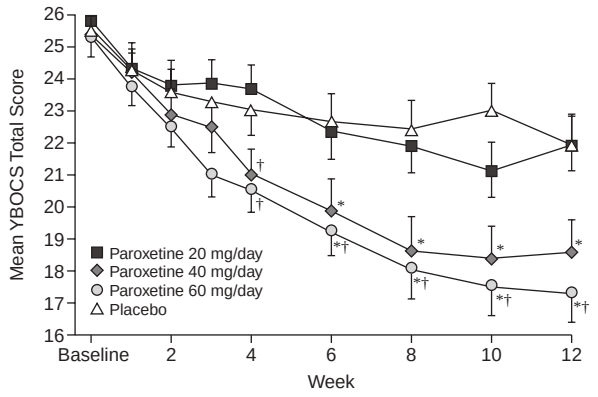
For phase 2, descriptive statistics are presented for informational purposes. Response to treatment is presented because it is a criterion for continuation into phase 3, not to assess the rate or extent of paroxetine efficacy. Because this phase was open-label rather than controlled, such data would be difficult to interpret; therefore, no statistical tests were performed.

RESULTS

Efficacy

Phase 1. Both the treatment effect ($F = 6.67$, $df = 3,322$; $p < .0001$) and linear trend ($F = 19.18$, $df = 1,322$; $p < .0001$) were statistically significant based on the change in YBOCS total score, the primary efficacy

Figure 2. Phase 1: Mean YBOCS Total Scores Over Time for Patients Treated With Paroxetine or Placebo (observed cases analysis)[a]



[a]Statistically significant differences in YBOCS score ($p \leq .0172$) using Dunnett's test as follows: *different from placebo; †different from paroxetine 20 mg/day.
Abbreviation: YBOCS = Yale-Brown Obsessive-Compulsive Scale.

measure (Figure 2). The mean reduction in YBOCS total score was 16% on 20 mg/day, 25% on 40 mg/day, and 29% on 60 mg/day of paroxetine compared with 13% on placebo. In paired comparisons, treatment with paroxetine 40 mg/day and 60 mg/day resulted in significantly greater improvement in OCD symptoms than did placebo (Figure 2, Table 2), an effect that was evident by week 6 and was maintained through the remaining 6 weeks of the trial. Specifically, both obsessions and compulsions, as measured by the YBOCS subscales, improved more in the treatment groups receiving 40 mg/day and 60 mg/day of paroxetine compared with placebo. Greater improvement was also observed on YBOCS total score (Figure 2) and on obsessive and compulsive subscales for the 60 mg/day versus the 20 mg/day of paroxetine groups.

Similarly, the treatment effect ($F = 9.53$, $df = 3,322$; $p < .0001$) and linear trend ($F = 24.83$, $df = 1,322$; $p < .0001$) were statistically significant based on change from baseline in the NIMH-OCS; the same was found for CGI-S scores ($F = 5.60$, $df = 3,322$; $p < .0001$ for the treatment effect and $F = 14.12$, $df = 1,322$; $p < .0001$ for the linear trend). Significant improvement in the NIMH-OCS was noted for the 40-mg/day ($F = 20.66$, $df = 1,322$; $p < .001$) and 60-mg/day ($F = 18.54$, $df = 1,322$; $p < .001$) paroxetine groups compared with placebo; likewise, there was significant improvement on CGI-S scores for these doses of paroxetine compared with placebo ($F = 12.73$, $df = 1,322$; $p < .001$ for 40 mg/day; $F = 10.33$, $df = 1,322$; $p = .001$ for 60 mg/day). For the NIMH-OCS, there was also a statistically greater improvement on 40 mg/day ($F = 7.98$, $df = 1,322$; $p = .005$) and 60 mg/day ($F = 6.70$, $df = 1,322$; $p = .01$) versus 20 mg/day of paroxetine.

Note that paroxetine 20 mg/day was not significantly more effective than placebo on any measure. Site and

Table 2. Phase 1: Number of Patients and Test Statistics for Statistically Significant Differences

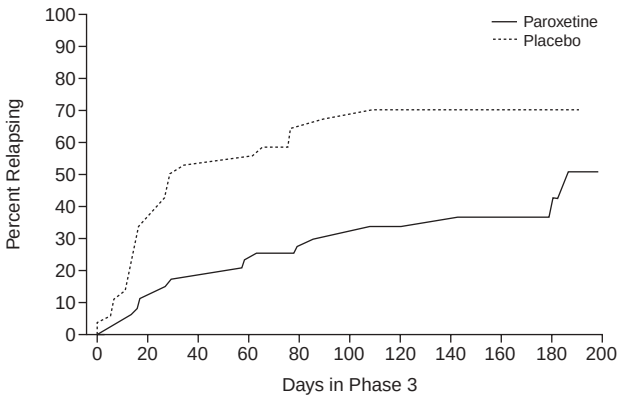
Period/Group	N	F	df	p
Paroxetine 40 mg vs placebo				
Week 6				
Paroxetine 40 mg	70	7.86	1,273	.005
Placebo	76			
Week 8				
Paroxetine 40 mg	71	11.23	1,271	.001
Placebo	75			
Week 10				
Paroxetine 40 mg	65	15.73	1,258	< .001
Placebo	72			
Week 12				
Paroxetine 40 mg	62	8.86	1,257	.003
Placebo	73			
Paroxetine 60 mg vs placebo				
Week 6				
Paroxetine 60 mg	71	13.74	1,273	< .001
Placebo	76			
Week 8				
Paroxetine 60 mg	67	15.50	1,271	< .001
Placebo	75			
Week 10				
Paroxetine 60 mg	68	24.28	1,258	< .001
Placebo	72			
Week 12				
Paroxetine 60 mg	65	16.95	1,257	< .001
Placebo	73			
Paroxetine 40 mg vs 20 mg				
Week 4				
Paroxetine 40 mg	76	5.93	1,295	.006
Paroxetine 20 mg	72			
Paroxetine 60 mg vs 20 mg				
Week 4				
Paroxetine 60 mg	72	6.94	1,295	.009
Paroxetine 20 mg	82			
Week 6				
Paroxetine 60 mg	71	6.87	1,273	.009
Paroxetine 20 mg	76			
Week 8				
Paroxetine 60 mg	67	7.52	1,271	.007
Paroxetine 20 mg	75			
Week 10				
Paroxetine 60 mg	68	6.65	1,258	.001
Paroxetine 20 mg	72			
Week 12				
Paroxetine 60 mg	65	12.35	1,257	.001
Paroxetine 20 mg	73			

site-by-treatment effects were examined in phase 1 for the key outcome variables (YBOCS, NIMH-OCS, and CGI-S). These were not marginally or statistically significant using a $p = .10$ level of significance.

Phase 2. Measures of OCD symptoms and overall illness decreased during the 6 months of open-label paroxetine treatment. At the end of phase 2, the mean YBOCS total score was 14.6 ($N = 151$) compared with a mean score of 19.8 ($N = 263$) at the end of phase 1 on paroxetine treatment. Similarly, the mean CGI-S score was 3.3 at the end of phase 2 compared with 4.1 at the end of phase 1.

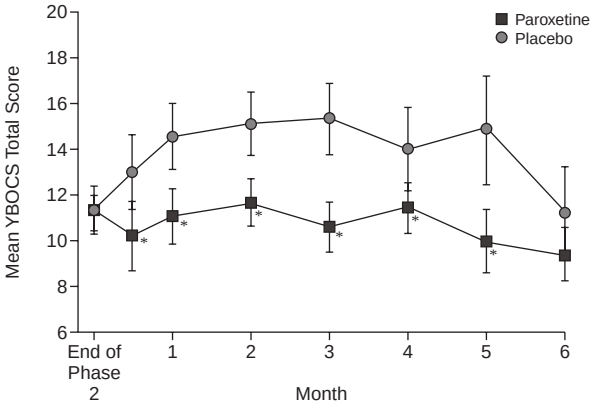
Phase 3. The survival analysis of time to relapse showed that patients in the placebo group were 2.7 times more likely to relapse at any time point than those taking paroxetine ($\chi^2 = 11.52$, $df = 1$, $p = .001$; 95% CI = 1.5 to

Figure 3. Phase 3: Kaplan Meier Survival Curves for Relapse During Treatment With Paroxetine or Placebo During the 6-Month Maintenance/Substitution Trial (intent-to-treat population: paroxetine, N = 53; placebo, N = 52)[a]



[a]Curves represent the percentage of patients who relapsed at each point.

Figure 4. Phase 3: Mean Yale-Brown Obsessive Compulsive Scale Total Scores for Patients Treated With Paroxetine or Placebo During the 6-Month Maintenance/Substitution Trial



*Statistically significant differences in YBOCS score ($p \leq .025$) from placebo group.

4.8) (Figure 3). The proportion of patients that relapsed was significantly greater for those who received placebo (58.8%, 30 of 51 with efficacy data) than for those who continued on paroxetine treatment during the 6-month randomized substitution/maintenance phase (37.7%, 20 of 53) ($\chi^2 = 4.56$, df = 1, $p \leq .033$). Mean time to relapse, including only those who relapsed, was 28.5 days for the placebo group and 62.9 days for the paroxetine group.

Patients randomized to placebo showed a rapid and significant recurrence of OCD symptoms after discontinuation of paroxetine treatment, while those who continued double-blind treatment with paroxetine showed sustained, and even improved, symptom relief compared with the end of the open-label paroxetine study phase. At the start of phase 3, YBOCS scores were similar between treatment groups ($F < 0.01$, df = 1,102; $p = .948$). During phase 3, YBOCS scores were lower for the paroxetine treatment group than for the placebo group as early as 2 weeks after beginning randomized treatment ($F = 5.25$, df = 1,68; $p \leq .025$) and were significant for all but the final week, despite the continuing removal from the study of all patients who met the lenient relapse criteria at 1 assessment and the resulting small sample sizes (Figure 4, Table 3).

Looking at those who relapsed according to the different criteria, we find that the vast majority of relapsers were determined to have relapsed based on the more lenient CGI-S criterion of a 1-point increase rather than the more conservative YBOCS criterion of return to baseline. Focusing on the conservative YBOCS criterion for relapse, 9.4% of the paroxetine-treated patients (5 of 53) compared with 21.6% of the placebo-treated group (11 of 51 with efficacy data) relapsed ($\chi^2 = 2.94$, df = 1, $p \leq .086$).

Table 3. Phase 3: Number of Patients and Test Statistics for Statistically Significant Differences

Period/Group	N	F	df	p
Week 2				
Paroxetine	19	5.83	1, 31	.022
Placebo	14			
Month 1				
Paroxetine	36	5.26	1, 8	.025
Placebo	34			
Month 2				
Paroxetine	50	8.90	1, 88	.014
Placebo	40			
Month 3				
Paroxetine	41	13.80	1, 66	< .001
Placebo	27			
Month 4				
Paroxetine	35	6.74	1, 55	.012
Placebo	22			
Month 5				
Paroxetine	28	5.78	1, 44	.021
Placebo	18			
Month 6				
Paroxetine	34	2.48	1, 48	.122
Placebo	16			

Safety

The incidence of adverse events that occurred in both acute and long-term treatment with paroxetine is noted in Table 4. Long-term treatment with paroxetine, phases 2 and 3, resulted in few new adverse events and no dramatic increases in the incidence of any adverse event compared with the short-term (12-week) treatment of phase 1. Although Fava et al.[30] reported weight gain to be a problem with long-term use of paroxetine, weight gain did not seem to be a significant problem in this study; none of the weight gain was rated as severe, it was equally split between mild and moderate, and no patients withdrew from this study due to weight gain. The percentage of patients

Table 4. Most Common Adverse Events (> 10% in any treatment group) in Acute and Long-Term Paroxetine Treatment[a]

	Phase 1				Phase 2	Phase 3	
		Paroxetine					
Adverse Event	Placebo (N = 89)	20 mg (N = 88)	40 mg (N = 86)	60 mg (N = 85)	Paroxetine (N = 263)	Placebo (N = 52)	Paroxetine (N = 53)
Abnormal dreams	0 (0)	3 (3)	5 (4)	2 (2)	8 (22)	15 (8)	13 (7)
Abnormal ejaculation[b]	2 (1)	19 (12)	32 (30)	30 (21)	23 (43)	0 (0)	11 (4)
Anxiety	6 (5)	3 (3)	5 (4)	5 (4)	6 (16)	17 (9)	11 (6)
Asthenia	9 (8)	22 (19)	17 (15)	22 (19)	17 (44)	15 (8)	8 (4)
Constipation	9 (8)	14 (12)	19 (16)	12 (10)	12 (32)	2 (1)	0 (0)
Decreased appetite	1 (1)	8 (7)	13 (11)	12 (10)	5 (12)	6 (3)	0 (0)
Depression	8 (7)	3 (3)	2 (2)	2 (2)	6 (15)	17 (9)	9 (5)
Diarrhea	12 (11)	13 (11)	12 (10)	14 (12)	8 (20)	6 (3)	0 (0)
Dizziness	8 (7)	15 (13)	8 (7)	12 (10)	14 (36)	35 (18)	9 (5)
Dry mouth	7 (6)	17 (15)	23 (20)	15 (13)	12 (31)	6 (3)	4 (2)
Headache	33 (29)	19 (17)	28 (24)	24 (20)	20 (52)	21 (11)	15 (8)
Impotence[b]	2 (1)	11 (7)	8 (5)	7 (5)	4 (8)	3 (1)	0 (0)
Infection	8 (7)	6 (5)	6 (5)	7 (6)	5 (13)	12 (6)	6 (3)
Insomnia	12 (11)	15 (13)	27 (23)	27 (23)	17 (44)	27 (14)	8 (4)
Nausea	8 (7)	20 (18)	26 (22)	18 (15)	11 (29)	27 (14)	9 (5)
Nervousness	8 (7)	10 (9)	7 (6)	11 (9)	8 (21)	21 (11)	8 (4)
Neurosis	0 (0)	1 (1)	0 (0)	1 (1)	3 (8)	33 (17)	13 (7)
Paresthesia	3 (3)	6 (5)	3 (3)	0 (0)	5 (12)	13 (7)	0 (0)
Respiratory disorder	15 (13)	9 (8)	8 (7)	9 (8)	15 (40)	10 (5)	4 (2)
Somnolence	10 (9)	25 (22)	23 (20)	33 (28)	22 (59)	4 (2)	4 (2)
Tinnitus	1 (1)	2 (2)	1 (1)	2 (2)	3 (7)	12 (6)	0 (0)
Tremor	1 (1)	9 (8)	15 (13)	11 (9)	7 (19)	10 (5)	2 (1)

[a]All values are shown as % (N).
[b]Percentage corrected for gender.

reporting weight gain after the 6 months of open-label treatment (phase 2) was 8.7%. There was no difference in weight gain between paroxetine and placebo in phase 1: of those on paroxetine, 0% on 20 mg, 1.1% on 40 mg, and 1.1% on 60 mg experienced weight gain compared with 1.0% on placebo.

During phase 1, a total of 36 patients withdrew from the trial prematurely due to adverse events, including 7 (7.9%) placebo-treated patients, 9 (10.2%) patients treated with 20 mg/day of paroxetine, 8 (9.3%) patients treated with 40 mg/day of paroxetine, and 12 (14.1%) patients treated with 60 mg/day of paroxetine. A total of 54 patients (20.5%) were withdrawn from paroxetine therapy during phase 2 due to adverse events. The most frequently reported adverse events leading to discontinuation were abnormal ejaculation (2.6% of males), nausea (2.3%), insomnia (2.3%), somnolence (1.9%), tremor (1.9%), and asthenia (1.9%).

During phase 3, 3 paroxetine-treated patients (5.7%) were withdrawn due to adverse events. In contrast, 20 placebo-treated patients (38.5%) were withdrawn, most frequently for dizziness (15.4%), nausea (13.5%), insomnia (11.5%), or "neurosis" (13.5%), defined as an increase in obsessive-compulsive symptoms. Of those adverse events that could be related to the discontinuation of paroxetine in phase 3, few were severe: nausea (N = 3, 5.7%), dizziness (N = 2, 3.8%), paresthesia (N = 1, 1.9%), and insomnia (N = 0). The assessment of OCD relapse was based on the YBOCS and CGI-S scores, not on the presence of neurosis.

DISCUSSION

This study demonstrated that paroxetine is effective and generally well tolerated in the treatment of OCD. These results also support the contention that higher doses are needed in the treatment of OCD than depression; for paroxetine treatment of OCD, doses of at least 40 mg/day are necessary. In addition, long-term paroxetine treatment can sustain the improvement in OCD symptoms obtained with short-term treatment and can prevent recurrence of symptoms.

These findings are in accord with other studies of long-term treatment in OCD. Greist and colleagues[18] reported that sertraline maintained significantly decreased YBOCS and CGI-S scores relative to baseline over a 48-week period with a trend toward additional improvement in YBOCS scores over time, as was seen in our study. Other studies of long-term fluoxetine and clomipramine treatment in OCD with different designs also suggest maintenance of therapeutic effects over time.[19,20]

Our criteria for determining response to treatment (≥ 25% reduction in YBOCS or 2-point decrease in CGI-S scores) were chosen to indicate clinically significant improvement and are similar to criteria used in other studies of OCD pharmacotherapy. However, it should be noted that while these patients had a meaningful improvement, they were not cured and, most likely, their symptoms were not reduced below diagnostic criteria. This research studied pharmacotherapy alone. At this time, it is generally considered that optimal treatment combines SSRI phar-

macotherapy with cognitive-behavioral treatment, yet there remains a need for additional options for treatment nonresponders and considerable room for improvement of OCD symptoms even in treatment responders.

Limitations of this research include the definition of relapse (worsening on 1 occasion), the predominantly male sample, the abrupt discontinuation from or dosage decrease of paroxetine in some patients, and the choice of criteria for response to treatment. These issues and the dropout rate between phase 2 and phase 3 are discussed in detail below.

While the relapse rate with paroxetine was significantly lower than with placebo, 38% of paroxetine-treated patients did relapse at a mean of 63 days into phase 3 (approximately month 8 or 11 of paroxetine treatment, depending on phase 1 randomization). Patients were withdrawn from the study at the first sign of relapse, measured in a single visit; thus patients classified as relapsed could have experienced a temporary stressor resulting in a 1-point worsening on the CGI-S, but overall may have been doing well with OCD symptoms. Relapse based on the YBOCS criterion was more clinically meaningful, but we are unable to determine whether this worsening was transient or sustained since patients were discontinued at the first sign of relapse due to ethical considerations. This may explain why the relapse rate for paroxetine (37.7%) was higher than that reported for sertraline (9%),[15] a study in which the determination of relapse required worsened symptoms over 3 consecutive visits at 2-week intervals rather than after an increase at only 1 rating timepoint.

It should be noted that the patients in this study were predominantly male (73.6% at the start of phase 1) due to a request by the U.S. Food and Drug Administration to exclude all women of childbearing potential. Although in this way the sample is not fully representative of the OCD population, neither efficacy nor safety measures showed any difference between men and women.

There was no increase in adverse events in subjects during long-term treatment in phase 2 and phase 3 compared with phase 1. However, this finding needs to be interpreted with caution given a potential for differential dropout in phase 2 due to adverse events. Because of the design of this study, patients randomized to placebo in phase 3 were abruptly withdrawn from open-label paroxetine rather than having the dose gradually decreased over time. Twenty patients (39%) withdrew from treatment after being assigned to placebo in phase 3, primarily as a result of dizziness, nausea, insomnia, and "neurosis," defined as an increase in obsessive-compulsive symptoms. Although it had not been established when this study was designed, such discontinuation symptoms have been noted after abrupt termination of paroxetine as well as other SSRIs with short half-lives.[31–36] This increase in placebo-related adverse events probably represents SRI discontinuation symptoms due to abrupt discontinuation of paroxetine. It should be noted that only 2 patients (4%) in the placebo group dropped out during the first 2 weeks of phase 3; an additional 3 patients (6%) dropped out at week 3. As a comparison, 2 patients (4%) in the paroxetine group also dropped out of phase 3 in the first 2 weeks and 1 more (2%) dropped out at week 3. Thus, discontinuation syndrome does not seem to have played a strong role in dropout from this study. While the symptoms observed upon paroxetine withdrawal were mild and self-limiting, it is important to note that good clinical practice would dictate that medication be tapered to avoid or minimize such effects.

An explanation is also warranted for the seemingly high percentage of patients (158/263; 60%) who withdrew from the study prior to entering phase 3. While 23% of these patients were considered to be nonresponders to treatment and 21% reported adverse experiences as the reason for withdrawal, the remaining patients withdrew primarily for other reasons. Of note, patients may conceivably have transiently decreased dosage from 60 mg to 20 mg on entering phase 2 due to the study design, which might have contributed to the higher dropout rate. One important consideration in choosing not to continue into phase 3 was the reluctance of some patients (and investigators) to enter into a study in which they might receive placebo. Given the often debilitating symptoms of OCD and their impact on daily activities, for some patients the possible switch to placebo was not a viable option. In addition, during the time this study was conducted, a number of SSRIs that were commercially available were reported to be effective in the treatment of OCD. These provided alternatives for treatment, especially for those concerned about symptom recurrence.

An important consideration in the management of patients with OCD is the high rate of comorbid conditions. Other psychiatric disorders such as depression and anxiety disorders can complicate the initial diagnosis of OCD as well as response to treatment and relapse rates.[37] While paroxetine has been demonstrated to be effective in treating depression, panic, social phobia, and OCD, future studies are needed to address long-term treatment and relapse in OCD patients with comorbid conditions.

Few prior studies have examined either optimal dosing or long-term efficacy of medications for the management of OCD. Given the chronic nature of this disorder and the rapid return of symptoms when pharmacotherapy is discontinued, there is a vital need for treatment that maintains efficacy over a prolonged period and is well-tolerated and safe for long-term administration. In summary, these results support the effectiveness and tolerability of paroxetine in maintaining symptom relief and preventing relapse for up to 1 year in patients with OCD.

Drug names: clomipramine (Anafranil), fluoxetine (Prozac and others), paroxetine (Paxil), sertraline (Zoloft).

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