Efficacy of Controlled-Release Paroxetine in the Treatment of Late-Life Depression

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Background: Depression is the second most common neuropsychiatric disorder in older Americans, with significant clinical and public health costs. Despite advances in treatment, late-life depression remains a clinical challenge. Although the selective serotonin reuptake inhibitors (SSRIs) are the most common pharmacologic intervention for late-life depression, few placebo-controlled trials have assessed the efficacy of SSRIs for this condition.

Method: In this 12-week, multicenter, placebo-controlled, flexible-dose, double-blind, randomized trial, 319 elderly patients (mean age = 70 years) were treated with controlled-release paroxetine (paroxetine CR) up to 50 mg/day (N = 104), immediate-release paroxetine (paroxetine IR) up to 40 mg/day (N = 106), or placebo (N = 109). Patients met DSM-IV criteria for major depressive disorder and had a total score of 18 or more on the 17-item Hamilton Rating Scale for Depression (HAM-D). The primary efficacy measure was change from baseline to endpoint in HAM-D total score.

Results: The primary efficacy analysis showed an adjusted difference between change from baseline in HAM-D score for paroxetine CR and placebo of –2.6 (95% confidence interval [CI] = –4.47 to –0.73, p = .007) at the week 12 last-observation-carried-forward (LOCF) endpoint. The adjusted difference between paroxetine IR and placebo was –2.8 (95% CI = –4.65 to –0.99, p = .003) at week 12. Paroxetine CR and IR were more effective than placebo, with mean ± SD endpoint HAM-D total scores of 10.0 ± 7.41 and 10.0 ± 7.10, respectively, for the active treatments compared with 12.6 ± 7.34 for placebo. Response, defined as a score of 1 or 2 on the Clinical Global Impressions-global improvement scale, was achieved by 72% of paroxetine CR patients (LOCF; p < .002 vs. placebo), 65% of paroxetine IR patients (p = .06 vs. placebo), and 52% of placebo patients. Remission, defined as a HAM-D total score ≤ 7, was achieved by 43% of paroxetine CR patients (LOCF; p = .009 vs. placebo), 44% of paroxetine IR patients (p = .01 vs. placebo), and 26% of placebo patients. In a post hoc analysis, mean HAM-D improvement for paroxetine CR and paroxetine IR was greater than for placebo in both chronically depressed patients (duration > 2 years) and those with short-term (≤ 2 years) depression. Dropout rates due to adverse events were 12.5% for paroxetine CR, 16.0% for paroxetine IR, and 8.3% for placebo.

Conclusion: Paroxetine CR and paroxetine IR are effective and well tolerated treatments for major depressive disorder in elderly patients, including those with chronic depression.

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Depression in later life is a significant clinical and public health concern that is receiving increasing attention as the population ages. Late-life depression is associated with disability, functional decline, chronicity, increased rates of hospitalization, diminished quality of life, mortality from comorbid medical conditions or suicide, demands on caregivers, and disproportionate utilization of health care services.[1–3] Major depressive disorder is frequently unrecognized and untreated in older individuals, particularly in primary care settings,[4] more often because of lack of awareness than lack of available treatments. An increasing number of controlled clinical trials of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have shown these agents to be equivalently effective treatments in older adults[5–8] and more effective than placebo.[9–12]

A new formulation of paroxetine has been developed to improve the traditional SSRI tolerability profile while maintaining the therapeutic benefits of paroxetine in the treatment of depression and anxiety disorders. Paroxetine HCl controlled-release (paroxetine CR) is an enteric, film-coated tablet containing a degradable polymeric matrix, which delays drug release until after the tablet passes through the stomach. This formulation controls the dissolution rate and gradually releases 80% of the dose over approximately 4 to 5 hours; 20% of the dose is retained in the tablet and is not available for systemic absorption. Although the polymeric matrix decreases the bioavailability and rate of absorption of paroxetine CR compared with paroxetine immediate release (IR), it has no effect on the distribution, metabolism, or excretion of paroxetine.

The efficacy and tolerability of paroxetine CR have been recently demonstrated in a general adult population with major depressive disorder.[13] The present report describes the findings of a multicenter, randomized, double-blind, placebo-controlled study of paroxetine CR and paroxetine IR treatment in elderly outpatients with major depressive disorder. The objectives were to compare paroxetine CR and paroxetine IR with placebo across domains of efficacy, safety, and tolerability. It was hypothesized that both paroxetine CR and paroxetine IR would be more effective than placebo treatment in decreasing baseline Hamilton Rating Scale for Depression (HAM-D) total scores. Secondary hypotheses of the study were that both paroxetine CR and paroxetine IR would cause greater improvement in the HAM-D depressed mood item score, the HAM-D anxiety item score, and Clinical Global Impressions global improvement (CGI-I) and Clinical Global Impressions-Severity of Illness (CGI-S) scores.

METHOD

Study Design

This 12-week, 31-site (29 U.S. and 2 Canadian sites), double-blind, placebo-controlled, flexible-dose, randomized trial evaluated the efficacy and tolerability of paroxetine CR and paroxetine IR in the treatment of major depressive disorder in an elderly population. Each investigative site received Institutional Review Board approval for the study, and all patients provided written informed consent. Patients who met enrollment criteria received placebo run-in medication during a 1-week screening period. The baseline visit concluded the screening period, and patients who remained eligible were randomly assigned to 1 of the 3 treatment arms. Study assessments occurred at weeks 1, 2, 3, 4, 6, 8, 10, and 12. On completion of the study or premature termination, an optional 10-day gradual taper in medication dose was recommended and used at the discretion of the investigator. Patients were seen at a final visit following this dosage-taper period for evaluation of safety parameters.

Patients recruited for this trial were at least 60 years of age and fulfilled *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, (DSM-IV) criteria for major depressive disorder[14] on the Structured Clinical Interview for DSM-IV.[15] Eligible patients had a HAM-D[16] (17-item) total score of at least 18 at both the screen and baseline visits.

Patients were ineligible if their HAM-D total score decreased by 25% or more between the screen and baseline visits. Additional exclusion criteria included concomitant therapy with psychoactive medication other than chloral hydrate (for sleep disturbance); diagnosis of a primary or predominant Axis I disorder (other than major depressive disorder) within 6 months of the screen visit; history of brief depressive episodes lasting ≤ 8 weeks with spontaneous remission; neurologic disorders contributing to secondary depression; dementia; Mini-Mental State Examination[17] score ≤ 24; serious medical conditions that would preclude paroxetine administration; history of seizure disorders; concomitant treatment with warfarin, phenytoin, cimetidine, sumatriptan, type 1C antiarrhythmic agents, or quinidine; history of DSM-IV substance abuse or dependence within 6 months; electroconvulsive therapy within 3 months; unresolved clinically abnormal laboratory or electrocardiogram (ECG) findings at baseline; and suicidal or homicidal tendencies.

Study Medication

Patients were randomly assigned at the baseline visit to receive placebo, paroxetine CR, or paroxetine IR. Doses of paroxetine CR were 25% higher than equivalent doses of paroxetine IR (i.e., 25 mg of paroxetine CR vs. 20 mg of paroxetine IR) to adjust for the 20% retention of paroxetine in the controlled-release tablet. All patients began treatment in this flexible-dose trial with paroxetine CR, 12.5 mg/day; paroxetine IR, 10 mg/day; or placebo. Study medication was dispensed to patients at each clinic visit and was overencapsulated in identically appearing capsules to maintain double-blind conditions. Beginning at week 2, dosage escalation was permitted if, in the investigator's judgment, therapeutic response was inadequate and the medication was well tolerated. Increases of daily dose for blinded study medications were allowed at a rate of 1 capsule per week up to a maximum of 4 per day, representing 12.5 to 50 mg of paroxetine CR or 10 to 40 mg of paroxetine IR.

Efficacy Assessments

At baseline and at weeks 1, 2, 3, 4, 6, 8, 10, and 12, efficacy was assessed with the 17-item HAM-D[16] and the CGI-S.[18] The CGI-I was administered at all visits except the baseline visit. Primary efficacy was evaluated by determination of the change from baseline to study endpoint in the 17-item HAM-D total score. Secondary analyses also were conducted, including change from baseline in the HAM-D depressed mood, HAM-D anxiety (i.e., item 10 psychic anxiety), and CGI-S scores. Therapeutic response was defined as the proportion of patients with a score of 1 or 2 on the CGI-I at the week 12 endpoint. Remission was defined as the proportion of patients with a HAM-D total score of ≤ 7 at the week 12 endpoint.[19] It is noteworthy that among the secondary analyses, the definitions of HAM-D anxiety (item 10) and remission (HAM-D score ≤ 7) were revised from the initial protocol as post hoc evaluations: HAM-D anxiety was initially defined as the sum of items 10, 11, 12, 13, 15, and 17, and HAM-D remission was initially defined as HAM-D score ≤ 8.

Safety Assessments

Safety and tolerability were monitored by assessing adverse experiences and vital signs at each visit. Open-

ended questions were used to elicit reporting of adverse experiences. Laboratory evaluations were performed at screen or baseline and at weeks 6 and 12 (or on premature termination). Physical examination and ECG were performed at screen and study completion or on premature termination.

Statistical Analysis

Paroxetine CR and paroxetine IR were compared with placebo at study endpoint using 2-tailed statistical tests. No statistical comparisons were made between paroxetine CR and paroxetine IR. The differences between each formulation of paroxetine and placebo were estimated from the analysis, and 95% confidence intervals (CIs) were constructed around the estimated differences.

A total of 90 assessable patients per treatment group was determined to be sufficient to detect an adjusted mean difference of 4.5 points in the changes from baseline to the week 12 last-observation-carried-forward (LOCF) endpoint in the HAM-D total score between each formulation of paroxetine and placebo. This determination is based on a variance of 76.5 and normally distributed errors. This adjusted mean difference was detectable with a power of 90%, given a significance level of 5% and using a 2-sided significance test.

The population of interest was the intention-to-treat (ITT) population, which was defined as all patients who were randomly assigned to treatment, received at least 1 dose of study medication, and had at least 1 postbaseline assessment. Any patient who received a dose of study medication was included in the safety analysis. Primary efficacy of paroxetine CR and paroxetine IR was determined by LOCF for the ITT population. Observed-cases (OC) analyses of the HAM-D total score change from baseline were also performed. In the LOCF analysis, the last observation on treatment was carried forward to estimate missing information for patients who withdrew before completing the 12-week study. The OC population consisted of patients who received study medication and completed the entire 12 weeks; missing data are not extrapolated in an OC analysis.

Categorical efficacy variables (CGI-I, HAM-D remission) were analyzed using logistic regression, and results were presented in terms of 95% CIs and odds ratios (ORs) for active treatment compared with placebo treatment. Adjustments were made for the effect of center and prospectively defined covariates (i.e., age, gender, duration of current depressive episode, baseline HAM-D total score). The assumptions of normality and homogeneity of variance were assessed by inspection of normal probability plots, plots of standardized residuals versus predicted values, and plots of standardized residuals versus continuous covariates. No major violations of these assumptions were found. Continuous variables, such as the HAM-D total score mean change from baseline, were evaluated using analysis of variance with 95% CI, adjusting for center and the prospectively defined covariates previously cited. The median change from baseline in CGI-S score was analyzed using the Wilcoxon rank sum test. All statistical tests were conducted at the 5% level, 2-sided, whereas potential interactions (i.e., treatment by center) were evaluated at the 10% level.

Table 1. Disposition of 319 Randomized Elderly Patients in the Intention-to-Treat Population, N (%)

Disposition	Paroxetine CR (N = 104)	Paroxetine IR (N = 106)	Placebo (N = 109)
Withdrawn (total)	23 (22.1)	30 (28.3)	25 (22.9)
Adverse experience	13 (12.5)	17 (16.0)	9 (8.3)
Lack of efficacy	4 (3.8)	2 (1.9)	5 (4.6)
Protocol deviation	3 (2.9)	8 (7.5)	3 (2.8)
Lost to follow-up	1 (1.0)	1 (0.9)	3 (2.8)
Other	2 (1.9)	2 (1.9)	5 (4.6)
Completed week 12 (total)	81 (77.9)	76 (71.7)	84 (77.1)

Abbreviations: CR = controlled release, IR = immediate release.

RESULTS

Baseline Characteristics and Disposition

A total of 323 patients were randomly assigned to treatment and received at least 1 dose of study medication. However, 2 patients in the paroxetine CR group and 2 in the paroxetine IR group were not included in the ITT analysis because postbaseline safety or efficacy assessments were not obtained. Thus, the ITT population consisted of 319 patients (paroxetine CR, 104; paroxetine IR, 106; placebo, 109). Reasons for study discontinuation are shown in Table 1; 78% of the patients in the paroxetine CR group, 72% of patients in the paroxetine IR group, and 77% of patients in the placebo group completed the study. The mean daily doses of paroxetine CR and paroxetine IR in the LOCF dataset at week 12 study endpoint were 30.4 mg and 25.7 mg, respectively.

The treatment groups had similar demographic characteristics and histories of depression (Table 2). The mean baseline HAM-D total scores were similar for the paroxetine CR, paroxetine IR, and placebo treatment arms. Most patients were enrolled in the study during their first episode of major depressive disorder. However, approximately 25% had recurrent major depressive disorder, and only 25% to 28% of these patients received antidepressant treatment for prior episodes of depression. The mean ± SD duration of the current depressive episode exceeded 2 years for each of the treatment groups (paroxetine CR, 2.9 ± 4.2 years; paroxetine IR, 3.4 ± 6.0 years; and placebo, 4.1 ± 8.8 years). The majority of patients (> 90%) had medical diagnoses and were receiving concomitant medications for these illnesses. This population can be characterized as medically ill elders with chronic (i.e., > 2 years' duration), late-onset major depressive disorder.

Table 2. Demographic Characteristics and Depression History of the 319 Randomized Elderly Subjects in the Intention-to-Treat Population

Parameter	Paroxetine CR (N = 104)	Paroxetine IR (N = 106)	Placebo (N = 109)
Age group, N (%)			
60–65 y	21 (20.2)	27 (25.5)	27 (24.8)
66–74 y	57 (54.8)	54 (50.9)	63 (57.8)
75–84 y	25 (24.0)	23 (21.7)	19 (17.4)
≥ 85 y	1 (1.0)	2 (1.9)	0 (0)
Age, mean (SD), y	70.4 (5.9)	70.1 (6.6)	69.4 (5.4)
Age range, y	60–88	60–88	60–82
Weight, mean (SD), lb	175.4 (34.2)	173 (42.0)	170 (33.9)
Gender, N (%)			
Female	50 (48.1)	60 (56.6)	69 (63.3)
Male	54 (51.9)	46 (43.4)	40 (36.7)
Race, N (%)			
White	100 (96.2)	101 (95.3)	103 (94.5)
African American	2 (1.9)	1 (0.9)	2 (1.8)
Asian	0 (0)	2 (1.9)	0 (0)
Other	2 (1.9)	2 (1.9)	4 (3.7)
No. of prior depressive episodes in past 5 years, N (%)			
None	80 (76.9)	76 (71.7)	85 (78.0)
1	13 (12.5)	12 (11.3)	11 (10.1)
2	3 (2.9)	6 (5.7)	6 (5.5)
3–4	1 (1.0)	5 (4.7)	4 (3.7)
≥ 5	7 (6.7)	7 (6.6)	3 (2.8)
Used antidepressants for prior depressive episode, N (%)	29 (27.9)	26 (24.5)	29 (26.6)
Duration of current episode, mean (SD), y	2.9 (4.2)	3.4 (6.0)	4.1 (8.8)
Interval between current and most recent episode, mean (SD), y	5.9 (12.4)	3.4 (8.2)	4.4 (8.2)
Concomitant medical diagnoses, N (%)	96 (92.3)	101 (95.3)	102 (93.7)
Concomitant medications, N (%)	103 (99.0)	99 (93.4)	103 (94.5)

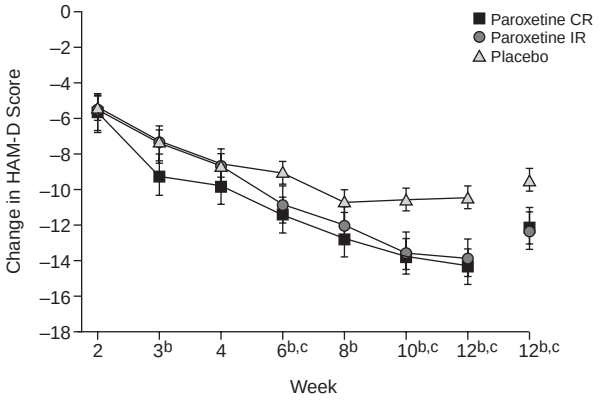
Abbreviations: CR = controlled release, IR = immediate release.

Table 3. Baseline and Change From Baseline in HAM-D Total Score in the Intention-to-Treat LOCF Population (adjusted for center and covariates)[a]

	Paroxetine CR (N = 104)		Paroxetine IR (N = 106)		Placebo (N = 109)	
Score	Mean	SD	Mean	SD	Mean	SD
Baseline	22.1	3.45	22.3	3.15	22.1	3.00
Change from baseline	–12.1	7.41	–12.3	7.10	–9.5	7.34
Week 12 endpoint	10.0	7.41	10.0	7.10	12.6	7.34

[a]Difference in change from baseline to week 12 endpoint between paroxetine CR and placebo: mean = –2.6, 95% CI = –4.47 to –0.73, F = 7.51, df = 1,289; p = .007. Difference in change from baseline to week 12 endpoint between paroxetine IR and placebo: mean = –2.8, 95% CI = –4.65 to –0.99, F = 9.17, df = 1,289; p = .003.
Abbreviations: CI = confidence interval, CR = controlled release, HAM-D = Hamilton Rating Scale for Depression, IR = immediate release, LOCF = last observation carried forward.

Figure 1. Change From Baseline in HAM-D Total Scores Across 12 Weeks of Treatment With Paroxetine CR, Paroxetine IR, or Placebo (OC dataset) and at Week 12 Study Endpoint (LOCF dataset)[a]



[a]Ranges are standard errors.
[b]Paroxetine CR vs. placebo, p < .05.
[c]Paroxetine IR vs. placebo, p < .01.
Abbreviations: CR = controlled release, HAM-D = Hamilton Rating Scale for Depression, IR = immediate release, LOCF = last observation carried forward, OC = observed cases.

LOCF Efficacy Analysis

Primary efficacy endpoint. The primary efficacy variable was mean change from baseline in the HAM-D total score. The statistical analysis of the primary variable showed an adjusted difference between change from baseline for paroxetine CR and placebo of –2.6 (95% CI = –4.47 to –0.73, p = .007) at the week 12 LOCF endpoint (Table 3). This analysis also revealed a difference between paroxetine IR and placebo of –2.8 (95% CI = –4.65 to –0.99, p = .003) at the week 12 LOCF endpoint. These differences demonstrate that paroxetine CR and paroxetine IR were effective relative to placebo, with mean ± SD endpoint HAM-D total scores of 10.0 ± 7.41 and 10.0 ± 7.10, respectively, for both active treatments compared with 12.6 ± 7.34 for placebo. At the week 12 endpoint, the mean differences between placebo and both of the active treatments were statistically significant (Figure 1).

Secondary efficacy endpoints. Paroxetine CR and paroxetine IR also alleviated symptoms of depressed mood and psychic anxiety. Patients in the paroxetine CR group exhibited a 51% improvement over the mean ± SD baseline score of 2.7 ± 0.61 in the HAM-D depressed mood item 1 compared with a 33% improvement over the baseline score of 2.7 ± 0.62 in the placebo group (F = 11.73, df = 1,287; p < .001 vs. placebo; adjusted difference = –0.5; 95% CI = –0.8 to –0.2). Similarly, a 50% improvement over the baseline score of 2.8 ± 0.61 in depressed mood symptoms occurred among patients in the paroxetine IR group (F = 13.74, df = 1,287; p < .001 vs. placebo; adjusted difference = –0.5; 95% CI = –0.8 to –0.3).

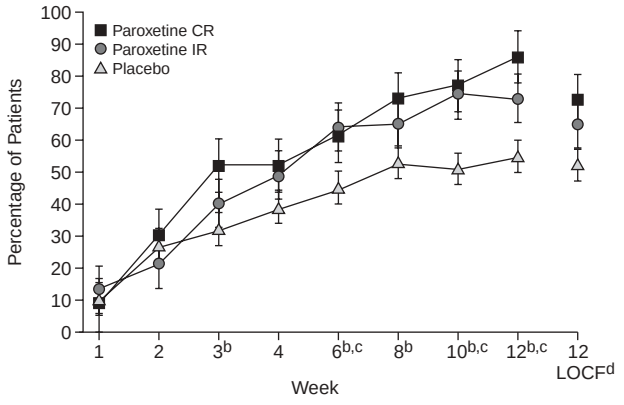
At LOCF endpoint in the HAM-D item 10 score, which measures psychic anxiety, patients in the par-

Table 4. Distribution of the Change From Baseline in CGI-S Score at Week 12 Endpoint, N (%)[a,b]

Change From Baseline	Paroxetine CR (N = 104)	Paroxetine IR (N = 106)	Placebo (N = 109)
–5	3 (2.90)	1 (1.00)	2 (1.90)
–4	5 (4.90)	4 (3.90)	3 (2.80)
–3	17 (16.50)	25 (24.30)	12 (11.30)
–2	32 (31.10)	25 (24.30)	22 (20.80)
–1	22 (21.40)	23 (22.30)	31 (29.20)
0	20 (19.40)	24 (23.30)	36 (34.00)
1	3 (2.90)	1 (1.00)	0 (0.00)
2	1 (1.00)	0 (0.00)	0 (0.00)

[a]One patient in the paroxetine CR group and 1 patient in the placebo group were not recorded.
[b]Comparisons of median reduction from baseline were as follows: paroxetine CR vs. placebo, p = .022; paroxetine IR vs. placebo, p = .019.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, CR = controlled release, IR = immediate release.

Figure 2. Weekly Therapeutic Response (CGI-I score of 1 or 2) Across 12 Weeks of Treatment With Paroxetine CR, Paroxetine IR, or Placebo (OC dataset) and at Week 12 Study Endpoint (LOCF dataset)[a]

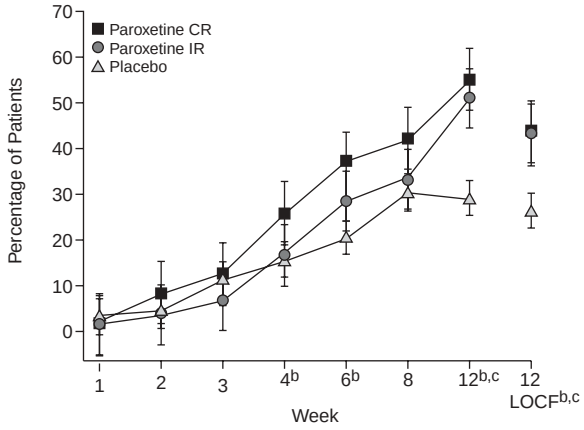


[a]Ranges are standard errors of the proportion.
[b]Paroxetine CR vs. placebo, p < .001.
[c]Paroxetine IR vs. placebo, p = .04.
[d]Paroxetine CR vs. placebo, p < .002; paroxetine IR vs. placebo, p = .06.
Abbreviations: CGI-I = Clinical Global Impressions-global improvement scale, CR = controlled release, IR = immediate release, LOCF = last observation carried forward, OC = observed cases.

oxetine CR group achieved a 50% improvement from the mean baseline score of 2.0 ± 0.71 compared with a 41% improvement from the baseline score of 2.2 ± 0.72 for the placebo group (F = 2.80, df = 1,282; p = .1; 95% CI = –0.5 to 0.04). There was a 52% improvement in anxiety symptoms over the baseline score of 2.1 ± 0.81 in the paroxetine IR group (F = 3.62, df = 1,282; p = .06 vs. placebo; 95% CI = –0.5 to 0.01).

Improvement in CGI-S scores also occurred among patients treated with paroxetine CR or paroxetine IR. Median baseline CGI-S scores were identical (a score of 4) for all 3 treatment groups. In the LOCF dataset, the median reduction from baseline at week 12 was 2 points for

Figure 3. Weekly Remission Rates (HAM-D total score ≤ 7) Across 12 Weeks of Treatment With Paroxetine CR, Paroxetine IR, or Placebo (OC dataset) and at Week 12 Study Endpoint (LOCF dataset)[a]



[a]Ranges are standard errors of the proportion.
[b]Paroxetine CR vs. placebo, p < .01.
[c]Paroxetine IR vs. placebo, p ≤ .02.
Abbreviations: CR = controlled release, HAM-D = Hamilton Rating Scale for Depression, IR = immediate release, LOCF = last observation carried forward, OC = observed cases.

both paroxetine CR (χ^2 = 5.2, df = 1, p = .022) and paroxetine IR (χ^2 = 5.5, df = 1, p = .019) compared with placebo (reduction of 1 point). In total, a 2-point (or greater) improvement in baseline CGI-S scores was achieved at endpoint by 55% of patients in the paroxetine CR group, 54% in the paroxetine IR group, and 37% in the placebo group. The proportion of patients achieving various degrees of change from baseline in the 7-point CGI-S score is shown in Table 4.

LOCF response analysis. Response, which reflects clinically relevant improvement in symptoms, was defined as a score of 1 or 2 on the CGI-I. At LOCF endpoint, 72% of paroxetine CR patients (χ^2 = 8.5, p < .002; adjusted OR = 2.6; 95% CI = 1.4 to 4.7) and 65% of paroxetine IR patients (χ^2 = 3.8, p = .06; adjusted OR = 1.7; 95% CI = 1.0 to 3.1) were responders compared with 52% of placebo patients (Figure 2).

LOCF remission analysis. Remission was defined as an endpoint HAM-D total score of 7 or less. The endpoint LOCF HAM-D remission analysis found that 43% of paroxetine CR-treated patients (χ^2 = 6.7, p = .009 vs. placebo; adjusted OR = 2.3; 95% CI = 1.2 to 4.3), 44% of paroxetine IR-treated patients (χ^2 = 6.7, p = .01 vs. placebo; adjusted OR = 2.3; 95% CI = 1.2 to 4.3), and 26% of placebo-treated patients achieved remission (Figure 3).

OC Efficacy Analysis

Primary efficacy endpoint. In the OC analysis, which captured patients who stayed on treatment for the full 12 weeks, statistical evaluation revealed an adjusted differ-

ence between paroxetine CR and placebo of –3.8 at week 12 endpoint (95% CI = –5.7 to –2.0; F = 16.71, df = 1,209; p < .001 vs. placebo). For paroxetine IR, statistical evaluation showed a difference between the active treatment and placebo of –3.4 (95% CI = –5.2 to –1.6; F = 13.50, df = 1,209; p < .001 vs. placebo). Similar to the LOCF analysis, these differences demonstrate efficacy for both active treatments, with a mean ± SD HAM-D total score at endpoint for the paroxetine CR group of 7.7 ± 6.26 compared with 11.6 ± 6.08 for the placebo group and a mean HAM-D total score at endpoint of 8.4 ± 5.98 for the paroxetine IR group. Paroxetine CR resulted in improvement in the HAM-D total scores that maintained significant separation from placebo beginning at week 6. Sustained statistical separation between paroxetine IR and placebo occurred at week 10 (Figure 1).

Secondary efficacy endpoints. In the OC endpoint analysis, mean HAM-D depressed mood scores improved 63% versus baseline for paroxetine CR (F = 21.65, df = 1,207; p < .001 vs. placebo; difference = –0.7; 95% CI = –1.1 to –0.4) and 57% for paroxetine IR (F = 15.05, df = 1,207; p < .001 vs. placebo; difference = –0.6; 95% CI = –0.9 to –0.3) compared with 33% for placebo. Patients in the paroxetine CR group achieved a 60% improvement versus baseline for HAM-D item 10 scores (F = 5.89, df = 1,232; p = .02; 95% CI = –0.6 to –0.07), which was a significantly greater change compared with the 50% improvement in the placebo group. In the paroxetine IR group, the mean HAM-D item 10 score improved 57% versus baseline, but did not separate statistically from placebo (F = 3.39, df = 1,232; p = .07; adjusted difference 95% CI = –0.6 to –0.02).

OC response analysis. At OC endpoint, 86% of paroxetine CR patients achieved a CGI-I score of 1 or 2 and were considered to be responders (χ^2 = 16.5, p < .001; adjusted OR = 6.5; 95% CI = 2.8 to 15.1) compared with 55% of patients in the placebo group. In the paroxetine IR group, 73% of patients were responders (χ^2 = 3.8, p = .04 vs. placebo; adjusted OR = 2.1; 95% CI = 1.0 to 4.4) (Figure 2).

OC remission analysis. The endpoint OC remission analysis revealed that 55% of patients in the paroxetine CR group (χ^2 = 8.8, p = .003 vs. placebo; adjusted OR = 3.0; 95% CI = 1.5 to 6.2), 51% of paroxetine IR patients (χ^2 = 5.9, p = .02 vs. placebo; adjusted OR = 2.4; 95% CI = 1.2 to 5.0), and 29% of placebo patients were remitters (Figure 3).

Treatment Interactions

Post hoc analyses. A post hoc OC analysis was conducted on the HAM-D total scores to determine if chronicity was a factor in response. Information regarding the duration of the current depressive episode was obtained through patient interviews and psychiatric history while determining study eligibility. Based on reductions in baseline HAM-D total scores, patients with chronic depression (i.e., episodes lasting longer than 2 years) appeared to respond as well as patients with more short-term episodes to both paroxetine CR and paroxetine IR. For example, the mean (SE) HAM-D total score at endpoint in the paroxetine CR group was 8.0 (0.82) for patients with depressive episodes lasting 2 years or less (p = .04 vs. placebo; baseline HAM-D total score = 22.3; difference = –2.2; 95% CI = –4.4 to –0.1) and 8.1 (1.09) in patients with chronic depression (p < .001 vs. placebo; baseline HAM-D total score = 21.7; difference = –6.8; 95% CI = –9.8 to –3.7). In the paroxetine IR group, mean (SE) HAM-D total scores at endpoint were 8.2 (0.91) (p = .07 vs. placebo; baseline = 22.4; difference = –2.0; 95% CI = –4.2 to 0.2) and 8.9 (1.26) (p = .0002 vs. placebo; baseline = 22.2; difference = –6.0; 95% CI = –9.2 to –2.9) for patients with shorter-term and chronic depression, respectively. In contrast, patients with chronic depression in the placebo group had higher adjusted mean (SE) endpoint HAM-D total scores (15.6 [1.21]; baseline = 22.7) compared with placebo-treated patients with episodes less than 2 years in duration (10.2 [0.85]; baseline = 21.8).

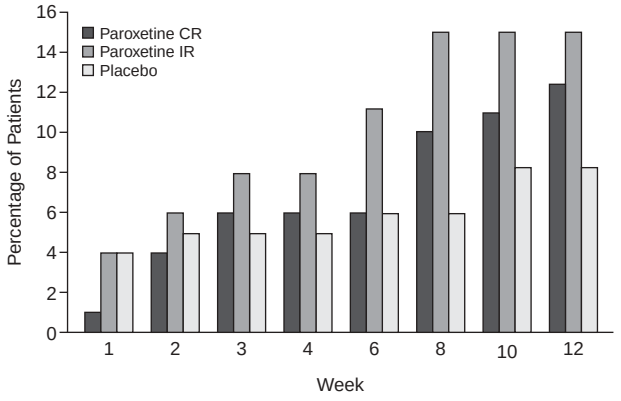
To determine if sex was a factor in treatment response, a post hoc OC analysis was conducted on mean baseline and mean endpoint HAM-D total scores. In the paroxetine CR group, mean (SE) HAM-D total scores at endpoint were 8.7 (0.90) for men (p = .0004 vs. placebo; difference = –4.6; 95% CI = –7.1 to –2.1) and 7.2 (0.93) for women (p = .02 vs. placebo; difference = –3.1; 95% CI = –5.8 to –0.4). Mean (SE) HAM-D total scores at endpoint in the paroxetine IR group were 7.5 (1.29) for men (p = .01 vs. placebo; difference = –3.0; 95% CI = –5.3 to –0.6) and 8.9 (0.88) for women (p = .0004 vs. placebo; difference = –4.3; 95% CI = –7.2 to –1.3). Thus, paroxetine CR and paroxetine IR were significantly more effective than placebo in both men and women.

Adverse Events and Adherence

Paroxetine CR was well tolerated in this population of medically ill elderly patients with chronic depression. The majority of reported adverse events were mild in severity for patients in all treatment groups. Rates of premature study withdrawal due to adverse events (Table 1) for paroxetine CR were 12.5%, 16.0% for paroxetine IR, and 8.3% for placebo. The weekly rate of premature withdrawals due to adverse events was consistently lower for patients in the paroxetine CR group compared with patients in the paroxetine IR group (Figure 4). Rates of medication adherence were high in paroxetine CR (96.3%), paroxetine IR (93.2%), and placebo (97.5%) patients who remained in the trial (i.e., OC dataset).

The most common adverse events, reported in > 10% of patients, were somnolence, dry mouth, headache, abnormal ejaculation, diarrhea, asthenia, nausea, constipation, dyspepsia, and decreased appetite. These adverse

Figure 4. Cumulative Weekly Withdrawal Rates Due to Adverse Events for Patients Treated With Paroxetine Controlled Release (CR), Paroxetine Immediate Release (IR), or Placebo



events are typical of those expected during treatment with an SSRI.

It is noteworthy that reports of hypotension and insomnia, events that are cause for concern in an elderly population, were similar in the paroxetine CR group (4.8% and 9.6%, respectively) and the placebo group (3.7% and 8.3%). Rates of hypotension and insomnia in the paroxetine IR group were 12.3% and 14.2%, respectively. Asthenia, nausea, dyspepsia, nervousness, and ECG abnormalities were reported at similar, low rates for all treatment groups.

Treatment with paroxetine CR and paroxetine IR was associated with minor, clinically insignificant changes in body weight, which was measured at baseline and study endpoint. The mean ± SD change at endpoint was +0.76 ± 5.80 lb (+0.34 ± 2.61 kg) for paroxetine CR, –1.89 ± 5.44 lb (–0.85 ± 2.45 kg) for paroxetine IR, and +0.56 ± 4.60 lb (+0.25 ± 2.07 kg) for placebo.

DISCUSSION

This multicenter, randomized, double-blind, placebo-controlled study is the first to report on the efficacy and tolerability of both paroxetine CR and paroxetine IR in the treatment of late-life depression. We chose to report both the LOCF and OC analyses. An LOCF analysis is a rigorous test of the data because it includes findings from all patients, even those who may have received as little as a single dose. In contrast, the OC analysis is a more clinically informative assessment of the data because it reflects the status of patients who completed the full course of therapy. Paroxetine CR and paroxetine IR demonstrated efficacy in this population in both LOCF and OC analyses. Paroxetine CR and paroxetine IR were effective on the primary efficacy measure, reduction in baseline HAM-D total score, and in improving symptoms of depressed mood and psychic anxiety.

We employed a standard definition of remission, an endpoint HAM-D total score ≤ 7.[19] We found that both paroxetine CR and paroxetine IR produced a robust therapeutic effect in this elderly patient population over a relatively short period of time. Nearly 45% of patients in the paroxetine CR and paroxetine IR groups fulfilled criteria for remission in the LOCF analysis. A majority of patients who continued paroxetine CR or paroxetine IR treatment to the end of the study (i.e., the OC analysis) achieved full remission after 12 weeks of treatment. These findings are striking and clinically important. Although high rates of remission were observed in the placebo group for the LOCF and OC analyses (i.e., 26% and 29%, respectively), these observations are consistent with studies in the general adult population.[13,20,21]

Patients treated with paroxetine CR demonstrated an earlier separation from placebo compared with patients in the paroxetine IR group. This pattern of results was also found in the rates of response and remission for paroxetine CR. The improved tolerability early in treatment with paroxetine CR may allow patients to experience the therapeutic benefits of paroxetine with minimal SSRI-associated adverse events. We caution against concluding that paroxetine CR is associated with earlier onset of action, because this study was not designed to test that hypothesis. Nonetheless, our findings are notable because of the baseline severity of depression and complexity of the patient sample. A growing number of psychopharmacologic treatment studies in late-life depression[5,8,22–24] are demonstrating that SSRIs are equivalently effective with other SSRIs or TCAs in this population. However, the patients enrolled in most studies are not generally medically ill or chronically depressed. In contrast to some of the other trials investigating late-life depression, the mean age of patients in our study was approximately 70 years, with approximately 20% of patients being 75 years of age or older. The majority of patients had 1 or more concomitant medical illness and were being treated with multiple nonpsychoactive medications. Although approximately 20% of patients in our study had recurrent depression, most had late-onset depression (i.e., first episode occurred after the age of 60 years). Late-onset depression is believed to have a different course and treatment response, and possesses unique findings on structural neuroimaging (e.g., increased white-matter hyperintensities)[25–27] in contrast to adult-onset major depressive disorder. Persons who experience their first episode of major depressive disorder in late life may be candidates for lifelong antidepressant treatment.[26] Thus, tolerable treatments that do not compromise medication adherence are essential. For these reasons, the demonstrated efficacy and tolerability of paroxetine CR in this complex cohort are particularly noteworthy.

The findings of our study are remarkable because this is one of the first reports of SSRI treatment in an elderly population that was identified by history as having chronic depression. The DSM-IV defines chronic depression as an episode of major depressive disorder lasting for 2 or more years.[14] Most patients in our study reported being ill for at least 3 years. The treatment of chronic depression is remarkably understudied in the general adult population, and published experience to date consists of 2 acute-treatment studies[21,28] and 2 maintenance studies.[29,30] Chronic depression is thought to be difficult to treat and may require higher doses and longer courses of therapy than are needed for shorter depressive episodes.[29–31] Moreover, chronic depression is associated with increased psychosocial impairment, relapse, recurrence, and risk of further chronicity.[32] Remarkably, there were no treatment-by-center interactions identified by the LOCF or OC analyses. Although issues related to concurrent medical illness, dementia, and mortality are frequently associated with the diagnosis of depression in older individuals,[33] these potential mediators were not significant factors in this study.

The post hoc analysis of patients with short-term versus chronic depression in our study suggested that those with chronic depression responded as well to paroxetine CR as did patients with more short-term courses. These are encouraging findings, because elderly patients frequently present with long-standing episodes of depression. Additional research in prospectively designed trials is needed to further address the issue of chronicity of depression and treatment response.

The findings of 1 prospective, randomized, controlled study[34] suggest that there is a gender difference in treatment response in major depressive disorder, with women demonstrating higher response rates to sertraline and lower rates of response to imipramine than men. Premenopausal women in that study were particularly likely to show a differential treatment response, suggesting that female reproductive hormones may influence response to SSRIs. To explore the role of gender in treatment response, we conducted a post hoc analysis in women versus men. Our preliminary findings did not suggest that there is a gender effect in response to paroxetine CR. This issue remains of interest, particularly in elderly postmenopausal women receiving hormone replacement therapy. Retrospective analyses of data from late-life depression studies of SSRI treatment of elderly women with major depression suggest that estrogen replacement therapy may be associated with enhanced antidepressant response compared with sertraline or fluoxetine alone.[35,36] Prospective studies of gender response to paroxetine CR and effect of hormone replacement therapy are warranted in this population.

Paroxetine CR and paroxetine IR demonstrated benign adverse effect profiles in this study, which is a desirable feature for antidepressant therapy, particularly in the medically complex population that is typical of late-life depression. It is noteworthy that hypotension and insomnia, which are of particular concern in the elderly population, occurred at a rate comparable to the rate observed with placebo. The reported adverse events of paroxetine CR in this study were generally mild to moderate in severity. The nature of adverse events leading to withdrawal from treatment for both active groups was similar to other evaluations of paroxetine CR and paroxetine IR.[13,22] However, the rate of treatment withdrawals due to adverse events was consistently lower for paroxetine CR than for paroxetine IR throughout the course of the trial. Our findings are important because the use of well-tolerated antidepressants, such as paroxetine CR, may facilitate greater treatment adherence, particularly in elderly patients who often are treated with multiple medications and are prone to medication intolerance and poor medication adherence.[37–39] The improved tolerability of paroxetine CR may be due to the expected performance of this new formulation, which provides a controlled release of paroxetine. This decreases the C_{max} of the compound and may decrease the likelihood of concentration-related side effects.

Although this study has evaluated the use of paroxetine CR and paroxetine IR in elderly patients with major depressive disorder, it has some limitations. We did not address the treatment of depression in patients who are residents of nursing homes or other long-term care facilities or in patients with more severe or unstable medical illness. Of course, these areas remain of considerable importance when the treatment of major depressive disorder in elderly patients is discussed. Equally important are concerns related to improvements in the quality of life for elderly depressed persons. This issue also deserves further exploration and should be the topic of future research. The relationship between patient age, age at onset of depression, and burden of medical illness with treatment response and adverse events was not addressed in this trial and deserves future study. Furthermore, our post hoc findings regarding chronicity and sex need to be viewed as exploratory findings and not conclusive results. Hormone replacement therapy, a possible influence on antidepressant response in elderly women, will be addressed in future manuscripts.

CONCLUSIONS

Paroxetine IR has been consistently demonstrated to be equivalently effective and well tolerated compared with other antidepressants for treatment of late-life depression.[6–8,22,24,40] Our study confirms these findings, demonstrating efficacy over placebo. In addition, this trial demonstrates the efficacy of paroxetine CR in this population, and with fewer adverse events compared with paroxetine IR. The findings of our study add to this evidence by demonstrating that treatment with paroxetine

CR results in high rates of remission in a population of older patients with major depressive disorder, which included patients with late-onset, chronic illness. Patients who can tolerate antidepressants are more likely to remain on therapy. Paroxetine CR was well tolerated in this group of patients, which suggests a benefit for medication adherence during long-term treatment. Additional studies of continuation and maintenance therapy of paroxetine CR are needed to better inform treatment decisions for elderly patients with major depressive disorder.

Drug names: cimetidine (Tagamet and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), paroxetine (Paxil), phenytoin (Cerebyx, Dilantin, others), sertraline (Zoloft), sumatriptan (Imitrex), warfarin (Coumadin and others).

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