# Effectiveness of Low Doses of Paroxetine Controlled Release in the Treatment of Major Depressive Disorder

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***Context:*** Paroxetine controlled release (CR) is approved for the treatment of major depressive disorder (MDD) in the dosage range of 25 to 62.5 mg daily. However, lower daily doses (12.5 mg and 25 mg) of this formulation have not been investigated in the treatment of MDD. If the 12.5-mg and 25-mg doses are found to be efficacious, these lower doses may well convey a superior tolerability profile for paroxetine CR in the treatment of MDD.

***Objective:*** To evaluate the antidepressant efficacy and tolerability profile of daily doses of paroxetine CR 12.5 mg and 25 mg versus placebo in the treatment of MDD.

***Design and Setting:*** Randomized, double-blind, placebo-controlled clinical trial conducted in 40 clinical investigation centers in the United States.

***Participants:*** 447 adult (≥ 18 years of age) outpatients who met DSM-IV criteria for MDD and with a baseline 17-item Hamilton Rating Scale for Depression (HAM-D) score of at least 20 comprised the intent-to-treat study population (mean age = 38.8 years; 58.4% female; 75.6% white).

***Intervention:*** Eligible patients completing a 1-week single-blind placebo run-in period were randomly assigned to receive once-a-day study medication (paroxetine CR 12.5 mg [N = 156], paroxetine CR 25 mg [N = 154], or placebo [N = 149]) in an 8-week, double-blind, parallel cell comparison.

***Main Outcome Measures:*** The primary efficacy measure was the change from baseline to study endpoint (week 8) as measured by the HAM-D. Secondary efficacy measures included change from baseline to study endpoint as assessed by both the depressed mood item on the HAM-D and the Clinical Global Impressions (CGI) Severity of Illness scale (CGI-S). The proportion of patients considered at study endpoint to be in response (CGI-Improvement score of 1 or 2) or in remission (HAM-D ≤ 7) in the 3 treatment groups was also compared. Quality of life was assessed by the change from baseline in total score of the short form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Safety observations were made by assessing the proportion of patients who had adverse experiences, including laboratory and electrocardiographic abnormalities, during the treatment period.

***Results:*** The primary efficacy analysis revealed that both the 12.5-mg and the 25-mg paroxetine CR treatment groups were associated with significant therapeutic effects (change in HAM-D score) from baseline to study endpoint (LOCF: p = .038, 95% CI = –3.38 to –0.09 and p = .005, 95% CI = –4.06 to –0.74, respectively). Results from the Wilcoxon rank sum test of the depressed mood item of the HAM-D (p = .011, 95% CI = –0.57 to –0.07) demonstrated significant efficacy in the 25-mg treatment group but not in the 12.5-mg group. However, LOCF analysis of the CGI-S revealed significant therapeutic effects for both the 12.5-mg (p = .018, 95% CI = –0.61 to –0.06) and 25-mg (p < .001, 95% CI = –0.78 to –0.22) treatment groups. Significantly more patients in the 25-mg paroxetine CR–treated group than in the placebo-treated group met criteria for response (CGI-Improvement score of 1 or 2, p = .035, OR = 1.68, 95% CI = 1.04 to 2.73) as well as for remission (HAM-D score ≤ 7, p = .013, OR = 1.96, 95% CI = 1.15 to 3.33). Neither HAM-D remission analysis nor CGI responder analysis showed statistical separation from placebo for paroxetine CR 12.5-mg treatment. Quality of life improvements were statistically significant for the 25-mg treatment (p = .041, 95% CI = 0.17 to 8.03) on the Q-LES-Q total score. Post hoc LOCF analyses of HAM-D sleep disturbance, psychic anxiety, and anxiety/somatization factors revealed significant improvements from baseline in the paroxetine CR 25-mg and 12.5-mg treatment groups. The types of adverse events reported in the 12.5-mg and 25-mg groups were similar to those reported with paroxetine CR at the customary 25-mg to 62.5-mg range; however, the lower doses of paroxetine CR were associated with a relatively reduced incident rate of these adverse events and an overall improved tolerability compared with the incident rate and tolerability profile associated with the customary dose range of paroxetine CR (25 to 62.5 mg).

***Conclusion:*** Paroxetine CR, at 12.5 mg/day and 25 mg/day, demonstrated significant antidepressant effects.

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Major depressive disorder (MDD) is recognized as a significant public health concern. The medical literature emphasizes the need for adequate management of this underrecognized and undertreated yet ubiquitous disorder.[1–3] Paroxetine hydrochloride and other selective serotonin reuptake inhibitors (SSRIs) have become first-line antidepressant therapy by combining efficacy and improved tolerability compared with older antidepressant classes such as tricyclic antidepressants (TCAs). However, SSRI-related adverse events such as nausea, weight gain, and sexual dysfunction may occur and can compromise SSRI treatment regimens that might otherwise be successful. Because of such events, patients have been known to develop patterns of nonadherence

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to treatment regimens or to prematurely withdraw from treatment completely.

A controlled release (CR) formulation of paroxetine was developed to provide comparable efficacy to the immediate release (IR) product, but with the hope of further improvements in paroxetine's tolerability profile. Two subsequent 12-week placebo-controlled trials[4] in MDD compared the IR and CR formulations and demonstrated similar efficacy for the 2 formulations; there was also evidence of improved tolerability for the CR versus IR formulation during these investigations. A flexible dosing regimen of 25 to 62.5 mg/day was employed during these studies. The patients were initially started on 25 mg/day and then increased 12.5 mg/day every 7 days as tolerated to a maximum daily dose of 62.5 mg/day as indicated for antidepressant efficacy. In the present study, 2 lower doses of the CR formulation (12.5 and 25 mg/day) were employed in a fixed-dose design to investigate efficacy and the relative tolerability of paroxetine CR at doses lower than the customary range used for depression (25–62.5 mg/day).

## METHOD

The study was an 8-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison of fixed doses of paroxetine CR (12.5 and 25 mg/day) in comparison with placebo in the treatment of MDD.

### Patients

Outpatients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[5] criteria for MDD were recruited at 40 academic or community centers between August 2001 and February 2002. Patient eligibility was assessed against the study-specific inclusion and exclusion criteria as well as via administration of the Mini International Neuropsychiatric Interview, version 4.4.[6]

Inclusion criteria included age ≥ 18 years, a primary diagnosis of MDD (DSM-IV criteria), and a minimum score of 20 on the 17-item Hamilton Rating Scale for Depression (HAM-D)[7] including a score > 2 on item 2 (depressed mood) of the HAM-D at both the screening assessment and the baseline visit.

Exclusion criteria included a decrease of ≥ 25% on the 17-item HAM-D total score between the baseline and screening visits; presence of current or recent (within 6 months prior to screening) Axis I disorder other than MDD that was considered by the investigator as the primary diagnosis; a lifetime history of schizophrenia, schizoaffective disorder, or bipolar disorder; met DSM-IV criteria for substance abuse (alcohol or drugs) within 3 months of screening visit or met DSM-IV criteria for substance dependence within 6 months of screening visit; participating in formal psychotherapy; considered by the investigator to be suicidal or homicidal or at significant risk of suicide or homicide; lifetime history of seizure disorder; received electroconvulsive therapy within 3 months; presence of clinically significant cardiac, renal, neurologic, cerebrovascular, metabolic, or pulmonary disease; abnormal electrocardiographic (ECG) findings present and not resolved by the baseline visit; presence of significant abnormal laboratory findings at screening assessment that were not resolved by baseline; current or recent use of other psychotropic drugs including monoamine oxidase inhibitors, all other antidepressants, sedatives, hypnotics, beta-adrenergic blockers, psychoactive herbal treatments, or depot neuroleptics; currently pregnant, lactating, or intending to become pregnant during study participation or not using medically acceptable method of contraception; previous nonresponse to adequate trials of SSRIs; use of an investigational drug or previous participation in an investigational trial within 12 months of the start of the current trial; and considered to be at significant risk for noncompliance with study conduct.

### Study Design

All patients provided written informed consent for participation prior to performance of any study-related procedures. Each participating site received approval by the appropriate institutional review board prior to initiating the study. Patients who remained eligible after a 1-week placebo run-in period were randomly assigned at the baseline visit to 1 of 3 treatment groups in a 1:1:1 ratio for the 8-week double-blind treatment phase. Sites telephoned a randomization service to receive a computer-generated treatment assignment. Blinding was accomplished through study drug administration kits that were designed to be indistinguishable between the 3 treatment groups.

Serial efficacy and safety assessments were performed at screening and baseline visits, as well as at weeks 1, 2, 3, 4, 6, and 8. The standardized efficacy evaluations included the 17-item HAM-D, the Clinical Global Impressions-Severity of Illness scale (CGI-S),[8] the Clinical Global Impressions-Improvement scale (CGI-I),[8] the Sheehan Disability Scale (SDS),[9] and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[10] An additional safety assessment was completed 14 days after discontinuation of study medication in all patients. Patients having any ongoing adverse experiences were also assessed within 28 days after their 14-day follow-up assessment.

The HAM-D, the CGI-I, and the CGI-S were administered at each study visit. The SDS and the Q-LES-Q were completed at baseline and at week 8 (or study endpoint). Physical examination, ECG, and laboratory evaluations were also completed at baseline and then repeated at the week 8 visit (or study endpoint). Adherence to treatment

regimens and concomitant therapies were assessed at every visit.

### Study Medications

The study medication was administered in a single-blind fashion during the placebo run-in phase. Study medications dispensed during the randomized double-blind phase (paroxetine CR 12.5 mg, paroxetine CR 25 mg, or placebo) were provided as overencapsulated tablets identical in appearance for the purpose of blinding. Patients were instructed to take 1 capsule of study medication every morning throughout the treatment phase. Assignment to double-blind study medication (paroxetine CR 12.5 mg/day, paroxetine CR 25 mg/day, or placebo) was conducted in a 1:1:1 ratio. Patients began and remained on the same dose regimen of double-blind study medication throughout their participation in the study. The randomization code was not broken until all data queries were completed at the conclusion of the trial.

### Efficacy Endpoints

The primary efficacy variable was the change from baseline to the week 8 last-observation-carried-forward (LOCF) endpoint as measured by the 17-item total HAM-D score. Prospectively defined secondary efficacy variables were also analyzed, including: (1) the change from baseline to study endpoint as measured by item 2 (depressed mood) on the HAM-D rating scale; (2) the change from baseline to endpoint as assessed by the CGI-S score; (3) the percentage of patients meeting remission criteria (HAM-D total score ≤ 7 at endpoint); and (4) the percentage of patients meeting response criteria (CGI-I score of 1 or 2 at endpoint). Additional analyses were performed on (1) the change from baseline to endpoint as measured by the total SDS and its individual subscales (work, family, and social life); (2) the change from baseline to endpoint as assessed by the total score on the Q-LES-Q; and (3) the change from baseline to endpoint in physical health, work, social relationships, leisure time activities, living/housing situations, household activities, mood, overall sense of well-being, and overall life satisfaction as measured by the Q-LES-Q, as well as overall satisfaction with medication at endpoint.

### Safety Assessments

Safety assessments conducted at each study visit included vital signs (sitting blood pressure and pulse) and general adverse experience monitoring. Safety assessments conducted at baseline and repeated at study endpoint included a full physical examination, an ECG, and clinical laboratory evaluations (hematology, blood chemistry, and urinalysis). Adverse experiences were defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product." Adverse experiences did not necessarily have a causal relationship with the study-related medication or treatment. The study physician was responsible for eliciting and recording adverse experiences based on an interview with the patient at each visit.

### Statistical Analysis

***Primary variable.*** The null hypothesis was that no difference existed between each dose of paroxetine CR (12.5 mg and 25 mg) and placebo in the change from baseline to the week 8 study endpoint as measured by the HAM-D total score with LOCF. The sample size calculation to test this hypothesis was based on the primary efficacy variable (the expected change from baseline to the week 8 endpoint as measured by the 17-item HAM-D total score and using an LOCF analysis). A sample size of 393 patients (131 patients per treatment group) is sufficient to detect a difference of 3.5 points in the 17-item HAM-D total score using a standard deviation of 8 and normally distributed errors with 90% power and a 2-sided nominal significance level of 5%.

The primary efficacy variable was analyzed using parametric analysis of covariance. The statistical model included terms for center, baseline HAM-D total score, and treatment group regardless of their significance. The 5% significance level was adjusted for multiple comparisons using the Hochberg modification to the Bonferroni inequality.[11]

***Secondary variables.*** Categorical secondary efficacy variables included the change from baseline to study endpoint on the depressed mood item of the HAM-D and on the CGI-S. These variables were analyzed using parametric analysis of covariance.

Binary efficacy variables included analyses of the proportion of patients with a therapeutic remission (HAM-D total score of ≤ 7 at endpoint) and the proportion of patients with a therapeutic response (CGI-I score of 1 or 2 at endpoint). These efficacy variables were analyzed using logistic regression adjusting for center group and baseline score (where applicable).

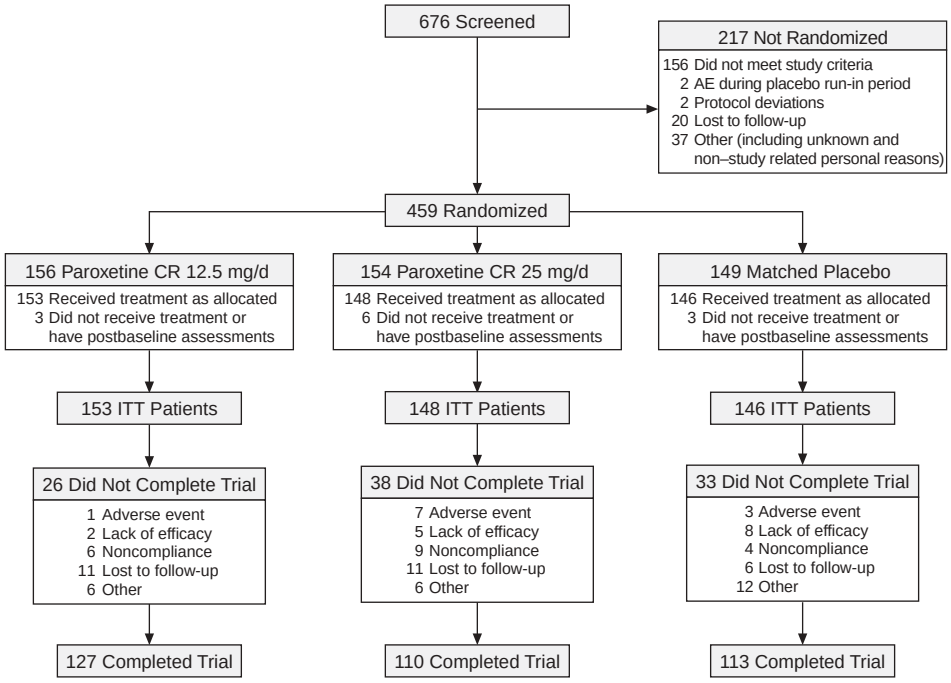
Continuous secondary efficacy variables included the change from baseline to endpoint on the SDS total, work item, family item, and social item scores. These continuous efficacy variables were evaluated using normal, linear models containing the covariates of center and baseline score.

The change from baseline to study endpoint in the total score on the Q-LES-Q was evaluated using parametric analysis of covariance. Individual items of the Q-LES-Q (i.e., physical health, work, social relationships, leisure time activities, living/housing situation, household activities, mood, sense of well-being, life satisfaction, and satisfaction with medication) were further evaluated using the Wilcoxon rank sum test.

Statistical analysis of adverse events was conducted employing the Fisher exact test.

Figure 1. Patient Flow




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

### Baseline Clinical and Demographic Characteristics

Six hundred seventy-six patients were screened for the study. Of these, 459 were randomly assigned to double-blind treatment: paroxetine CR 12.5 mg/day (N = 156), paroxetine CR 25 mg/day (N = 154), and placebo (N = 149) (Figure 1). Two hundred seventeen patients were considered to be screen/run-in failures and discontinued prior to receiving the double-blind study medication. These subjects did not enter the double-blind treatment phase due to the following factors: did not meet study criteria (N = 156), adverse events (N = 2), protocol deviations (N = 2), lost to follow-up (N = 20), and other reasons (N = 37). Twelve patients from the sample randomly assigned to double-blind study medication were not included in the statistical evaluation since they did not take any double-blind study medication or because no postbaseline data were obtained or recorded. Consequently, 447 patients comprised the intent-to-treat (ITT) population: 153 patients assigned to paroxetine CR 12.5 mg, 148 patients assigned to paroxetine CR 25 mg, and 146 patients assigned to placebo (the ITT population is defined as patients who were randomly assigned to double-blind medication, received at least 1 dose of double-blind medication, and had at least 1 postbaseline assessment available).

The baseline demographic and clinical characteristics of the ITT population are shown in Table 1. There were no significant differences between treatment groups with regard to race, gender, or age. Overall, the majority of randomized patients were female, less than 65 years of age, and white. There were no significant differences in the baseline total HAM-D scores in the 3 treatment groups. Most of the patients in this study reported previous episodes of depression. In those patients who had previously been treated for past depressive episodes, most had received SSRIs. Other medications reported as previous psychotropic medications were benzodiazepines and tricyclic antidepressants. Twenty-seven randomized patients (6%) had previously been diagnosed with Axis I disorders such as posttraumatic stress disorder, generalized anxiety disorder, panic disorder, alcohol or substance dependence, manic episodes, or bulimia. These previous diagnoses were distributed evenly across treatment groups. No patients in this trial were currently participating in psychotherapy.

## RESULTS

### Patient Disposition

Of the 447 patients in the ITT population, 350 (78%) completed 8 weeks of double-blind treatment. The reasons for premature termination are provided in Figure 1. Only 3% of patients withdrew for lack of efficacy, most of which were in the placebo group. Adverse events accounted for termination of 7 patients (4.7%) in the paroxetine CR 25-mg regimen but only 1 patient (0.7%) in the

**Table 1. Demographic and Clinical Characteristics of Intention-to-Treat Population at Baseline**

| Characteristic | Placebo (N = 146) | Paroxetine CR 12.5 mg (N = 153) | Paroxetine CR 25 mg (N = 148) |
|---|---|---|---|
| Women, % | 61.6 | 54.2 | 59.5 |
| Age, mean (SD), y | 38.4 (11.7) | 38.6 (12.1) | 39.4 (10.8) |
| Race, % | | | |
| White | 74.0 | 76.5 | 76.4 |
| Black | 11.0 | 14.4 | 12.2 |
| Asian | 4.1 | 0.7 | 2.0 |
| Other | 11.0 | 8.5 | 9.5 |
| Depression diagnosis, %[a] | | | |
| No previous episodes | 37.7 | 37.3 | 37.2 |
| 1 previous episode | 17.1 | 17.0 | 23.6 |
| ≥ 2 previous episodes | 42.5 | 43.8 | 37.2 |
| Previous medications, % | | | |
| SSRIs | 8.2 | 13.1 | 11.5 |
| Benzodiazepines | 3.4 | 2.0 | 2.0 |
| Other | 11.6 | 8.5 | 12.2 |
| TCAs | 1.4 | 0.7 | 0.7 |
| HAM-D total score, mean (SD) | 23.8 (3.2) | 23.2 (2.9) | 23.5 (3.3) |
| HAM-D depressed mood item score, mean (SD) | 2.8 (0.5) | 2.8 (0.5) | 2.7 (0.5) |
| CGI-S score, mean (SD) | 3.0 (0.5) | 3.0 (0.5) | 3.0 (0.5) |
| Q-LES-Q total score, mean (SD) | 47.0 (14.8) | 48.3 (13.1) | 47.5 (12.7) |
| Sheehan Disability Scale total score, mean (SD) | 17.2 (6.2) | 16.9 (6.4) | 17.5 (5.9) |

[a]This question may not have been completed on all case report forms; therefore, totals may be less than 100%.
Abbreviations: CGI = Clinical Global Impressions scale, CGI-S = CGI-Severity of Illness, CR = controlled release, HAM-D = Hamilton Rating Scale for Depression, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

12.5-mg paroxetine CR regimen. Interestingly, 3 patients (2.0%) in the placebo group withdrew due to an adverse event. Table 2 summarizes the completion and dropout data for each of the 3 treatment groups.

## Efficacy Results

The mean change at study endpoint (end of week 8 by LOCF) for each of the primary and secondary efficacy measures are summarized in Table 3. Analysis of the primary efficacy variable (HAM-D total score) revealed statistically significant benefit for both regimens of paroxetine CR compared with placebo from baseline to endpoint. There is evidence of a dose response in the observed therapeutic response, in that the adjusted mean difference in change from baseline on the total HAM-D score for paroxetine CR 25 mg versus placebo was –2.4 points ($p = .005$, 95% CI = –4.06 to –0.74), whereas for the 12.5-mg regimen of paroxetine CR versus placebo, the difference was –1.74 ($p = .038$, 95% CI = –3.38 to –0.09). There was no statistical evidence of a treatment-by-center interaction.

Figure 2 presents the change in HAM-D total score over the course of the treatment period for the LOCF dataset. Although this study was not designed to assess time to therapeutic effect, these data suggest that statistically significant differences in the amount of improvement with paroxetine CR versus placebo as measured by the total HAM-D score may be detectable as early as week 3 for the 25 mg/day dose and as early as week 4 for the 12.5 mg/day dose. This significant separation between the improvement on paroxetine CR versus placebo was maintained throughout the course of treatment.

Analyses of the secondary efficacy measures also confirmed the therapeutic efficacy of paroxetine CR (especially at 25 mg/day) over placebo in the treatment of depression. Paroxetine CR at 25 mg/day was significantly more effective than placebo as measured by improvement from baseline to study endpoint on the depressed mood item of the HAM-D as well as on the CGI-S (Table 3). Paroxetine CR at 12.5 mg/day was also significantly more effective than placebo as measured by improvement from baseline to endpoint on the CGI-S, but not as assessed by the change from baseline to endpoint on the depressed mood item of the HAM-D. Significantly more of the patients receiving the 25 mg/day dose of paroxetine CR were classified as responders (CGI-I score of 1 or 2 at endpoint) in comparison with those receiving placebo ($p = .035$, OR = 1.68, 95% CI = 1.04 to 2.73). In addition, a significantly greater proportion of patients achieved remission at study endpoint (HAM-D score ≤ 7, $p = .013$, OR = 1.96, 95% CI = 1.15 to 3.33) while taking paroxetine CR 25 mg/day in comparison with placebo (Figure 3). Neither the HAM-D remission analysis nor the CGI responder analysis showed statistical separation from placebo for the paroxetine CR 12.5-mg treatment at the week 8 LOCF endpoint (although the HAM-D remission analysis showed statistical significance at week 6 in the observed cases analysis).

Analysis of the Q-LES-Q showed statistical superiority for paroxetine CR 25 mg and numerical superiority for paroxetine CR 12.5 mg relative to placebo. Conversely, analyses of the SDS failed to demonstrate any significant difference from baseline to study endpoint between paroxetine CR (25 mg or 12.5 mg/day) and placebo administration. Both the Q-LES-Q and SDS analyses are presented in Table 3.

## Post Hoc Analyses

In a post hoc LOCF analysis of the sleep disturbance factor (HAM-D items 4, 5, and 6), statistical evidence of efficacy was seen for paroxetine CR 25 mg ($p = .009$, 95% CI = –0.91 to –0.13) and 12.5 mg ($p = .037$, 95% CI = –0.79 to –0.02) compared with placebo. Similarly, in an LOCF analysis of psychic anxiety (HAM-D item 10), changes from baseline showed statistical evidence of efficacy for paroxetine CR 25 mg ($p < .001$, 95% CI = –0.64 to –0.21) and paroxetine CR 12.5 mg ($p = .010$, 95% CI = –0.50 to –0.07). Analyses for both the sleep disturbance and psychic anxiety factors are depicted graphically in Figure 4.

**Table 2. Disposition of Patients**

| Reason for Study Conclusion | Paroxetine CR 25 mg (N = 148) N | % | Paroxetine CR 12.5 mg (N = 153) N | % | Placebo (N = 146) N | % | Total (N = 447) N | % |
|---|---|---|---|---|---|---|---|---|
| Completed study[a] | 110 | 74.3 | 127 | 83.0 | 113 | 77.4 | 350 | 78.3 |
| Withdrew early | 38 | 25.7 | 26 | 17.0 | 33 | 22.6 | 97 | 21.7 |
| Adverse events | 7 | 4.7 | 1 | 0.7 | 3 | 2.1 | 11 | 2.5 |
| Lack of efficacy | 5 | 3.4 | 2 | 1.3 | 8 | 5.5 | 15 | 3.4 |
| Protocol deviation[b] | 9 | 6.1 | 6 | 3.9 | 4 | 2.7 | 19 | 4.3 |
| Lost to follow-up | 11 | 7.4 | 11 | 7.2 | 6 | 4.1 | 28 | 6.3 |
| Other[c] | 6 | 2.0 | 6 | 3.9 | 12 | 6.2 | 24 | 4.0 |

[a]A patient was considered to be a study completer if he or she remained in the study up to and including week 8.
[b]Includes noncompliance.
[c]Includes unknown and non–study-related personal reasons.
Abbreviation: CR = controlled release.

**Table 3. Efficacy of Paroxetine CR at Week 8 in Patients With Major Depressive Disorder**

| Efficacy Measure | N | Least Squares Mean | F Test | p (overall) | Pairwise Comparison With Placebo p | 95% CI |
|---|---|---|---|---|---|---|
| HAM-D total score | | | | | | |
| Placebo | 142 | –10.0 | 4.32 | .038 | | |
| 12.5 mg/day | 151 | –11.7 | | | .038 | –4.06 to –0.74 |
| 25.0 mg/day | 143 | –12.4 | | | .005 | –3.38 to –0.09 |
| HAM-D depressed mood item[a] | | | | | | |
| Placebo | 142 | –1.2 | 6.42 | .011 | | |
| 12.5 mg/day | 151 | –1.4 | | | .173 | –0.41 to 0.07 |
| 25.0 mg/day | 143 | –1.6 | | | .011 | –0.57 to –0.07 |
| CGI-Severity of Illness[a] | | | | | | |
| Placebo | 142 | –1.2 | 12.25 | < .001 | | |
| 12.5 mg/day | 151 | –1.5 | | | .018 | –0.61 to –0.06 |
| 25.0 mg/day | 144 | –1.7 | | | < .001 | –0.78 to –0.22 |
| Q-LES-Q total score | | | | | | |
| Placebo | 129 | 8.2 | 4.21 | .041 | | |
| 12.5 mg/day | 131 | 11.9 | | | .064 | –0.22 to 7.58 |
| 25.0 mg/day | 127 | 12.3 | | | .041 | 0.17 to 8.03 |
| Sheehan Disability Scale total score | | | | | | |
| Placebo | 131 | –4.2 | 1.21 | .300 | | |
| 12.5 mg/day | 141 | –4.8 | | | .444 | –2.29 to 1.00 |
| 25.0 mg/day | 135 | –5.5 | | | .121 | –2.99 to 0.35 |

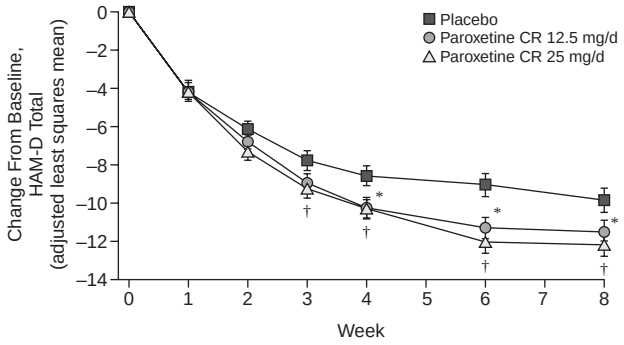
[a]Mean Wilcoxon z score.
Abbreviations: CGI = Clinical Global Impressions scale, CR = controlled release, HAM-D = Hamilton Rating Scale for Depression, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

To further investigate anxiety and somatic components of depression in this study population, a retrospective analysis was also conducted on the anxiety/somatization subfactor of the HAM-D. This LOCF evaluation revealed a statistically significant difference in favor of paroxetine CR at 25 mg (p = .011, 95% CI = –1.37 to –0.17) and at 12.5 mg (p = .015, 95% CI = –1.32 to –0.15). Illustrations of these analyses appear in Figure 5.

## Safety Results

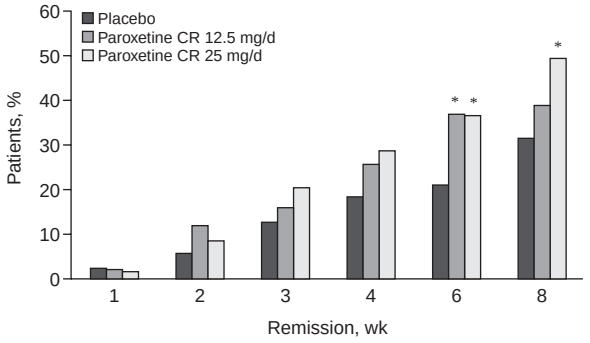
There were no reports of unexpected adverse events (AEs) in this clinical trial. Generally, AEs reported were considered mild in severity and were more likely to occur early than late during the double-blind phase. The most commonly occurring adverse events (defined as > 5% incidence in the paroxetine CR [12.5 or 25 mg/day] treatment group and > 2 times the rate associated with placebo administration during the study) are listed in Table 4. As illustrated in Table 4, there was a similar incidence of adverse events between the paroxetine and the placebo treated groups, except for the report of sweating. Notably, the AE incidence did not exceed 7.8% (libido decreased) in the 12.5-mg group or 10.0% (abnormal ejaculation) in the 25-mg group, indicating an overall low frequency of AEs associated with both active treatments. The incidence of AEs in the paroxetine CR 12.5-mg group, such as abdominal pain, constipation, anxiety, and abnormal ejaculation, was similar to the incidence reported during placebo administration. Impotence was reported in 2 men (3.3%) in the paroxetine CR 25-mg–treated group, 1 man (4.4%) in the paroxetine CR 12.5-mg–treated group, and 0 men in the placebo group; the incidence of impotence

**Figure 2. Change From Baseline in HAM-D Total Score[a,b]**



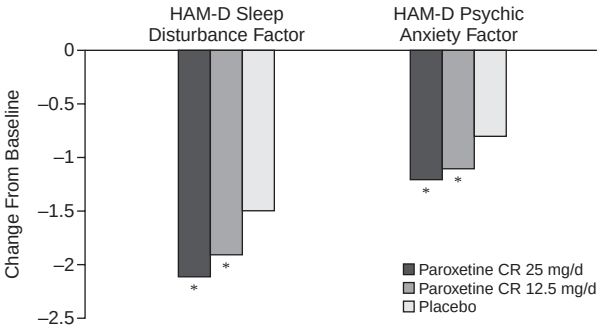

[a]Intent-to-treat population (last observation carried forward).
[b]Bars represent the standard error multiplied by 2.
*p < .05 for 12.5 mg vs. placebo.
†p < .05 for 25 mg vs. placebo.
Abbreviations: CR = controlled release, HAM-D = Hamilton Rating Scale for Depression.

**Figure 3. HAM-D Remission Analysis (HAM-D score ≤ 7 at study endpoint) (observed cases dataset)**



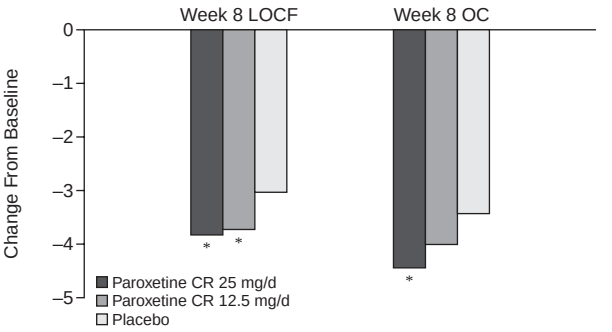

*p < .05 compared with placebo.
Abbreviations: CR = controlled release, HAM-D = Hamilton Rating Scale for Depression.

**Figure 4. HAM-D Sleep Disturbance and Psychic Anxiety Evaluation**




*p < .05.
Abbreviations: CR = controlled release, HAM-D = Hamilton Rating Scale for Depression.

**Figure 5. HAM-D Anxiety/Somatization Evaluation**




*Statistically significant compared with placebo.
Abbreviations: CR = controlled release, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, OC = observed cases.

was not significantly different between paroxetine CR and placebo. None of the adverse events related to sexual dysfunction (abnormal ejaculation, impotence) were associated with treatment withdrawal. The rate of patient withdrawals due to adverse events was exceptionally low in this study, particularly in the paroxetine CR 12.5 mg–treated group, and is much lower than that reported in previous trials with paroxetine.[4]

## DISCUSSION

This double-blind, randomized, placebo-controlled trial is the first to report fixed-dose data with controlled release paroxetine in the treatment of depression. Although paroxetine CR is already approved by the U.S. Food and Drug Administration for the treatment of MDD, previous studies utilized a flexible-dose design with a range of 12.5 mg to 62.5 mg of paroxetine CR daily. Therefore, the relative efficacy and tolerability of specific doses of paroxetine CR within this range cannot be accurately assessed. In addition, the lowest effective dose of paroxetine CR in depression treatment cannot be determined from the previously conducted flexible-dose studies. By directly comparing 2 fixed doses of paroxetine CR (12.5 mg and 25 mg) with placebo, more information can be inferred about the potential association between the daily dosing of paroxetine CR and efficacy and safety/tolerability. Previous flexible-dose studies have described a low rate of early onset nausea and withdrawals due to overall side effects in patients taking the controlled release formulation of paroxetine.[4] Given this preliminary information, the current study utilized relatively lower doses of paroxetine CR than those customarily used in order to provide more information about the potential efficacy of low-dose paroxetine CR (12.5 and 25 mg/day)

**Table 4. Most Commonly Reported Adverse Events**

| | Placebo (N = 146) | | Paroxetine CR 12.5 mg (N = 153) | | | Paroxetine CR 25 mg (N = 148) | | |
|---|---|---|---|---|---|---|---|---|
| Adverse Event | N | % | N | % | p | N | % | p |
| Abdominal pain | 6 | 4.1 | 6 | 3.9 | 1.000 | 13 | 8.8 | .153 |
| Constipation | 6 | 4.1 | 7 | 4.6 | 1.000 | 12 | 8.1 | .223 |
| Anxiety | 2 | 1.4 | 4 | 2.6 | .685 | 8 | 5.4 | .104 |
| Trauma | 3 | 2.1 | 10 | 6.5 | .086 | 7 | 4.7 | .335 |
| Abnormal ejaculation[a] | 2 | 3.6 | 4 | 5.7 | .692 | 6 | 10.0 | .274 |
| Sweating | 1 | 0.7 | 10 | 6.5 | .011 | 6 | 4.1 | .121 |
| Female genital disorders[a] | 1 | 1.1 | 2 | 2.4 | .608 | 5 | 5.7 | .116 |
| Libido decreased | 4 | 2.7 | 12 | 7.8 | .700 | 4 | 2.7 | 1.000 |
| Infection | 4 | 2.7 | 10 | 6.5 | .171 | 4 | 2.7 | 1.000 |
| Rhinitis | 3 | 2.1 | 9 | 5.9 | .139 | 4 | 2.7 | 1.000 |

[a]Corrected for gender.
Abbreviation: CR = controlled release.

and to also explore the relative incidence of adverse events on low versus customary doses of paroxetine CR for depression.

Paroxetine CR 12.5 mg and 25 mg daily demonstrated significant therapeutic efficacy as measured by the primary efficacy measure (change from baseline to study endpoint in the total score of the HAM-D). This therapeutic efficacy may be dose-related inasmuch as the drug/placebo difference was relatively greater in the 25-mg–treated group than in the 12.5-mg–treated group (–2.4 and –1.74, respectively); however, no formal statistical analyses were conducted on this portion of the data. Both paroxetine doses were also significantly more effective than placebo as measured by improvement from baseline to endpoint on the CGI-S. Secondary efficacy measures including the depressed mood item on the HAM-D, analyses of response and remission rates, and the Q-LES-Q revealed significant efficacy for paroxetine CR at 25 mg/day (but not at 12.5 mg/day) over placebo.

In the LOCF analysis of the primary efficacy variable, the small yet statistically significant effect size for the 12.5-mg dose of paroxetine CR suggests that it may be efficacious in some patients with depression. Given the small effect size for paroxetine CR 12.5 mg/day on the primary efficacy measure, it is not particularly surprising that this dose of paroxetine CR did not separate significantly from placebo on the majority of secondary efficacy measures. In contrast, paroxetine CR at 25 mg demonstrates clearly superior efficacy over placebo on the primary efficacy variable as well as all the secondary efficacy variables.

Retrospective efficacy analyses revealed that both doses of paroxetine CR (12.5 and 25 mg/day) were significantly better than placebo in reducing symptoms of psychic anxiety and sleep disturbance. Since anxiety and insomnia are often core symptoms of MDD, antidepressants that effectively manage these symptoms may more effectively treat the full depressive syndrome and thus enhance the patient's quality of life. Another retrospective analysis involving changes from baseline in the HAM-D anxiety/somatization factors (psychic and somatic anxiety, general and gastrointestinal somatic symptoms, hypochondriasis, and illness insights) revealed that paroxetine CR was highly effective in attenuating somatic complaints. This finding may provide some interesting insight regarding the potential link between antidepressant response and the presence of concurrent somatic symptoms.[12] Favorable outcomes in these aspects of the patient's illness also may serve to improve quality of life.

Interestingly, neither paroxetine CR 25 mg nor paroxetine CR 12.5 mg separated from placebo for the SDS total score or individual items in any of the statistical analyses. Greater correlation between improvement of depressive symptoms and recovery from disability may have occurred in a trial of longer duration.

A review of the safety and tolerability profiles of these treatment groups shows substantial reduction of the incidence of adverse events compared with previously conducted clinical trials involving paroxetine CR.[4] As shown in Table 4, there is parity between placebo and the 12.5-mg group for several adverse events such as anxiety, constipation, abdominal pain, abnormal ejaculation, and female genital disorder. These AEs are frequently associated with excessive discomfort and premature withdrawal from SSRI therapy. The frequencies of AEs in the 25-mg treatment group also were substantially lower than those described in the paroxetine CR approved labeling. It is noteworthy that among all AEs in the active treatments, only sweating in patients receiving 12.5 mg daily was significantly different from placebo (p = .011). The withdrawal rate associated with AEs was also low for both active treatments.

Although this was a well-designed clinical study with overall positive outcomes, it was not without limitations. One such limitation and concern might be the duration of the trial. The lack of statistical efficacy observed in the secondary efficacy variables for paroxetine CR 12.5 mg may be a function of the relatively abbreviated duration of this trial—8 weeks rather than 10 or 12 weeks. Another limitation is that in concluding that paroxetine CR 12.5 mg is effective in some patients while others require upward titration to 25 mg/day, this study does not address the issue of identifying an adequate treatment period at the 12.5-mg level before prescribing increased daily doses. This issue requires further study for complete recommendations of upward dose titrations to be made. Finally, the study did not completely assess quality of life, occupational function, or pharmacoeconomic issues, nor was an itemized sexual function inventory employed to assess sexual functions. Both of these issues require further study and presentation in future manuscripts.

These data suggest that paroxetine CR 12.5 mg is effective in the treatment of MDD. However, the small effect size accompanying this dose in an 8-week trial indicates that there may be limited applicability for the duration of most depressive episodes. One must also consider that this study did not enroll patients with dysthymia or minor depression, which raises the speculation that the response rate at 12.5 mg/day may be enhanced in depression of lesser severity. Still, coupled with its efficacy, this dose has a clear advantage because of the limited occurrence of adverse events for patients enrolled in this trial. Thus, paroxetine CR 12.5 mg can probably be employed as an effective starting dose and in some patients may be efficacious for the duration of the depressive episode. In patients who do not respond to an adequate trial of this dose, elevation to the 25-mg level is recommended. Yet, even at this higher dose, there are fewer side effects than previously associated with a broader dosage range of paroxetine CR (25 mg to 62.5 mg/day).[4]

This trial has demonstrated efficacy for paroxetine CR doses of 12.5 mg and 25 mg compared with placebo. The advantages of efficacy and safety substantiated in this trial offer the clinician statistical and clinical evidence that specific low doses of paroxetine CR can effectively treat depression. This option may lead to improved tolerability, adherence to treatment regimens, and continuation of treatment and therefore enhanced therapeutic outcomes.

*Drug name:* paroxetine (Paxil and others).

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