Efficacy and Tolerability of Controlled-Release and Immediate-Release Paroxetine in the Treatment of Depression

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Background: Antidepressant efficacy may be compromised by early discontinuation of treatment secondary to common, treatment-emergent side effects, including nausea, agitation, and somnolence. Paroxetine controlled-release (CR) was developed to improve general tolerability and, in particular, gastrointestinal tolerability.

Objective: To determine the antidepressant efficacy and tolerability of paroxetine CR in adult patients 18 to 65 years of age with DSM-IV major depressive disorder.

Method: Paroxetine CR (25–62.5 mg/day; N = 212) and paroxetine immediate-release (IR; 20–50 mg/day; N = 217) were compared with placebo (N = 211) in the pooled dataset from 2 identical, double-blind, 12-week clinical trials.

Results: Both paroxetine CR and paroxetine IR exhibited efficacy in major depressive disorder as assessed by the reduction in 17-item Hamilton Rating Scale for Depression total score compared with placebo. Moreover, depressed mood and psychic anxiety symptoms improved as early as treatment week 1 in the paroxetine CR group compared with the placebo group. After 6 weeks of treatment, response and remission rates were 41.5% and 20.5% for placebo, 52.8% and 29.6% for paroxetine IR, and 58.9% and 34.4% for paroxetine CR, respectively. After 12 weeks of treatment, response and remission rates were 61.2% and 44.0% for placebo, 72.9% and 52.5% for paroxetine IR, and 73.7% and 56.2% for paroxetine CR, respectively. Rates of nausea were significantly lower for paroxetine CR (14%) than for paroxetine IR (23%; $p \leq .05$) during week 1. Rates of dropout due to adverse events were comparable between paroxetine CR and placebo, while significantly ($p = .0008$) more patients treated with paroxetine IR withdrew from the study prematurely compared with those treated with placebo.

Conclusion: Paroxetine CR is an effective and well-tolerated antidepressant exhibiting symptomatic improvement as early as week 1. Paroxetine CR is associated with low rates of early-onset nausea and dropout rates due to adverse events comparable to those of placebo. The clinical improvement seen with paroxetine CR, coupled with its favorable adverse event profile, suggests a benefit for therapeutic outcome with paroxetine CR.

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The selective serotonin reuptake inhibitors (SSRIs) have become the most commonly prescribed class of antidepressants due to their well-tolerated safety profile and broad range of efficacy in mood and anxiety disorders, including major depressive disorder, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, obsessive-compulsive disorder, and premenstrual dysphoric disorder. Despite these benefits, however, poor adherence to antidepressant treatment is common and remains a leading cause of less than optimal treatment outcome, including relapse and recurrence.[1] Nearly one third of patients discontinue antidepressant therapy in the first month of treatment.[2,3] Among depressed patients treated in a primary care setting, the best predictor of treatment noncompliance is the emergence of antidepressant side effects.[2,4]

Nausea, one of the most common side effects associated with SSRI therapy,[5–7] is a leading cause of premature treatment discontinuation for the SSRIs[8–11] and serotonin-norepinephrine reuptake inhibitors.[12] A meta-analysis of 25 double-blind trials involving 4016 patients assessed the adverse effect profile and rates of treatment discontinuation during fluoxetine treatment of major depressive disorder.[6] Nausea was the most frequently reported adverse event associated with fluoxetine (21.6% vs. 9.0% for placebo; $p < .001$) and was the most common reason for treatment discontinuation (3.9% for fluoxetine; $p = .002$ vs. placebo). In studies of other SSRIs, head-

ache, somnolence, insomnia, agitation and nervousness, sexual dysfunction, and gastrointestinal disturbances (e.g., nausea) were the most commonly reported adverse events.[13–18] Although nausea and other treatment-emergent adverse events are typically mild and transient, they may nonetheless result in reduced medication compliance, delays or failure to reach full therapeutic dose, premature treatment discontinuation, and associated poor treatment outcomes.

Paroxetine HCl controlled-release (CR), an enteric-coated formulation, was developed with the goal of improving the SSRI tolerability (e.g., gastrointestinal tolerability) profile while maintaining the therapeutic benefits of paroxetine in the treatment of depression and anxiety disorders. The enteric coating delays tablet dissolution until it passes into the small intestine, where dissolution and absorption are slowed by the controlled-release mechanism. These features are believed to potentially minimize nausea, perhaps by reducing stimulation of upper gastrointestinal 5-HT_3 receptors. The efficacy and tolerability of paroxetine CR and paroxetine immediate-release (IR) were evaluated in 2 multicenter, double-blind, randomized controlled clinical trials of patients with major depressive disorder.

METHOD

Study Design

Patients were enrolled in 1 of 2 randomized, double-blind, flexible-dose, placebo-controlled, 12-week studies of identical design. Data from both studies were pooled. After a screening period and a 1-week placebo washout phase, eligible patients were randomly assigned to 1 of 3 treatment arms: paroxetine CR, paroxetine IR, or placebo. Patients were evaluated at baseline and at weeks 1, 2, 3, 4, 6, 8, and 12.

The study medications were over-encapsulated in identical capsules, thus creating a double-blind design. The studies were not prospectively designed to compare both active treatments, but rather were powered to compare each of the active treatments with placebo.

The dosing schedule was designed to compare similarly bioavailable dosage ranges of paroxetine CR and paroxetine IR with placebo. Paroxetine CR exhibits distinctive controlled-release characteristics that differentiate it from the immediate-release formulation. Paroxetine CR is an enteric, film-coated tablet containing a degradable polymeric matrix, which delays the start of the drug release until the tablet has passed through the stomach. This geomatrix is designed to control the dissolution rate and to release 80% of the paroxetine content over approximately 4 to 5 hours. Since the remaining 20% of the paroxetine contained within each tablet is not released, the individual dose of paroxetine CR needs to be 25% higher than that of paroxetine IR to achieve equivalent dosing. Although the polymeric matrix decreases the bioavailability and rate of absorption of paroxetine CR compared with paroxetine IR, it does not affect the distribution, metabolism, or excretion once the absorption has taken place.

The dosing was titrated by the principal investigators on the basis of clinical response and tolerability. Patients in each of the active treatment arms received comparable amounts of paroxetine. All patients in the paroxetine CR group started the study at 25 mg/day; comparable doses of paroxetine IR were initiated at 20 mg/day. Doses were increased at the discretion of the investigator (depending on efficacy and tolerability) in weekly increments of 12.5 mg (paroxetine CR) or 10 mg (paroxetine IR) up to maximum allowed daily doses of 62.5 mg (paroxetine CR) or 50 mg (paroxetine IR). Dosage reductions due to adverse events were allowed after the first up-titration. Patients were withdrawn from the study if their therapy was interrupted for more than 2 days during the first week of the study or if they required more than 1 dosage reduction after the first week of treatment.

Patients were recruited in the United States and Canada at 20 centers for each study (40 sites in total). All patients provided written informed consent prior to enrollment, the institutional review board at each site reviewed and approved the protocol, and the studies were conducted in accordance with good clinical practices and the Helsinki Declaration.

Patient Population

Eligible patients were 18 to 65 years of age and fulfilled *Diagnostic and Statistical Manual for Mental Disorders*, Fourth Edition (DSM-IV)[19] criteria for major depressive disorder. Eligible patients were required to have a total score on the 17-item Hamilton Rating Scale for Depression (HAM-D)[20] of 20 or more that did not decrease by more than 25% between screening and baseline. Patients with a history of brief depressive episodes (≤ 8 weeks' duration with spontaneous remission), electroconvulsive therapy within 3 months of screening, diagnosis of another Axis I disorder or substance abuse/dependence within 6 months of screening, suicidal behavior, or homicidal risk were not eligible for enrollment. Patients were ineligible if they were currently taking paroxetine or if they had a history of paroxetine nonresponse or intolerability. Other exclusionary criteria included current psychotherapy and concomitant treatment with a monoamine oxidase inhibitor, benzodiazepine, or other psychoactive agent (excluding chloral hydrate). Eligible patients were washed out of any psychotropic medication prior to study entry. Although refractory patients were not excluded from the study, such patients were not specifically identified.

Efficacy Assessment

The primary efficacy measure was 17-item HAM-D total score. Secondary efficacy measures evaluated in this

pooled analysis included depressed mood (HAM-D item 1) and psychic anxiety (HAM-D item 10) scores. A responder analysis, in which response was defined as a 50% or greater reduction in baseline HAM-D total score at the end of treatment, was also conducted. Moreover, remission rates were calculated using the standard criterion of a HAM-D total score less than or equal to 7.[21]

Safety Assessment

Adverse events and vital signs were evaluated at screening and at each visit. Investigators elicited adverse event information by asking patients a nonleading question (e.g., "Do you feel differently in any way since starting the new treatment?"). Heart rate, sitting blood pressure, and weight were recorded at each visit. Routine clinical laboratory assessments were obtained at screening and at weeks 6 and 12 or on premature withdrawal from the study.

Statistical Analysis

Changes from baseline in the HAM-D total, mood, and psychic anxiety scores were evaluated using an analysis of covariance that allowed for the effect of prospectively defined covariates (e.g., age, gender, duration of depressive episode, baseline severity). Pairwise comparisons between each active treatment and placebo were 2-tailed and performed at an α level of .05.

Efficacy analyses were carried out on the intent-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. Safety analyses were based on all patients receiving drug. Datasets from the ITT population that are considered herein are the last observation carried forward (LOCF) and the observed cases (OC). For completeness, both the LOCF and OC analyses are presented. In the LOCF analysis, the last observation during 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 had available data at each of the weeks in the study. 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.

Finally, additional analyses of the HAM-D scores were conducted using random-effects mixed modeling (REMM). This analysis was included to provide a more sensitive and accurate estimation of overall symptom improvement for each of the 3 groups. Although the LOCF method is often used for imputing data missing in longitudinal clinical trials, this approach is limited by its overly conservative estimate of the treatment effect. In the event that missing longitudinal data must be estimated in these analyses, the LOCF approach should be considered with caution due to concerns over the stability of outcome values after dropout.

Table 1. Demographic Characteristics of ITT Population[a]

Characteristic	Paroxetine CR (N = 212)	Paroxetine IR (N = 217)	Placebo (N = 211)
Gender, N, M/F	78/134	67/150	78/133
Age, mean ± SD, y	40.7 ± 10.8	39.9 ± 11.4	39.7 ± 10.8
Weight, mean ± SD, lb	179.0 ± 48.3	170.8 ± 36.3	171.1 ± 39.6
Race, N (%)			
White	187 (88.2)	188 (86.6)	180 (85.3)
Black	10 (4.7)	11 (5.1)	11 (5.2)
Asian	3 (1.4)	1 (0.5)	1 (0.5)
Other	12 (5.7)	17 (7.8)	19 (9.0)

[a]Abbreviations: CR = controlled-release, F = female, IR = immediate-release, ITT = intent-to-treat, M = male.

A further advantage of the random-effects approach is that it can be applied when the patients are not measured at the same number of timepoints. Assuming that values are missing at random (i.e., dropouts can be explained by data observed during the trial), the random-effects regression model will account for missing data that may vary over time. Random-effects regression models allow for missing data elements, serial correlation over time, and varying measurement intervals, which are examples of major advantages of this approach over traditional methods used in the analysis of longitudinal data (such as analysis of variance for repeated measures). To apply REMM methodology, time-by-treatment interactions were assessed to identify if the treatment outcomes differed among the 3 treatments. When this term was significant, additional contrasts were performed to compare paroxetine CR with placebo and paroxetine IR with placebo over time to determine which of the active treatments yielded different outcomes from placebo. Finally, where the treatment-by-time interactions were significant, week-by-week comparisons of least squares means were performed to better understand weekly treatment differences. Thus, to provide the most accurate and complete estimates of treatment effects in the current study, the OC, LOCF, and REMM analyses are presented where appropriate.

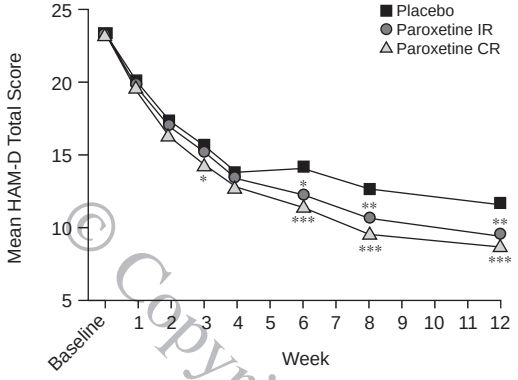
RESULTS

Patient Disposition and Demographics

A total of 820 patients for both studies were screened, 172 did not fulfill entrance criteria, and 648 were randomly assigned to treatment. Of these, 640 patients received study medication and had at least 1 postbaseline assessment, comprising the ITT population. The treatment groups were similar with regard to demographic characteristics (Table 1). The majority of patients were female and white, and their mean age was approximately 40 years. At week 12, the mean daily doses of paroxetine CR and paroxetine IR were 48.2 mg and 38.2 mg, respectively.

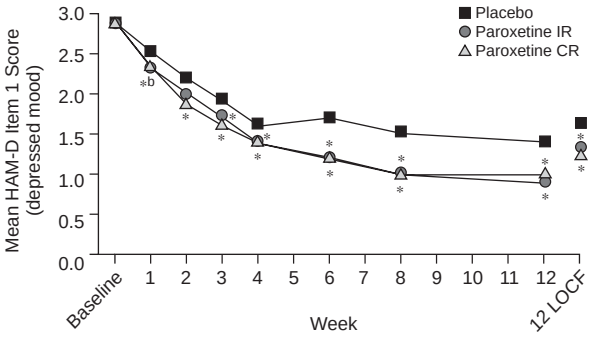
A significant treatment-by-site interaction was noted in 1 of the studies. Treatment response at this site to both active treatments was significantly higher than at other

Figure 1. Weekly Mean HAM-D Total Score Among Patients Treated With Paroxetine CR, Paroxetine IR, or Placebo (from random-effects mixed model analysis)[a]



[a]Abbreviations: CR = controlled-release, HAM-D = Hamilton Rating Scale for Depression, IR = immediate-release.
*p ≤ .05 vs. placebo.
**p ≤ .01 vs. placebo.
***p ≤ .001 vs. placebo.

Figure 2. Weekly Mean HAM-D Depressed Mood Score (item 1) Among Patients Treated With Paroxetine CR, Paroxetine IR, or Placebo (OC dataset and endpoint LOCF dataset)[a]



[a]Abbreviations: CR = controlled-release, HAM-D = Hamilton Rating Scale for Depression, IR = immediate-release, LOCF = last observation carried forward, OC = observed cases.
[b]Asterisk indicates statistical difference between paroxetine CR and placebo.
*p ≤ .05 vs. placebo.

centers, and the placebo response was considerably lower. Because of this finding, efficacy data from the 18 patients treated at that site (i.e., 6 in each treatment arm) were excluded from the final statistical analyses to provide the most conservative estimate of the treatment response. The ITT population included in the efficacy analyses, therefore, consisted of 622 patients: 206 in the paroxetine CR group, 211 in the paroxetine IR group, and 205 in the placebo group. The OC population consisted of 449 patients: 153 in the paroxetine CR group, 145 in the paroxetine IR group, and 151 in the placebo group.

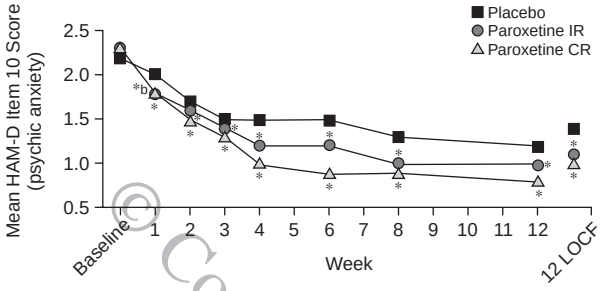
Efficacy

The time course of change in HAM-D total scores is illustrated in Figure 1. An overall difference among the 3 treatments over time was observed ($p < .008$), with paroxetine CR ($p = .0004$) and paroxetine IR ($p = .036$) showing significantly lower HAM-D scores than placebo. Both active treatments resulted in robust improvement: mean endpoint HAM-D total scores were 8.8 for paroxetine CR ($p = .0003$ vs. placebo; REMM analysis) and 9.5 for paroxetine IR ($p = .008$ vs. placebo; REMM analysis). Improvements in HAM-D scores for paroxetine CR began to differ statistically from placebo between weeks 2 and 3, with significance also observed at study endpoint. Statistically significant differences between paroxetine IR and placebo were observed between weeks 4 and 6 onward. Analysis of the LOCF dataset revealed endpoint HAM-D total scores of 10.6 for paroxetine CR ($p = .002$ vs. placebo) and 12.0 for paroxetine IR ($p = .18$ vs. placebo), compared with a mean score of 13.0 for placebo. The OC analysis resulted in endpoint HAM-D scores of 8.5 for paroxetine CR ($p < .005$ vs. placebo), 9.2 for paroxetine IR ($p < .05$ vs. placebo), and 11.0 for placebo.

Paroxetine CR demonstrated significant alleviation of depressed mood and anxiety symptoms early in the course of therapy. Improvement in HAM-D depressed mood (item 1) for paroxetine CR was greater than that for placebo at week 1 (OC and LOCF, $p \le .05$), and this difference between groups persisted throughout the study (Figure 2). Greater improvement in depressed mood was also observed in the paroxetine IR group compared with the placebo group, with statistical separation occurring from week 3 onward ($p \le .05$). A similar pattern of early improvement occurred with the REMM analysis, with the overall treatment-by-week results significant ($p < .0001$). Moreover, both paroxetine CR and paroxetine IR showed significant endpoint differences from placebo (CR and IR vs. placebo, $p < .0001$; REMM analysis). At week 12, paroxetine CR and paroxetine IR showed a 66% improvement from baseline in depressive symptom scores. Improvement in psychic anxiety symptoms (HAM-D item 10) occurred at week 1 among patients treated with paroxetine CR and paroxetine IR compared with those treated with placebo (OC and LOCF, $p \le .05$; Figure 3). Moreover, these differences from placebo persisted from week 1 to endpoint (OC and LOCF, $p < .05$ at all timepoints). REMM analysis supported the improvements in psychic anxiety with both formulations of paroxetine (treatment-by-week interaction, $p < .005$). At endpoint, patients treated with paroxetine CR exhibited a 65% mean improvement in psychic anxiety ($p < .0001$), and patients treated with paroxetine IR exhibited a 60% mean improvement in psychic anxiety ($p < .005$).

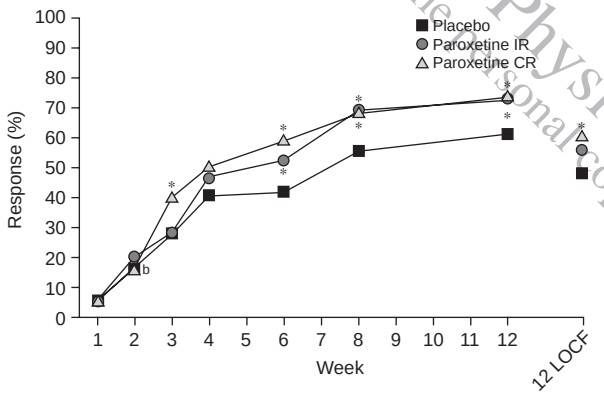
Response, which reflects clinically relevant improvement in depressive symptoms, was defined as a ≥ 50% reduction in baseline HAM-D total score. HAM-D response rates in the paroxetine CR group were significantly higher

Figure 3. Weekly Mean HAM-D Psychic Anxiety Score (item 10) Among Patients Treated With Paroxetine CR, Paroxetine IR, or Placebo (OC dataset and endpoint LOCF dataset)[a]



[a]Abbreviations: CR = controlled-release, HAM-D = Hamilton Rating Scale for Depression, IR = immediate-release, LOCF = last observation carried forward, OC = observed cases.
[b]Point represents both the paroxetine IR and paroxetine CR groups.
*p ≤ .05 vs. placebo.

Figure 4. Weekly HAM-D Response Rates Among Patients Treated With Paroxetine CR, Paroxetine IR, or Placebo (OC dataset and endpoint LOCF dataset)[a]

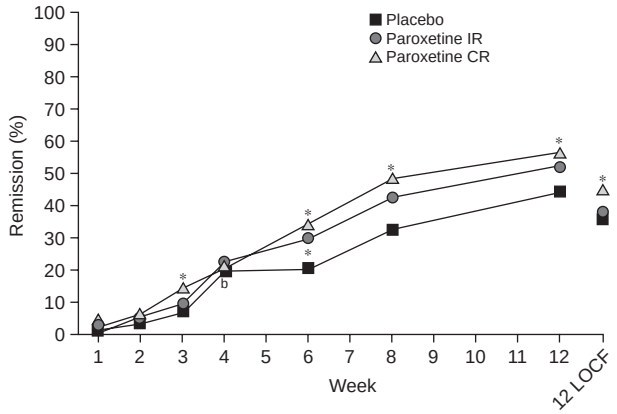


[a]Response is defined as a ≥ 50% reduction in baseline HAM-D total score. Abbreviations: CR = controlled-release, HAM-D = Hamilton Rating Scale for Depression, IR = immediate-release, LOCF = last observation carried forward, OC = observed cases.
[b]Point represents both the paroxetine CR and placebo groups.
*p ≤ .05 vs. placebo.

than in the placebo group as early as week 3 (OC and LOCF, p ≤ .05). At OC endpoint, response rates among patients who completed the study were 74% for paroxetine CR (p ≤ .05 vs. placebo), 73% for paroxetine IR (p ≤ .05 vs. placebo), and 61% for placebo. At the LOCF endpoint, HAM-D response rates were 60% for paroxetine CR (p ≤ .05 vs. placebo), 56% for paroxetine IR (p = .11 vs. placebo), and 48% for placebo (Figure 4).

Remission was defined as a HAM-D score of 7 or less, which usually corresponds to a reduction of approximately 70% or more in baseline symptoms.[21] By week 3, a greater proportion of paroxetine CR patients achieved remission compared with placebo patients (OC and LOCF,

Figure 5. Weekly HAM-D Remission (HAM-D total score ≤ 7) Rates Among Patients Treated With Paroxetine CR, Paroxetine IR, or Placebo (OC dataset and endpoint LOCF dataset)[a]



[a]Abbreviations: CR = controlled-release, HAM-D = Hamilton Rating Scale for Depression, IR = immediate-release, LOCF = last observation carried forward, OC = observed cases.
[b]Point represents both the paroxetine CR and placebo groups.
*p < .05 vs. placebo.

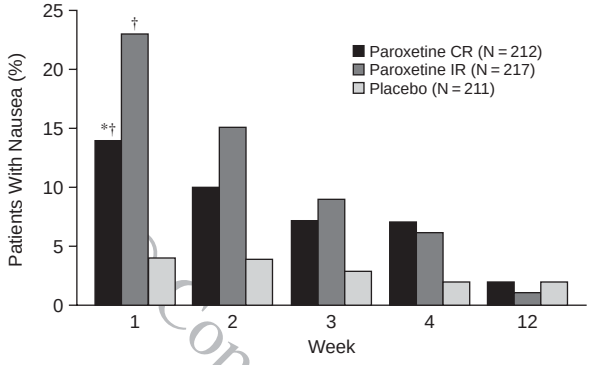
p < .05) (Figure 5). At endpoint, 56% of paroxetine CR patients were classified as remitters (OC, p < .05 vs. placebo) compared with 53% for paroxetine IR and 44% for placebo. A similar pattern of remission was achieved with the LOCF dataset, with 45% of paroxetine CR patients in remission (p < .05 vs. placebo) compared with 37% for paroxetine IR and 34% for placebo.

Tolerability

Paroxetine CR was well tolerated in this sample of patients with major depressive disorder. Moreover, it was associated with lower rates of nausea than was paroxetine IR in the first few weeks of treatment (Figure 6). During the first week of treatment, nausea rates were 14% for paroxetine CR and 23% for paroxetine IR (p ≤ .05). Nausea was reported by 4% of patients in the placebo group during week 1 (p ≤ .05 vs. paroxetine CR and IR). By the second week of treatment, nausea rates began to decline in both paroxetine groups, and there were no significant between-group differences in nausea rates in that week or any other point thereafter.

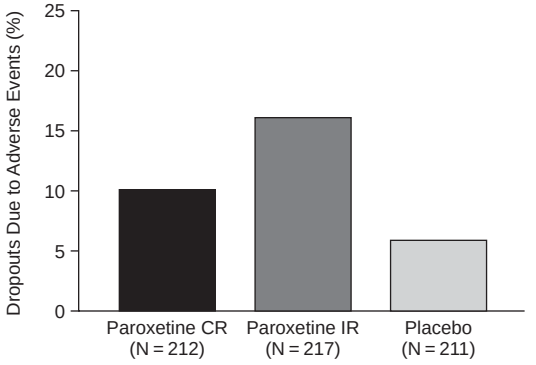
Other commonly reported adverse events associated with paroxetine CR and paroxetine IR are similar to those reported with serotonergic antidepressants[22] and are reported in Table 2. Most of the treatment-emergent adverse events were rated as mild to moderate in severity and occurred early in the study. There were no unexpected adverse events, and serious adverse events were uncommon (15 of the 429 patients treated with paroxetine CR or paroxetine IR). No clinically significant changes in laboratory test results or vital signs were generally observed during these studies.

Figure 6. Rates of Nausea With Paroxetine CR Versus Paroxetine IR During Early Treatment[a]



[a]Abbreviations: CR = controlled-release, IR = immediate-release.
*p ≤ .05 vs. paroxetine IR.
†p ≤ .05 vs. placebo.

Figure 7. Overall Dropout Rates Due to Adverse Events for Paroxetine CR, Paroxetine IR, and Placebo[a]



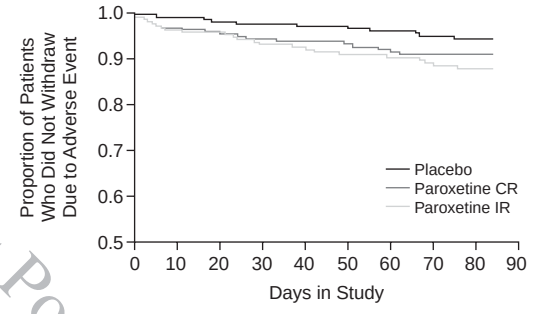
[a]Paroxetine IR vs. placebo, p = .0008. Abbreviations: CR = controlled-release, IR = immediate-release.

Table 2. Most Common Adverse Events in Patients Treated With Paroxetine CR, Paroxetine IR, or Placebo[a]

Adverse Event	Paroxetine CR (N = 212) N (%)	Paroxetine IR (N = 217) N (%)	Placebo (N = 211) N (%)
Nausea	50 (23.6)*	67 (30.9)*	30 (14.2)
Abnormal ejaculation[b]	21 (26.9)*	16 (23.9)*	1 (1.3)
Somnolence	49 (23.1)*	47 (21.7)*	17 (8.1)
Dizziness	41 (19.3)*	36 (16.6)*	10 (4.7)
Diarrhea	39 (18.4)*	29 (13.4)*	15 (7.1)
Infection	20 (9.4)	27 (12.4)*	13 (6.2)
Constipation	22 (10.4)*	26 (12.0)*	9 (4.3)
Female genital disorders[b]	14 (10.4)*	8 (5.3)*	1 (0.8)
Sweating	14 (6.6)*	21 (9.7)*	6 (2.8)
Tremor	15 (7.1)*	15 (6.9)*	5 (2.4)

[a]"Most common" defined as paroxetine CR or paroxetine IR rate of at least 5% and twice the rate of placebo. Abbreviations: CR = controlled-release, IR = immediate-release.
[b]Percentage corrected for gender.
*p < .05 vs. placebo.

Figure 8. Time to Withdrawal Due to Adverse Event: Kaplan-Meier Survival Curve (intent-to-treat population)[a]



[a]Abbreviations: CR = controlled-release, IR = immediate-release.

Weight change was assessed at each visit. No significant differences emerged in the mean weight change from baseline to endpoint. The mean ± SD change from baseline to week 12 was 0.0 ± 7.0 lb (0.0 ± 3.2 kg) for paroxetine CR, 0.8 ± 5.1 lb (0.4 ± 2.3 kg) for paroxetine IR, and 1.0 ± 5.8 lb (0.5 ± 2.6 kg) for placebo. Weight change was also assessed using a criterion for substantial weight increase or decrease (change of ≥ 7% of baseline body weight). Overall rates of substantial weight change were low. For example, substantial weight increase was observed in 4.2%, 3.8%, and 1.4% of paroxetine IR, paroxetine CR, and placebo patients, respectively. Substantial weight decrease was reported in 2.3%, 4.3%, and 1.4% of paroxetine IR, paroxetine CR, and placebo patients, respectively.

Rates of dropout due to adverse events were comparable between paroxetine CR and placebo (10% and 6%, respectively, p = .14) (Figure 7). A greater proportion of patients treated with paroxetine IR, however, withdrew from the study prematurely due to adverse events (16%) compared with placebo (p = .0008). Treatment discontinuation due to nausea occurred in 3% of patients in the paroxetine CR group, 4% of patients in the paroxetine IR group, and 0.5% of patients in the placebo group. Time to withdrawal due to adverse events is shown in Figure 8.

DISCUSSION

The results of this pooled analysis of 2 placebo-controlled studies demonstrate that, like paroxetine IR, paroxetine CR is an effective and well-tolerated treatment for major depressive disorder and associated anxiety. Patients were randomly assigned to receive a 12-week course of treatment with paroxetine CR, paroxetine IR, or placebo. Changes in HAM-D total scores were significantly better with paroxetine CR and paroxetine IR compared with placebo and represented clinically meaningful improvement in symptoms of depression. Significant

improvement in symptoms of depression and anxiety were apparent beginning at week 1 and persisted through study endpoint for patients randomly assigned to paroxetine CR.

Remission, or a return to premorbid levels of functioning, has become the gold-standard therapeutic goal in the treatment of major depressive disorder.[21] These results demonstrate that despite high rates of placebo response, patients treated with paroxetine CR not only respond well to treatment, but also achieve superior rates of remission compared with patients treated with placebo. Indeed, considerable attention has been awarded to the pooled analysis of antidepressant remission by Thase et al.,[23] who reported remission rates of 25% for placebo, 35% for SSRIs, and 45% for venlafaxine. In the present study, we observed remission rates of 45% for paroxetine CR compared with 34% for placebo using the LOCF analysis. The efficacy of paroxetine CR may be attributable to its property of blocking both serotonin and norepinephrine reuptake.[24] Response and remission for paroxetine CR occurred as early as week 3 relative to placebo. These data support the view that paroxetine CR is an effective antidepressant, improving both depression and associated anxiety.

The present study demonstrates that the overall adverse event profile of paroxetine CR is largely similar to that of paroxetine IR, with some evidence for improved tolerability. It is noteworthy that nausea rates were significantly lower during the first week of treatment with paroxetine CR compared with paroxetine IR (14% vs. 23%, respectively). This difference is likely to be clinically relevant, particularly as it relates to risk of medication noncompliance during the initial stages of antidepressant treatment. Those patients who tolerate antidepressant therapy, especially during the first week of treatment before clinical improvement becomes apparent, and remain compliant are obviously more likely to complete their full course of treatment and achieve a better long-term outcome (i.e., remission).

Of particular note was the observation that no significant difference emerged in rates of premature study withdrawal due to adverse events in the paroxetine CR and placebo groups, a rare finding in SSRI treatment studies. Patients treated with paroxetine IR, however, exhibited a higher dropout rate due to adverse events than those treated with placebo. These differential rates of treatment discontinuation due to adverse events are clinically meaningful, particularly as they relate to treatment adherence and clinical response during the initial stages of antidepressant treatment.

While nausea rates were significantly lower in the paroxetine CR group compared with the paroxetine IR group during the initial week of treatment, other SSRI side effects were observed with similar frequency in these 2 active treatment arms. This frequency is to be expected due to the pharmacokinetic properties of the 2 paroxetine formulations. The CR formulation, as described above, delays the gastrointestinal absorption of paroxetine so that stimulation of upper gastrointestinal 5-HT_3 receptors (and consequent nausea) is avoided. Other SSRI side effects are mediated via stimulation of 5-HT receptors in the brain, rather than the gastrointestinal tract. Thus, the comparable rates of other side effects suggest that the bioavailability and concentrations of paroxetine reaching the central nervous system were similar in both the CR and IR treatment groups. At the same time, most clinical trials are designed and powered to test for differences in efficacy rather than differences in specific adverse events. Thus, the clinical trials reported here may have been underpowered to test for differences in the rates of specific adverse events between paroxetine CR and IR.

Although early-onset adverse events with the SSRIs are generally mild and transient, they contribute to patient dissatisfaction, medication noncompliance, and premature discontinuation of therapy. In clinical trials, effective and well-tolerated antidepressants, such as paroxetine CR, are likely to increase treatment compliance and may result in a beneficial therapeutic outcome.

CONCLUSION

These data demonstrate that paroxetine CR is an effective and well-tolerated therapy for major depressive disorder. Treatment with paroxetine CR results in early improvement in depressive and anxiety symptoms and early achievement of clinically significant response and remission. As expected with a controlled-release formulation, paroxetine CR has significantly lower rates of early-onset nausea compared with paroxetine IR. More importantly, dropouts due to adverse events with paroxetine CR were low and not statistically different from placebo.

Drug names: fluoxetine (Prozac and others), paroxetine (Paxil), venlafaxine (Effexor).

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