Low Doses of Controlled-Release Paroxetine in the Treatment of Late-Life Depression: A Randomized, Placebo-Controlled Trial

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Objective: To evaluate the efficacy and tolerability of low daily doses of controlled-release (CR) paroxetine in patients with late-life depression.

Method: This was a 10-week, multicenter, placebo-controlled, double-blind, fixed-dose trial randomly assigning patients ≥ 60 years old to daily doses of paroxetine CR 12.5 mg (N = 168), paroxetine CR 25 mg (N = 177), or placebo (N = 180). Patients had major depressive disorder (DSM-IV criteria) and 17-item Hamilton Rating Scale for Depression (HAM-D) total scores of ≥ 18. The primary efficacy variable was the change from baseline to study endpoint in total HAM-D scores. The study was conducted from June 2003 to October 2004.

Results: The drug/placebo difference in HAM-D change from baseline at study endpoint was –1.8 (95% CI = –3.41 to –0.19, p = .029) for paroxetine CR 12.5 mg, and –3.3 (95% CI = –4.84 to –1.68, p < .001) for paroxetine CR 25 mg. A significantly larger percentage of patients achieved remission (HAM-D total score ≤ 7 at endpoint) with paroxetine CR 25 mg (41%), but not with 12.5 mg (31%), as compared with placebo (28%) (p = .008). Both doses of paroxetine CR also achieved statistical significance compared to placebo for the Clinical Global Impressions-Severity of Illness scale (p < .01) and the patient-rated measures of depression severity (p < .05) and quality of life (p ≤ .001). Both active treatments were generally well tolerated, with adverse event withdrawal rates of 6%, 8%, and 7% for paroxetine CR 12.5 mg, paroxetine CR 25 mg, and placebo, respectively.

Conclusion: These data demonstrate that paroxetine CR 12.5 mg and 25 mg daily are efficacious and well tolerated in the treatment of major depressive disorder in patients ≥ 60 years of age, although effect sizes are relatively smaller with the 12.5 mg/day dose.

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Depression in the elderly is a significant public health concern: the disability, diminished quality of life, and costs it generates constitute major burdens both to society and to depressed individuals and their families.[1–3] However, late-life depression remains underdiagnosed and undertreated, especially in primary care settings.[4] Even when appropriately diagnosed, patients with late-life depression pose unique challenges to the professionals who treat them.[5,6] Older individuals are more likely to have concurrent medical illnesses and to be taking other medications, which increases the risk of drug-drug interactions. The physiologic changes that occur with aging, particularly those affecting renal and hepatic functioning, may alter metabolism of medications and can heighten sensitivity to drug-related adverse events.

Despite these challenges, antidepressant medications have been shown to be effective in treating late-life depression. For the reasons stated above, the prescribing principles generally accepted for antidepressant usage in the elderly suggest starting with lower initial doses than are typically used for younger patients and very gradual dose increases until the desired therapeutic response is achieved. Selective serotonin reuptake inhibitors (SSRIs) have largely replaced tricyclic antidepressants (TCAs) as first-line treatments for depression in the elderly.[6,7] SSRIs are generally equivalent to TCAs in efficacy but have significantly superior tolerability and safety profiles.[8–12]

Paroxetine HCl is an SSRI available in both an immediate release (IR) and controlled-release (CR) formulation.

The CR formulation has both a delayed and slower rate of absorption in the gastrointestinal tract, which is unique among the SSRIs, and thus may possess an improved tolerability profile.[13] Because approximately 20% of the CR formulation's drug content is eliminated unchanged from the gastrointestinal tract, 20% higher doses of paroxetine CR are required to obtain the same bioavailability as the IR formulation.[13] Thus, a paroxetine CR dose of 12.5 mg is equivalent to a 10 mg of IR, and a 25-mg dose of CR is equivalent to a 20-mg dose of IR.

In a dose-range finding study with fixed doses of 10, 20, 30, and 40 mg of paroxetine IR and placebo, all but the 10-mg dose were superior to placebo, suggesting that 20 mg was the minimal effective paroxetine IR dose in adult patients with major depressive disorder (MDD).[14] Other analyses of both individual studies and pooled data from the worldwide database of MDD patients treated with paroxetine IR confirmed that the therapeutic dose range for paroxetine IR was 20 mg to 50 mg/day in nonelderly adults. Although a fixed dose of paroxetine IR 10 mg/day has not been adequately studied, pharmacokinetic studies suggest that, in the elderly, plasma concentrations achieved from 10 mg paroxetine IR may be comparable to those achieved in younger patients taking higher doses.[15] Thus, the upper limit of the recommended dose range for paroxetine IR is 40 mg/day in the elderly with MDD, as this is the highest dose that has been studied.[14]

In direct comparison studies, IR and CR paroxetine formulations showed equivalent treatment efficacy for patients with MDD: the cohorts studied included both nonelderly adults[16] and the elderly, aged 60 years and older.[17] Paroxetine CR was given in flexible doses with upper limits of the permitted dose range of 62.5 mg/day for younger adults and 50 mg/day for adults over the age of 60 years. For nonelderly adults, the mean endpoint dose for paroxetine CR was 48.2 mg/day, and for the elderly sample it was 30.4 mg/day, which is about the midpoint of the recommended dose range (12.5 to 50 mg/day) for physicians treating elderly patients in clinical practice. The efficacy and tolerability of specific dose levels, as well as the minimal effective dose of paroxetine CR, could not be determined by these flexible dose studies. In nonelderly adults, a subsequent examination of 2 fixed doses corresponding to the lowest available doses of the CR formulation (12.5 and 25 mg/day)[18] showed that 25 mg/day was highly effective as compared with placebo on the primary outcome variable (change in Hamilton Rating Scale for Depression from baseline to 8-week treatment endpoint) and several secondary efficacy measures. Paroxetine CR 12.5 mg/day was also superior to placebo on the primary, but not on some of the same secondary measures. Since a dose as low as 12.5 mg/day of paroxetine CR appeared to be adequate for some adult MDD patients, a similar study of 12.5 and 25 mg/day doses of paroxetine CR in patients with late-life MDD was undertaken in order to assess their efficacy in this population.

Thus the challenges of treating late-life depression inspire continued efforts to develop treatments that are more effective, safer, and better tolerated. The current study examined the efficacy, safety, and tolerability of fixed daily doses of paroxetine CR (12.5 mg and 25 mg) compared with placebo in patients with MDD aged 60 years or older. We hypothesized that both 12.5 mg/day paroxetine CR and 25 mg/day paroxetine CR would be more effective than placebo for the treatment of MDD in individuals over the age of 60 years.

METHOD

Subjects

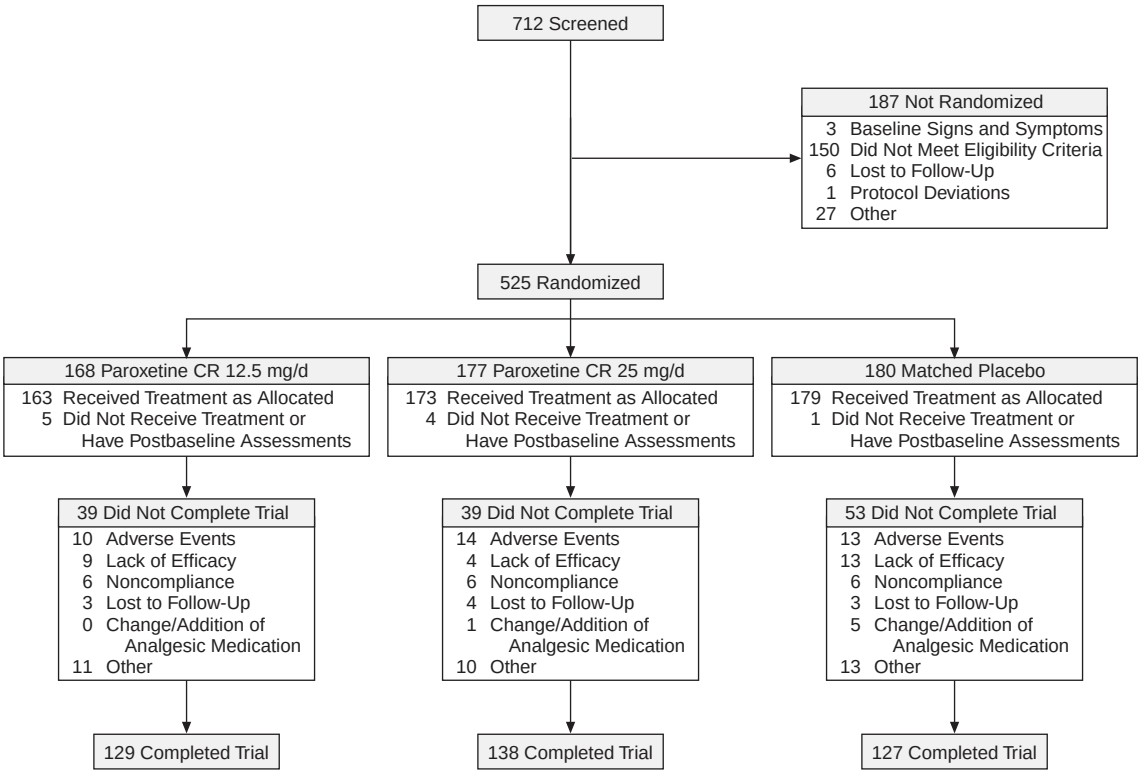
Study participants were men and women aged 60 years or older, who met criteria for a primary diagnosis of MDD (without psychotic features), single or recurrent episode, according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[19] Eligibility criteria also included a current episode of depression of at least 2 months in duration and a 17-item Hamilton Rating Scale for Depression (HAM-D)[20] score ≥ 18 at both screening and baseline, with a score on item 1 (depressed mood) ≥ 2.

Patients who met any of the following criteria were not eligible for participation in the study: ≥ 25% decrease in HAM-D total score between screening and baseline; primary or predominant DSM-IV Axis I disorder (within 6 months prior to screening) other than MDD; lifetime schizophrenia, schizoaffective disorder, or bipolar disorder; alcohol or substance abuse or dependence within 6 months prior to screening; current diagnosis of dementia; Mini-Mental State Examination (MMSE)[21] score ≤ 24; depression secondary to a medical condition; a history of brief depressive episodes (≤ 8 weeks with spontaneous remission); formal psychotherapy concurrently or in the 12 weeks prior to screening; attempted suicide within 6 months prior to screening or current suicidal or homicidal risk; electroconvulsive therapy or transcranial magnetic stimulation within 6 months prior to screening; lifetime history of seizure disorder; clinically significant electrocardiogram (ECG) abnormalities or abnormal laboratory findings; any current or recent use of other psychoactive drugs; history of intolerance to paroxetine; investigational drug use or other clinical trial participation within 3 months prior to screening; or likelihood of nonadherence with study procedures or study medication.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study evaluating the efficacy and tolerability of 12.5 mg and 25 mg daily doses of paroxetine CR versus placebo in elderly outpatients

Figure 1. Patient Disposition in the Trial of Controlled-Release (CR) Paroxetine in Geriatric Patients With Major Depressive Disorder



with MDD. The study was conducted at 46 centers in the United States from June 2003 to October 2004. All participating sites obtained approval from an institutional review board. Prior to the initiation of any study procedure, each patient provided written informed consent after receiving a complete explanation of the study and potential treatment side effects.

Consenting patients underwent physical and psychiatric evaluations, including a structured psychiatric interview with the Mini-International Neuropsychiatric Interview (MINI),[22] and completed psychometric assessments at an initial screening visit. Patients who remained eligible after a 1-week, single-blind, placebo run-in period were randomly assigned at a baseline visit to 1 of 3 treatment groups (see Randomization, Study Treatments, and Blinding). During 10 weeks of double-blind treatment, visits occurred at weeks 1, 2, 3, 4, 6, 8, and 10. At the week 10 visit, or at an early termination visit if patients were discontinued from treatment prematurely, patients were dispensed a 7-day supply of taper medication and scheduled for a safety follow-up visit corresponding to 14 days after the final dose of double-blind medication.

Randomization, Study Treatments, and Blinding

At the baseline visit, patients were assigned in a 1:1:1 ratio to paroxetine CR 12.5 mg/day, paroxetine CR 25 mg/day, or placebo (Figure 1) on the basis of a permuted block randomization scheme (block size of 6 within study centers). Active medications were provided as over-encapsulated tablets, which were identical in appearance to placebo. Study participants were instructed to take study medication each morning as a single daily dose.

For all patients assigned to paroxetine CR, the initial dose was 12.5 mg. Those assigned to paroxetine CR 25 mg had their dose increased to 25 mg after 2 weeks. During the double-blind, 1-week medication taper following the 10-week treatment period, patients in the paroxetine CR 12.5 mg treatment group were given placebo, whereas those in the paroxetine CR 25 mg treatment group received paroxetine CR 12.5 mg for 1 week.

Concomitant use of other psychotropic medications was prohibited during the study, with the exception of zolpidem or zaleplon to treat sleep disturbance during the run-in phase and the first 2 weeks of the double-blind study. Patients were instructed not to take these sleep medications the evening prior to any clinic visit. The use of opioid analgesics was prohibited during this study. Continued use of nonopioid analgesics, such as nonsteroidal anti-inflammatory drugs, taken prior to study entry was permitted, provided that the dosage did not change during the study. Patients who required new analgesic medications or needed to adjust analgesic medication

dosage after entering the study were terminated from the trial. (The use of once-daily aspirin for cardiovascular prophylaxis was permitted.)

Efficacy Assessments

Clinician-rated efficacy scales were administered at baseline and treatment weeks 1, 2, 3, 4, 6, 8, and 10 (or study endpoint). At each visit, patients were rated for symptoms of depression and anxiety via the Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scales (SIGH-AD),[23] which incorporates all items of the 17-item HAM-D[20] and Hamilton Rating Scale for Anxiety (HAM-A).[24] To establish interrater reliability prior to the study, all raters participating in the study received formal training in the administration and scoring of the SIGH-AD at the investigators meeting and were required to meet or exceed a minimum scoring criterion while rating a videotaped interview. In addition, the Clinical Global Impressions-Severity of Illness (CGI-S) and CGI-Improvement (CGI-I) scales[25] were assessed. Self-reported depressive symptoms were measured with the Geriatric Depression Scale (GDS) 15-item Short Form[26] at the same visits. The 16-item short form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[27] was administered at baseline and week 10 (or study endpoint). Patient-rated assessments of several different dimensions of pain were also obtained at baseline and at various visits post baseline. Because these pain measurements were employed for exploratory purposes and are not germane to the core hypotheses of this article, the methods and obtained results are not presented here.

The primary efficacy variable was change from baseline to study endpoint in HAM-D total score derived from SIGH-AD ratings. Secondary efficacy variables included baseline to endpoint changes in HAM-D item 1 (depressed mood), HAM-D item 13 (somatic symptoms, general), HAM-D sleep factor (items 4, 5, and 6), HAM-A total score based on the SIGH-AD, CGI-S score, GDS Short Form score, the Q-LES-Q total score (items 1–14), and the Q-LES-Q additional item scores for overall life satisfaction and satisfaction with medication. Additional secondary outcomes included the proportions of patients in each group achieving therapeutic response and remission during treatment. Therapeutic response was defined in 2 ways: score of 1 or 2 on the CGI-I at endpoint and 50% reduction from baseline to endpoint in HAM-D total score. Remission was defined as HAM-D total score ≤ 7 at endpoint.

Safety Assessments

Complete medical, psychiatric, and medication histories were obtained at the screening visit, along with a physical examination, 12-lead ECG, and laboratory testing. At the baseline visit, laboratory tests and/or ECG were repeated if screening assessments were abnormal. At each visit during double-blind treatment, spontaneously reported adverse experiences were recorded, vital signs were assessed, and concomitant medications were recorded. Additionally, at the week 10 (or study endpoint) visit, physical examination, ECG, and laboratory assessments were repeated. At the safety follow-up visit, adverse experiences, vital signs, and concomitant medications were recorded. Laboratory assessments and ECG were repeated only if abnormalities were evident at the week 10 (or study endpoint) visit.

Statistical Analyses

All analyses were based on a modified intent-to-treat (ITT) population. The modified ITT efficacy population consisted of all patients who were randomly assigned, received at least 1 dose of double-blind study medication, and had at least 1 postbaseline efficacy assessment. The primary time point of interest for all efficacy analyses was week 10 (or study endpoint). In the last-observation-carried-forward (LOCF) data set, which was used for primary inference, the most recent on-treatment efficacy assessment was carried forward to estimate missing values at scheduled time points. In the observed case data set, all efficacy data actually collected at a given time point were used in the analysis, without estimating any missing values. Analyses based on the observed case data set were considered supportive. All statistical tests were 2-tailed, with a significance level of .05.

Primary efficacy variable. The primary efficacy variable was the change from baseline in the HAM-D total score. The 2 primary comparisons of interest were paroxetine CR 12.5 mg/day versus placebo and paroxetine CR 25 mg/day versus placebo. The nominal α level of .05 was adjusted for multiple comparisons using Hochberg's[28] modification to the Bonferroni inequality.

A total sample of 468 evaluable subjects (156 per treatment group) were determined to be sufficient to detect a mean difference of 3.0 points in the HAM-D total score with 90% power, assuming a common standard deviation of 7.5 and normally distributed errors with a 2-sided nominal significance level of 5% (actual significance level of 2.5%, adjusting for 2 treatment comparisons). With an additional assumption that 10% of subjects would be discontinued from the study prior to the first assessment point, the targeted number of randomly assigned subjects was 522 (approximately 174 in each treatment arm).

The primary variable was analyzed using a parametric analysis of variance (ANOVA) model with center and treatment as main effects. Center-by-treatment interaction was found to be nonsignificant (i.e., $p > .10$) and was removed from the model. Inference was based on the Hochberg procedure. Least squares means and 95% confidence intervals for the pairwise comparisons of each paroxetine CR treatment group with placebo were

presented as summaries. No deviations from normality were evident for the data set. Robustness of the results for the HAM-D total score at the week 10 LOCF endpoint was explored using longitudinal data analysis. For this repeated-measures model, treatment, center, and time were treated as fixed effects, and the patient was treated as a random effect. Treatment-by-time interaction was also assessed.

Secondary efficacy variables. Continuous secondary efficacy variables, such as the change from baseline on the depressed mood item, somatic symptoms item, and sleep factor score of the HAM-D; CGI-S; HAM-A; GDS; and Q-LES-Q total and additional items (overall life satisfaction and satisfaction with treatment) scores, were analyzed using the same ANOVA model employed for the primary variable analysis.

Categorical secondary efficacy variables included the proportion of patients in each treatment group achieving (1) therapeutic response on the CGI-I (score of 1 or 2 at endpoint), (2) therapeutic response on the HAM-D (≥ 50% reduction from baseline to endpoint in total score), and therapeutic remission (HAM-D total score ≤ 7 at endpoint). These categorical variables were analyzed using logistic regression, adjusting for treatment. The number needed to treat (NTT), a measure of the number of patients requiring treatment before one will show a significant benefit of drug over placebo, was also computed for the HAM-D criteria for therapeutic response and remission.

The results were presented in terms of adjusted odds ratios, 95% confidence intervals, and significance levels. The secondary efficacy analyses were not adjusted for multiplicity.

Safety variables. Safety and demographic data were summarized by appropriate descriptive statistics using a modified ITT safety population, which consisted of all randomly assigned patients receiving at least 1 dose of double-blind study medication and having at least 1 valid postbaseline safety assessment. Missing values were not imputed. No statistical comparisons were planned for safety variables.

RESULTS

Patient Disposition and Baseline Characteristics

The disposition of all patients providing consent for study participation is depicted in Figure 1. Of 712 patients screened for the study, 525 met all criteria for inclusion at baseline and were randomly assigned to receive either paroxetine CR (12.5 or 25 mg/day) or placebo. Nine randomly assigned patients were not included in the modified ITT population because they did not take at least 1 dose of postrandomization study medication or did not have a valid postbaseline assessment. As a result, the modified ITT population consisted of 516 patients. Overall, 394 randomly assigned patients (76%) completed the study. The reasons for study discontinuation within each treatment group are provided in Figure 1.

Demographics and other baseline characteristics of the patient population are summarized in Table 1. The 3 treatment groups were well matched with respect to mean age, gender distribution, race, height, weight, and most characteristics related to psychiatric history and treatment. The patients were moderately to severely depressed, with comparable mean baseline HAM-D total scores among treatments (22.56 for paroxetine CR 12.5 mg, 23.10 for paroxetine CR 25 mg, and 22.73 for placebo). Across the entire sample, the percentage of patients with prior psychiatric diagnoses other than MDD, as determined by the MINI, was low. The most common prior psychiatric diagnoses were generalized anxiety disorder (5.8%) and dysthymia (4.2%). Patients with current primary psychiatric conditions other than MDD were excluded from the study. The most frequent comorbid illnesses for this study population were hypertension (43%); rheumatoid arthritis, osteoarthritis, and other arthritic diagnoses (35%); and hyperlipidemia (30%). For these disorders, patients were most frequently treated with the following medication classes: analgesics (38%), statins (25%), diuretics (22%), nonsteroidal anti-inflammatory agents (21%), angiotensin converting enzyme inhibitors (18%), β-blockers (17%), calcium channel blockers (13%), angiotensin receptor blockers (8%), and cyclooxygenase-2 (COX-2) inhibitors (9%).

Adherence to treatment was comparable overall for the 3 treatment groups. Rates of nonadherence (i.e., patients in the modified ITT population having total capsule counts during the study outside of the 80%–120% range) were 5%, 4%, and 4% of patients, respectively, for the paroxetine CR 12.5 mg, paroxetine CR 25 mg, and placebo groups. Interruptions in treatment of 3 or more days were reported by 10%, 13%, and 7% of patients in the paroxetine CR 12.5 mg, paroxetine CR 25 mg, and placebo groups, respectively.

Efficacy Results

Changes from baseline. Mean changes from baseline to the end of week 10 are summarized for primary and secondary efficacy variables in Table 2. A statistically significant benefit was observed for both paroxetine CR doses on the primary endpoint (change from baseline in HAM-D total score by LOCF). The paroxetine CR 25 mg treatment arm was associated with a –3.26-point change from baseline in the HAM-D total score compared with placebo; the paroxetine CR 12.5 mg treatment arm exhibited a –1.80-point change. Although the paroxetine CR 25 mg treatment arm may have had a more robust treatment effect than the CR 12.5 mg treatment arm, the study was not designed to test this hypothesis explicitly through a head-to-head comparison of the 2 active treatment arms. Figure 2

Table 1. Demographic and Clinical Characteristics of Intent-to-Treat Study Population at Baseline

Characteristic	Paroxetine CR 12.5 mg (N = 164)	Paroxetine CR 25 mg (N = 173)	Placebo (N = 179)
Female, %	60	60	63
Age, mean (SD), y	67 (6.11)	67 (6.56)	68 (6.73)
Age group, N (%)			
≥ 60 and < 70 y	120 (73)	119 (69)	113 (63)
≥ 70 and < 80 y	35 (21)	44 (25)	54 (30)
≥ 80 y	9 (5)	10 (6)	12 (7)
Race, N (%)			
White	131 (80)	148 (86)	143 (80)
Black	10 (6)	5 (3)	14 (8)
Asian	1 (1)	0	2 (1)
Other	22 (13)	20 (12)	20 (11)
No. of previous depressive episodes, mean (SD)	4.6 (11.0)	7.8 (20.3)	4.8 (11.2)
Age at onset of previous episodes, mean (SD), y	63.5 (11.9)	63.0 (11.6)	63.7 (13.3)
Duration of previous depressive episodes, mean (SD), y	4.2 (9.7)	4.4 (9.7)	4.7 (11.0)
Previous psychoactive medications, N (%)			
SSRIs	36 (22)	27 (16)	39 (22)
Benzodiazepines	9 (5)	11 (6)	7 (4)
TCAs	1 (1)	1 (1)	6 (3)
Other	20 (12)	22 (13)	14 (8)
Herbal medications	7 (4)	6 (3)	1 (1)
HAM-D total score, mean (SD)[a]	22.56 (3.59)	23.10 (3.93)	22.73 (4.00)
HAM-A total score, mean (SD)[a]	18.31 (5.39)	17.90 (5.21)	17.46 (5.57)
CGI-S score, mean (SD)[a]	4.31 (0.56)	4.32 (0.55)	4.28 (0.52)
GDS total score, mean (SD)[a]	8.93 (3.55)	9.13 (3.48)	8.68 (3.44)
Q-LES-Q total score, mean (SD)[a]	40.06 (7.33)	39.71 (7.90)	39.95 (8.20)

[a]Across efficacy rating scales, N = 177 to 179 for patients in the placebo group, N = 162 to 164 in the paroxetine 12.5-mg group, and N = 171 to 173 in the paroxetine 25-mg group.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, CR = controlled release, GDS = Geriatric Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, 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.

depicts the mean changes in HAM-D total scores over the course of treatment for the LOCF dataset. The observed case (completer) analysis demonstrates similar results. The repeated-measures analysis also supports the inference based on the LOCF week 10 analysis of the primary efficacy variable.

As shown in Table 2, secondary efficacy measures assessing symptomatic improvement also demonstrate greater efficacy for paroxetine CR than placebo. Both paroxetine CR treatment groups showed statistically significant differences relative to placebo on most secondary measures, although the degree of symptomatic change was numerically greater for the 25-mg group than the 12.5-mg group on most items. The HAM-D sleep factor (for both paroxetine CR treatments) and the HAM-D somatic symptoms item (for the 12.5 mg treatment) did not separate from placebo. For nearly all comparisons of secondary variables between paroxetine CR and placebo groups, the observed case analyses demonstrate a pattern of results similar to the LOCF analyses. Caution should be used in interpreting the analyses for the secondary measures because no adjustment for multiplicity was performed.

Treatment response and remission. The percentage of treatment responders in the CGI analysis (CGI-I score of 1 or 2) at the week 10 LOCF endpoint was significantly higher for paroxetine CR 12.5 mg (53%; $p = .007$, OR = 1.81, 95% CI = 1.18 to 2.79) and paroxetine CR 25 mg (61%; $p < .001$, OR = 2.44, 95% CI = 1.59 to 3.75), as compared with placebo (39%). Likewise, with treatment response defined as ≥ 50% reduction from baseline to endpoint in HAM-D total score, the rate of response was significantly greater in each of the paroxetine CR treatment groups (52% and 58%, respectively, for paroxetine CR 12.5 mg and paroxetine CR 25 mg) than in the placebo group (40%) (Figure 3). The NNT to have a treatment response (≥ 50% reduction from baseline to endpoint in HAM-D total score) was 9 (95% CI = 4.4 to 196.6) for paroxetine CR 12.5 mg and 6 (95% CI = 3.5 to 14.2) for paroxetine 25 mg. The LOCF remission analysis (HAM-D total score ≤ 7 at week 10 endpoint) revealed that a significantly larger percentage of patients achieved remission by week 10 in the paroxetine CR 25-mg dose group (41%), but not in the 12.5-mg group (31%), as compared with placebo (28%) (Figure 3). The NNT to achieve remission was 8 (95% CI = 4.2 to 32.2) for paroxetine CR 25 mg.

Patient-rated scales. On the GDS and Q-LES-Q total score, paroxetine CR 12.5-mg and 25-mg recipients rated themselves as having significantly greater improvement at week 10 than those taking placebo. Results of the analyses for the GDS and Q-LES-Q total scores are presented in Table 2. In addition, both paroxetine CR groups had significantly greater improvements in their ratings of

Table 2. Efficacy of Paroxetine CR at Week 10 in Geriatric Patients With Major Depressive Disorder (last observation carried forward for intent-to-treat efficacy population)

			Pairwise Comparison With Placebo		
LOCF Efficacy Measure	N	Least Squares Mean (SE)[a]	Difference[b]	p Value	95% CI
HAM-D total score					
Placebo	178	–8.85 (0.60)	…	…	…
Paroxetine CR 12.5 mg/d	161	–10.65 (0.63)	–1.80	.029[c]	–3.41 to –0.19[d]
Paroxetine CR 25 mg/d	173	–12.11 (0.61)	–3.26	< .001[c]	–4.84 to –1.68[d]
HAM-D item 1 (depressed mood)					
Placebo	178	–1.10 (0.09)	…	…	…
Paroxetine CR 12.5 mg/d	161	–1.46 (0.10)	–0.36	.004	–0.61 to –0.12
Paroxetine CR 25 mg/d	173	–1.63 (0.09)	–0.53	< .001	–4.84 to –1.68
HAM-D sleep factor					
Placebo	178	–1.61 (0.16)	…	…	…
Paroxetine CR 12.5 mg/d	161	–1.67 (0.16)	–0.06	.773	–0.47 to 0.35
Paroxetine CR 25 mg/d	173	–1.89 (0.16)	–0.28	.174	–0.69 to 0.12
HAM-D item 13 (somatic, general)					
Placebo	178	–0.54 (0.07)	…	…	…
Paroxetine CR 12.5 mg/d	161	–0.64 (0.07)	–0.11	.252	–0.29 to 0.08
Paroxetine CR 25 mg/d	173	–0.77 (0.07)	–0.24	.010	–0.42 to –0.06
CGI-S score					
Placebo	178	–1.09 (0.10)	…	…	…
Paroxetine CR 12.5 mg/d	160	–1.46 (0.10)	–0.37	.006	–0.64 to –0.11
Paroxetine CR 25 mg/d	172	–1.61 (0.10)	–0.53	< .001	–0.79 to –0.27
HAM-A total score					
Placebo	178	–5.91 (0.52)	…	…	…
Paroxetine CR 12.5 mg/d	161	–7.83 (0.54)	–1.92	.006	–3.30 to –0.55
Paroxetine CR 25 mg/d	173	–8.16 (0.52)	–2.25	.001	–3.60 to –0.90
GDS score					
Placebo	177	–2.17 (0.32)	…	…	…
Paroxetine CR 12.5 mg/d	161	–3.24 (0.34)	–1.07	.016	–1.93 to –0.20
Paroxetine CR 25 mg/d	171	–3.50 (0.33)	–1.33	.002	–2.18 to –0.48
Q-LES-Q total score					
Placebo	150	5.34 (1.40)	…	…	…
Paroxetine CR 12.5 mg/d	138	11.40 (1.42)	6.06	.001	2.38 to 9.73
Paroxetine CR 25 mg/d	145	11.49 (1.43)	6.15	< .001	2.53 to 9.76
Q-LES-Q item 15 (satisfaction with medication)					
Placebo	109	0.23 (0.113)	…	…	…
Paroxetine CR 12.5 mg/d	107	0.31 (0.115)	0.07	.615	–0.21 to 0.36
Paroxetine CR 25 mg/d	102	0.27 (0.118)	0.04	.785	–0.25 to 0.33
Q-LES-Q item 16 (overall life satisfaction)					
Placebo	150	0.29 (0.094)	…	…	…
Paroxetine CR 12.5 mg/d	138	0.60 (0.095)	0.30	.015	0.06 to 0.55
Paroxetine CR 25 mg/d	146	0.82 (0.095)	0.53	< .001	0.29 to 0.77

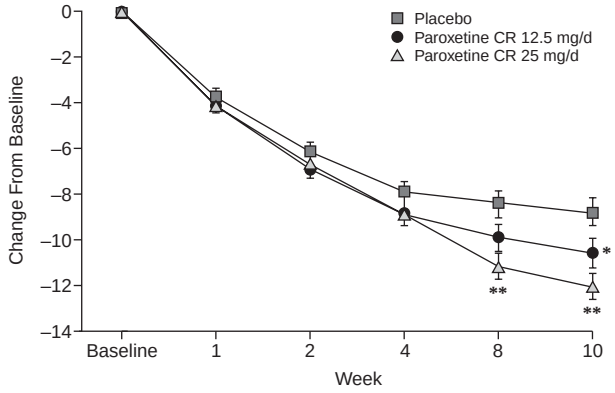
[a]Change from baseline to week 10 endpoint.
[b]Difference in adjusted least squares means (paroxetine CR minus placebo).
[c]Based on Hochberg's adjustment for multiple comparisons.
[d]Confidence intervals presented for summary.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, CR = controlled release, GDS = Geriatric Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.
Symbol: … = not applicable.

the Q-LES-Q item for overall life satisfaction than the placebo group. There were no differences between either of the paroxetine CR groups and the placebo group on the Q-LES-Q satisfaction with medication item.

Safety Results

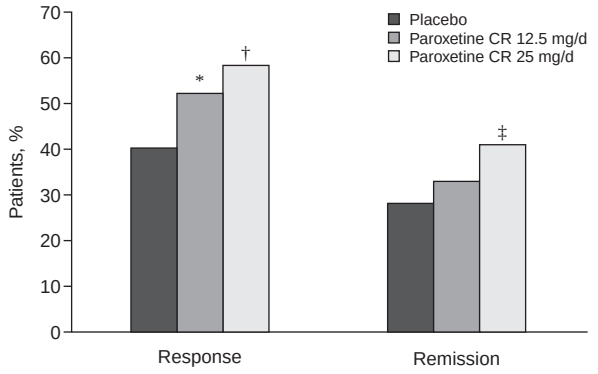
The most frequent treatment-emergent adverse events in this study (≥ 5% incidence in any treatment group) are shown in Table 3. Overall, the incidence of these events in the active groups appeared generally similar to those reported in the placebo group. However, 3 treatment-emergent adverse events—somnolence, influenza, and nasopharyngitis—frequently occurred (≥ 5% incidence in either of the paroxetine CR dosage groups and twice the rate of placebo). Treatment-emergent adverse experiences in the overall sample considered by investigators to be related or possibly related to study medication occurred in 88 of 164 patients (54%) and 102 of 173 patients (59%) for the paroxetine CR 12.5-mg and 25-mg groups, respectively, compared with 86 of 179 patients (48%) for the placebo group. There were no gender-specific adverse events reported by female patients. For men, gender-specific adverse events (including erectile and ejaculation disorders) considered related or possibly related to study

Figure 2. Mean 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 paroxetine CR 12.5-mg dose group.
**p < .001 for paroxetine CR 25-mg dose group.
Abbreviations: CR = controlled release, HAM-D = Hamilton Rating Scale for Depression.

Figure 3. Rates of Therapeutic Response (≥ 50% reduction from baseline in HAM-D total score) and Remission (HAM-D total score ≤ 7) After 10 Weeks of Treatment[a] With Paroxetine CR 12.5 mg, Paroxetine CR 25 mg, or Placebo



[a]Intent-to-treat population (last observation carried forward).
*Paroxetine CR 12.5 mg versus placebo, p = .032, OR = 1.60, 95% CI = 1.04 to 2.47.
†Paroxetine CR 25 mg versus placebo, p < .001, OR = 2.06, 95% CI = 1.35 to 3.16.
‡Paroxetine CR 25 mg versus placebo, p = .008, OR = 1.83, 95% CI = 1.17 to 2.87.
Abbreviations: CR = controlled release, HAM-D = Hamilton Rating Scale for Depression.

medication occurred in 2 of 66 patients (3%) in the paroxetine CR 12.5-mg group, 4 of 70 patients (6%) in the paroxetine CR 25-mg group, and 2 of 66 patients (3%) in the placebo group.

Overall, adverse events were generally mild or moderate in intensity, regardless of treatment group. Serious adverse events (defined as those that are life threatening or result in death, require or prolong hospitalization, cause disability, or result in a congenital anomaly or birth defect) were reported in 4% (6/164), 2% (4/173), and 1% (2/179) of patients in the paroxetine CR 12.5-mg, paroxetine CR 25-mg, and placebo treatment groups, respectively. Table 4 presents all serious adverse events. It is noteworthy that among the serious events, there were no reports of completed suicides, suicidal ideation, or suicide attempts.

The rates of patient withdrawal from the study due to adverse events were generally low and similar for all treatment groups. These rates are depicted in Figure 4. The most frequently reported adverse events leading to study withdrawal were nausea, diarrhea, dizziness, and fatigue.

During the medication taper and follow-up periods of the study, 16% (26/164) of patients taking paroxetine CR 12.5 mg and 18% (32/173) taking paroxetine CR 25 mg reported adverse events, compared with 12% (22/179) in the placebo group. The most frequently reported adverse events during the taper and follow-up periods were similar to those reported during the 10-week treatment period (i.e., dizziness, nausea, and headache). No specific adverse events occurred with a frequency of ≥ 5% in any of the treatment groups during the medication taper and follow-up periods.

At the week 10 study endpoint, the proportions of patients who exhibited no clinically significant ECG readings (paroxetine CR 12.5 mg, 96%; paroxetine CR 25 mg, 94%; placebo, 97%) were similar to the proportions of patients that presented without clinically significant ECG reading at the screening visit (paroxetine CR 12.5 mg, 94%; paroxetine CR 25 mg, 96%; placebo, 93%). Additionally, at study endpoint, there were no remarkable changes from baseline on vital signs for any of the treatment groups.

DISCUSSION

A prior study in patients with late-life depression, which utilized a flexible dosing regimen (daily dose range, 12.5 to 50 mg; actual mean daily dose of 30.4 mg), provided evidence that paroxetine CR was effective and generally well tolerated.[17] Such a study offered generally useful information about paroxetine CR as a treatment option for elderly depressed patients. However, it did not provide pertinent information about actual dose levels of paroxetine CR that may be utilized in treatment settings, particularly the lowest available daily doses (12.5 mg and 25 mg), which seem to be indicated as more conservative treatment approaches in the elderly. The main objectives of the current study were to compare the efficacy, safety, and tolerability of these lower, fixed doses of paroxetine CR with placebo for the treatment of elderly outpatient volunteers with MDD using a double-blind, placebo-controlled, parallel-group design.

Table 3. Summary of Frequent (≥ 5% in any group) Treatment-Emergent Adverse Events

	Paroxetine CR 12.5 mg (N = 164)			Paroxetine CR 25 mg (N = 173)			Placebo (N = 179)	
Treatment-Emergent Event	N	%	p Value[a]	N	%	p Value[a]	N	%
Headache	26	16	.962	31	18	.567	27	15
Diarrhea	19	12	.900	26	15	.452	21	12
Dry mouth	14	9	.425	22	13	.905	21	12
Dizziness	15	9	.523	21	12	.117	12	7
Constipation	14	9	.965	20	12	.314	14	8
Nausea	18	11	.313	18	10	.394	13	7
Fatigue	5	3	.270	15	9	.483	11	6
Somnolence[b]	8	5	.467	15	9	.032	5	3
Insomnia	14	9	.520	9	5	.879	11	6
URTI	12	7	.511	11	6	.758	9	5
Back pain	11	7	.993	5	3	.226	11	6
Influenza[b]	6	4	.100[c]	8	5	.038[c]	1	< 1
Sedation	9	5	.324	5	3	.790	5	3
Nasopharyngitis[b]	8	5	.169	4	2	.964	3	2

[a]p Values based on χ^2 test, in comparison with placebo.
[b]Commonly occurring adverse event (≥ 5% in any active group and twice the frequency of placebo).
[c]Due to low counts, χ^2 test may not be appropriate.
Abbreviations: CR = controlled release, URTI = upper respiratory tract infection.

Table 4. Summary of Serious Treatment-Emergent Adverse Events

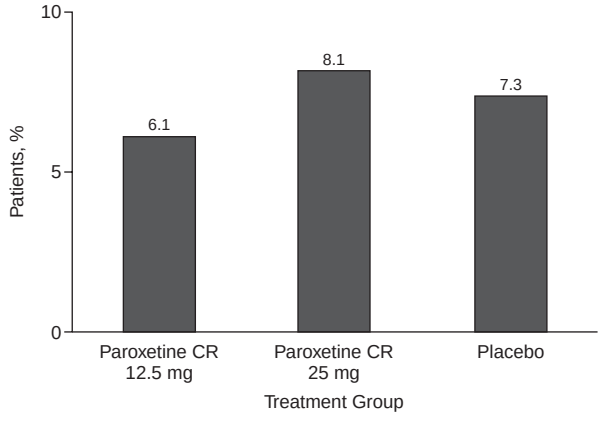
	Paroxetine CR 12.5 mg (N = 164)		Paroxetine CR 25 mg (N = 173)		Placebo (N = 179)	
Serious Adverse Event	N	%	N	%	N	%
Chest pain	2	1	0	0	0	0
Osteoarthritis	1	< 1	0	0	0	0
Ankle fracture	1	< 1	0	0	0	0
Atrial fibrillation	1	< 1	0	0	0	0
Femur fracture	1	< 1	0	0	0	0
Coronary artery occlusion	0	0	1	< 1	0	0
Pneumonia	0	0	1	< 1	0	0
Confusional state	0	0	1	< 1	0	0
Depression	0	0	1	< 1	0	0
Nephrolithiasis[a]	0	0	0	0	1	< 1
Aortic aneurysm[a]	0	0	0	0	1	< 1

[a]Events occurred in the same patient.
Abbreviation: CR = controlled release.

In both the 12.5-mg and 25-mg paroxetine CR treatment groups, the primary outcome variable (change from baseline in total HAM-D score) was statistically superior to placebo. Analysis of the observed case sample also showed statistically significant differences between each paroxetine CR dose group and placebo, which further supports the LOCF analysis. As noted in Results, both doses of paroxetine CR were also superior to placebo on most secondary efficacy variables. However, across the primary and secondary measures of efficacy, with few exceptions, improvement in the paroxetine CR 25-mg group was numerically larger than in the paroxetine CR 12.5-mg group (Table 2). This may suggest a dose-response relationship, although the study was not designed to test this hypothesis. Also, because the secondary hypotheses did not include corrections for multiplicity, the data should be interpreted with caution.

Analyses of response and remission rates suggest that a significant proportion of elderly MDD patients receiving

Figure 4. Patients Withdrawn Due to Adverse Experiences During 10 Weeks of Treatment With Paroxetine CR 12.5 mg, Paroxetine CR 25 mg, or Placebo



Abbreviation: CR = controlled release.

paroxetine CR treatment at these lower dose levels are likely to obtain a meaningful therapeutic response. These observations are particularly noteworthy, in light of a substantial placebo response in this study (e.g., as high as 40% for the response definition based on HAM-D total score reduction). Clinical remission, defined as total HAM-D score ≤ 7 at treatment endpoint, is an indication of full therapeutic response in antidepressant trials.[29] In the present study, the percentage of remitted patients in the paroxetine CR 25-mg group (41%) was significantly greater than in the placebo group (28%). By comparison, the paroxetine CR 12.5-mg group did not achieve a significant percentage of remission (31%) versus the placebo group.

The results of the key efficacy analyses in the present study are consistent with the findings from the Rapaport et al.[17] study and offer further empirical evidence of the efficacy of paroxetine CR in the treatment of patients with late-life depression. These findings are particularly relevant, given the recent failures to demonstrate efficacy of SSRIs in placebo-controlled treatment studies involving elderly patients with major depression.[30,31] The current study extends the findings from the earlier study by Rapaport et al.[17] by providing evidence that fixed lower doses of paroxetine CR, corresponding to the lowest available doses for clinical use, are effective in treating late-life depression. In addition, efficacy of paroxetine CR was demonstrated not only by clinician ratings but also by patient-reported outcomes in this study. Patients receiving both low fixed doses of paroxetine CR perceived a more substantial improvement in depressive symptoms over the course of treatment as compared to patients receiving placebo. Moreover, even during a relatively brief treatment period of just 10 weeks, patients taking paroxetine CR at low doses reported a significant improvement in overall quality of life as compared to patients taking placebo. Although these findings require replication, they are consistent with a clinically meaningful response to paroxetine CR in the elderly.

The anxiolytic properties of paroxetine CR have previously been established in studies of patients with primary anxiety disorders[32,33]; however, this is the first trial to assess the effect of paroxetine CR on the anxiety associated with MDD. Changes in HAM-A scores provide evidence that paroxetine CR in fixed doses as low as 12.5 mg decrease symptoms of anxiety in elderly patients with MDD. Some authors have suggested that treatment of both the depressive and anxious components of MDD simultaneously could result in greater adherence to treatment and overall treatment satisfaction.[34]

Paroxetine CR 12.5 mg and 25 mg daily regimens were generally well tolerated in this elderly depressed sample as evidenced by the low incidence of premature withdrawals from treatment due to adverse experiences (6% and 8%, respectively, for the paroxetine CR 12.5-mg and 25-mg groups, compared with 7% for placebo). Although retrospective comparisons with other studies should be undertaken cautiously, the rates of discontinuation due to adverse events in the present study stand in contrast with the rate observed in a prior study of depressed elderly patients treated with paroxetine IR, in which 26% of the patients withdrew due to adverse experiences while receiving a flexible regimen of 20 mg to 40 mg daily.[35] The currently observed rates of withdrawal are also numerically lower than the rate of 13% reported in elderly patients taking paroxetine CR within a higher traditional dosage range of 12.5 mg to 50 mg daily.[17] The most frequently reported adverse events that led to withdrawal in the current study were nausea, diarrhea, dizziness, and fatigue. In addition, there was a low incidence of adverse experiences overall.

The most commonly occurring adverse experiences, reported by ≥ 5% in either of the paroxetine CR groups and at least twice the proportion reported by placebo patients, were somnolence, influenza, and nasopharyngitis. Interestingly, commonly occurring adverse experiences did not include those typically reported with SSRI use[36] or observed in prior studies of MDD patients treated with paroxetine CR,[16–18] such as headache, diarrhea, dry mouth, dizziness, constipation, nausea, and adverse events related to sexual functioning. It is also important to note that earlier antidepressant trials in the elderly have found troublesome adverse events, such as anxiety, agitation, and insomnia, at rates exceeding 10%.[35,37] In contrast, with the low doses of paroxetine CR employed in the present study, the incidence of agitation and anxiety appeared to be substantially lower (≤ 1% and 3%, respectively, across treatment groups). Additional work is needed to confirm these observations. Some investigators have stated that SSRIs may worsen the occurrence of insomnia experienced by elderly patients[35]: the incidence of insomnia was 9% and 5% for 12.5 mg and 25 mg of paroxetine CR, respectively, in this study, which was similar to the rate observed in the placebo group (6%). Cardiovascular changes are always of particular concern with elderly patients. Therefore, the lack of electrocardiographic events or significant changes in blood pressure during treatment in this study is worth noting as well. There were no reports of completed suicides, suicidal ideation, or suicide attempts in this study. This is of particular interest because of the high suicide rate among older adults.[38–40]

The study had several limitations. Although patients taking most concomitant medications or those diagnosed with specific comorbid medical illnesses were not excluded from study participation, certain comorbid conditions, including hypertension, arthritis, and hyperlipidemia, occurred most frequently among these patients. Other illnesses, such as diabetes (types I and II) and cancer diagnoses, were represented in much lower numbers.

The current study did not evaluate whether specific safety issues exist in paroxetine CR–treated patients who have specific comorbid medical illnesses or in those taking particular concomitant medications. These issues could be topics of future research with more naturalistic study designs or addressed in subsequent manuscripts based on pooled analyses of safety data across studies of elderly depressed patients treated with paroxetine CR. Finally, this study did not allow for evaluation of the very old. More than two thirds of the study sample were below the age of 70 years, and only 6% were above the age of 80 years, limiting extrapolation of these data to this important segment of the general population.

The data provided by this study show that paroxetine CR at fixed doses as low as 12.5 mg/day separated from placebo-treatment in elderly depressed patients and support dosing recommendations that were previously based only on inferences from pharmacokinetic studies of paroxetine. In general, elderly individuals exhibit greater interindividual variability in their pharmacokinetic profiles than do younger individuals, and this has been specifically demonstrated with paroxetine.[41] Elderly individuals also have higher mean steady-state plasma concentrations and area under the concentration versus time curve values than younger adults at the same doses of paroxetine.[41] These factors may explain, at least in part, the efficacy observed at the 12.5 mg/day dose of paroxetine CR in the current study. With the exception of a single study[18] suggesting some efficacy with 12.5 mg/day of paroxetine CR in younger adults, doses lower than 20 mg/day of paroxetine IR have not been shown to be effective.[14]

In conclusion, this study provides evidence that a 25-mg daily dose of paroxetine CR is efficacious in the treatment of MDD in an elderly population, with rates of treatment response and remission that are significantly greater than with placebo. The study also provides evidence for the efficacy of paroxetine CR 12.5 mg/day in older depressed adults. However, the effect size with 12.5 mg/day was smaller than with 25 mg/day, and the 12.5-mg dose was not more effective than placebo in achieving remission. Both doses showed favorable safety profiles and a low likelihood of withdrawal due to adverse experiences. This study complements previously reported data on the use of paroxetine CR in late-life depression[17] and offers empirical support for another potentially useful treatment option in this growing and clinically challenging population.

Drug names: paroxetine (Paxil, Pexeva, and others), zaleplon (Sonata and others), zolpidem (Ambien and others).

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