

# Escitalopram in the Acute Treatment of Depressed Patients Aged 60 Years or Older

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**Objective:** The present study examined the efficacy and tolerability of acute escitalopram treatment in depressed patients aged 60 years or older. **Methods:** Patients aged  $\geq 60$  years with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition major depressive disorder were randomized to 12 weeks of double-blind, flexible-dose treatment with escitalopram (10–20 mg/day;  $N = 130$ ) or placebo ( $N = 134$ ). The prospectively defined primary efficacy end point was change from baseline to week 12 in Montgomery-Asberg Depression Rating Scale (MADRS) total score using the last observation carried forward approach. **Results:** A total of 109 (81%) patients in the placebo group and 96 (74%) patients in the escitalopram group completed treatment. Mean age in both groups was approximately 68 years. Mean baseline MADRS scores were 28.4 and 29.4 for the placebo and escitalopram treatment groups, respectively. Escitalopram did not achieve statistical significance compared with placebo in change from baseline on the MADRS (least square mean difference:  $-1.34$ ; last observation carried forward). Discontinuation rates resulting from adverse events were 6% for placebo and 11% for escitalopram. Treatment-emergent adverse events reported by  $>10\%$  of patients in the escitalopram group were headache, nausea, diarrhea, and dry mouth. **Conclusions:** Escitalopram treatment was not significantly different from placebo treatment on the primary efficacy measure, change from baseline to week 12 in MADRS. In patients aged 60 years or older with major depression, acute escitalopram treatment appeared to be well tolerated. (Am J Geriatr Psychiatry 2008; 16:14–20)

**Key Words:** SSRI, depression, elderly

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Major depression in elderly patients is a prevalent and serious disorder that is associated with reduced quality of life and increased morbidity and mortality.<sup>1–3</sup> In elderly outpatients (aged  $\geq 65$  years), the prevalence of depression ranges from 7%–36%,<sup>4</sup> whereas in elderly patients with medical illness or in residential settings, prevalence rates range from 9%–42%.<sup>3</sup> Pharmacotherapy in elderly patients who are depressed can be challenging because evi-

dence suggests there is significant variability in the magnitude and temporal characteristics of treatment response, which may result from the inherent heterogeneity of this patient population; this is notable in terms of the potential differential response between young-old (aged 60–74 years) and old-old (aged  $\geq 75$  years) patients.<sup>5</sup> Several studies conducted in the old-old have demonstrated difficulty in effectively treating this population.<sup>6,7</sup> In addition, safety and

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tolerability issues, including potential drug–drug interactions, are paramount because elderly patients have increasingly complex medication regimens and in general are more sensitive to potential adverse effects of treatment.<sup>8</sup>

Several placebo-controlled studies of serotonin reuptake inhibitors (SRIs) in elderly patients have demonstrated efficacy in improving symptoms of depression<sup>9,10</sup>; however, a similar number of placebo-controlled studies have failed to show separation of active treatment from placebo.<sup>7,11</sup> The failure rate for SRI trials in elderly patients is similar to that in nonelderly patients.<sup>12</sup> This is the second multicenter, randomized, double-blind, placebo-controlled trial of escitalopram in the acute treatment of a prospectively defined elderly depressed population. The first study included a total of 518 patients (1:1:1 randomization) with a mean age of 75 years. Neither escitalopram nor the active comparator (fluoxetine) was significantly different from placebo on the primary efficacy end point of change from baseline to week 8 using last observation carried forward (LOCF).<sup>13</sup> The present study examined the efficacy and tolerability of acute escitalopram treatment in patients aged 60 years or older.

## METHODS

This randomized, double-blind, placebo-controlled study evaluated the efficacy and tolerability of 10–20 mg/day escitalopram in patients aged  $\geq 60$  years diagnosed with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* major depressive disorder. Informed written consent was obtained from all study participants and the study protocol was approved by the Institutional Review Board associated with each study site. The study was conducted at 25 sites between April 10, 2003, and August 10, 2004. This study was not registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### Patient Selection

Male and female outpatients (aged  $\geq 60$  years) who met *DSM-IV* criteria for major depressive disorder with an ongoing major depressive episode of at least 4 weeks' duration were eligible to participate in the study. Psychiatric diagnosis was established using

the Mini International Neuropsychiatric Inventory, a structured diagnostic interview.<sup>14</sup> In addition, patients were required to have qualifying scores of  $\geq 24$  on the Mini-Mental State Examination and  $\geq 22$  on the Montgomery-Asberg Depression Rating Scale (MADRS) at baseline and screening visits. Normal or clinically insignificant physical examination results, laboratory test results, and electrocardiographic findings, as assessed by the investigator at the screening visit, were also required for eligibility.

Patients were ineligible to participate in the study if they currently met *DSM-IV* diagnostic criteria for bipolar disorder, schizophrenia, obsessive-compulsive disorder, mental retardation, or any cognitive or pervasive developmental disorder. Patients were also excluded from the study based on the presence of any of the following criteria: an axis I diagnosis other than major depressive disorder; personality disorder severe enough to interfere with study participation as determined by the investigator; *DSM-IV*-defined history of psychotic disorder or psychotic features; suicide risk (MADRS item 10 score,  $\geq 5$ ; suicide attempt within the past year); *DSM-IV*-defined substance abuse or dependence within the previous six months (except nicotine); or diagnosed dementia. Patients with clinically significant medical conditions (such as malignancy, hypertension, hypotension, renal disease, hepatic disease, gastrointestinal disorder, neurologic disease, endocrine disease, pulmonary disease, or cardiovascular disease) were excluded from the study unless the condition was stable for the prior year and was judged by the investigator to not interfere with the patient's ability to participate in the study. Use of a depot neuroleptic within six months of study entry was prohibited as was the use of any neuroleptic, antidepressant, or anxiolytic medication within two weeks (five weeks for fluoxetine) of first administration of double-blind study medication. Patients who had previously participated in an escitalopram investigational study, had been treated with escitalopram, or had failed to respond to citalopram or two other selective SRIs (SSRIs) were also excluded. Patients who received electroconvulsive therapy within three months of study entry or currently requiring treatment with electroconvulsive therapy were excluded from study participation. Participation in an investigational drug study within one month of study entry was prohibited as was the use of any investigational drug within one month (or five half-lives) of study initiation. Patients requiring treatment

with any psychotropic medication, except zolpidem or zaleplon as needed for sleep, were excluded.

### **Study Design**

Patients who met eligibility requirements at the screening visit entered a one-week single-blind, placebo lead-in period in which they received one placebo tablet daily. Patients who completed the lead-in phase and continued to meet eligibility requirements at the baseline visit were randomized by a computer-generated schedule to 12 weeks of double-blind treatment with either escitalopram or placebo on a 1:1 basis. For the first four weeks, double-blind treatment consisted of either a once-daily 10-mg escitalopram tablet for patients randomized to the escitalopram group or a once-daily placebo tablet for patients randomized to the placebo group. After week 4, escitalopram dosage could be titrated upward to 20 mg/day if, in the opinion of the investigator, the therapeutic response was not satisfactory. A 20-mg escitalopram tablet was dispensed so that administration could continue on a once-daily basis. If necessary, subsequent dose adjustments were permitted to attain therapeutic effect or limit adverse events. The minimum and maximum permitted escitalopram dosages were 10 mg/day and 20 mg/day, respectively.

### **Assessments**

Patients were evaluated at screening, baseline, and at the end of weeks 1, 2, 4, 6, 8, 10, and 12 of the double-blind treatment phase or on early termination from the study. The MADRS and 24-item Hamilton Depression Rating Scale (HAMD<sub>24</sub>) were assessed at screening and all subsequent visits. The Clinical Global Impressions–Severity Scale (CGI-S) was administered at baseline and all subsequent visits, while the Clinical Global Impressions–Improvement Scale (CGI-I) was administered at all visits after baseline. The Mini-Mental State Examination was performed at screening, baseline, and at the end of weeks 4, 8, and 12. Scores on the Geriatric Depression Scale, Hamilton Anxiety Scale, and Quality of Life Scale were measured at baseline and at the end of weeks 4, 8, and 12.

Safety was assessed at every study visit as well as on early study termination. Specific evaluations were performed on the following schedule: physical examination at screening and at the end of week 12; vital

signs at every visit; 12-lead electrocardiography at screening, beginning, and end of baseline visit and at the end of weeks 4 and 12; laboratory tests were performed at screening and at the end of week 12 with the exception of a urine drug test and thyroid function test, which were only conducted at screening. Adverse events (AEs) reported by patients and/or observed by study personnel and use of concomitant medications were documented at each visit. A treatment-emergent AE was defined as an AE that was either not present at or before baseline or had increased in severity during the double-blind treatment period. A serious adverse event (SAE) was one that resulted in death, was an immediate threat to life, required hospitalization, resulted in significant disability/incapacity, or was a congenital abnormality or birth defect. In addition, other important medical events were considered SAEs if, based on appropriate medical judgment, they were considered to have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed above.

### **Statistical Analysis**

All patients who received at least one dose of double-blind study medication were included in the safety population. The intention-to-treat (ITT) population included patients in the safety population with at least one postbaseline assessment of MADRS. The prospectively defined primary efficacy end point in this study was mean change in MADRS total score from baseline to week 12. Secondary efficacy parameters included change from baseline to week 12 in HAMD<sub>24</sub> and CGI-S score and CGI-I score at week 12. Efficacy analyses were performed using the LOCF approach on the intention-to-treat population.

Imbalance between the two treatment groups at baseline was tested using a two-way analysis of variance model with treatment group and study center as factors for continuous variables. The Cochran-Mantel-Haenszel test, controlling for study center, was used for categorical variables. Analysis of the proportion of patients prematurely discontinuing from the study in each treatment group was performed using Fisher's exact test. Comparison of escitalopram and placebo on the primary efficacy variable was performed using an analysis of covariance (ANCOVA) model with treatment group and study

center as factors and baseline score as the covariate. Post hoc analysis was performed using the mixed-effects model for repeated measures (MMRM) methodology with study center, treatment group, visit, and treatment group-by-visit interaction as factors and baseline score as the covariate; an unstructured covariance matrix was used for the repeated measures across visits. Secondary efficacy variables were analyzed using the same ANCOVA model as for the primary efficacy variable. For CGI-I, the baseline CGI-S score was used as the covariate. A logistic regression with treatment group, center, and baseline value as explanatory variables was used to compare percentages of MADRS responders (defined as a  $\geq 50\%$  improvement from baseline to end point). Remission, analyzed post hoc, was defined as a MADRS score  $\leq 10$ . All statistical tests were two-sided with a 5% significance level for main effects.

Safety analyses were performed on the safety population and included incidence of treatment-emergent AEs and study discontinuation resulting from

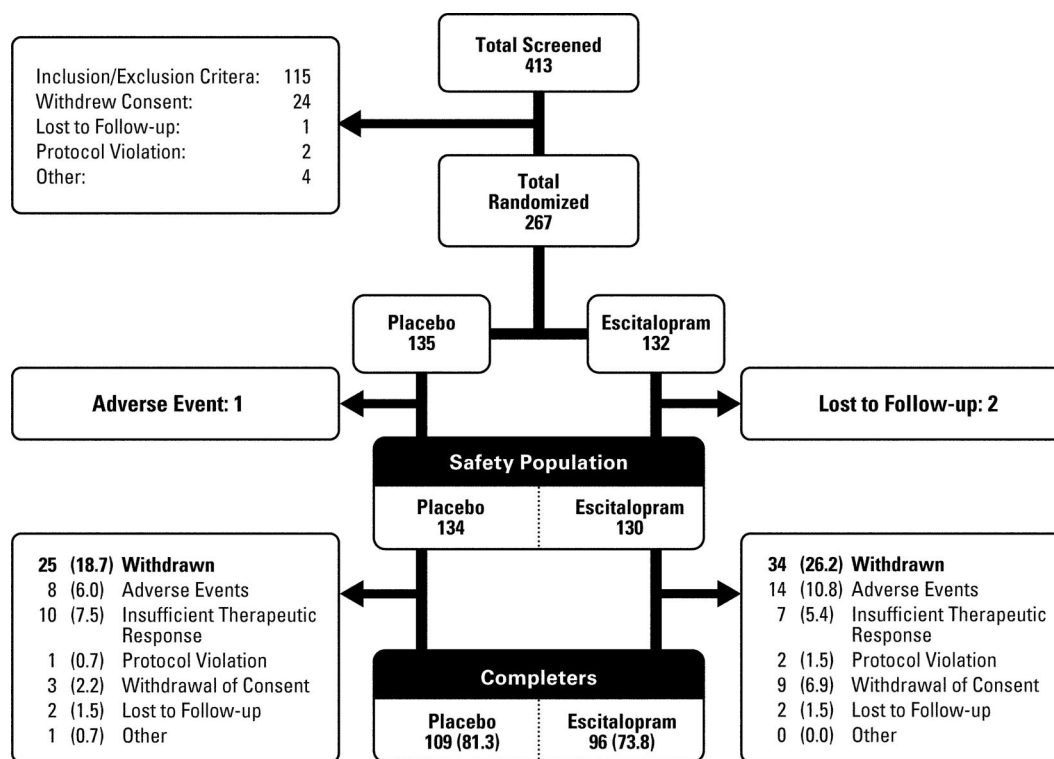
AEs. Other safety variables included analyses of the number of patients with clinically significant post-baseline values for laboratory tests, vital signs, and electrocardiographic parameters.

## RESULTS

A total of 267 patients were randomized to double-blind treatment; 264 patients were included in the safety population (134 placebo, 130 escitalopram; Figure 1). The ITT population consisted of 263 patients: 134 in the placebo group and 129 in the escitalopram group. A total of 109 (81%) placebo-treated patients and 96 (74%) escitalopram-treated patients completed the study. Discontinuations due to AEs occurred in eight (6%) placebo-treated patients and 14 (11%) escitalopram-treated patients ( $p=0.185$ ; Fisher's exact test).

There were no imbalances between the two treatment groups in demographics or patient characteris-

**FIGURE 1. Reasons for Discontinuation (safety population)**



**TABLE 1. Demographics and Baseline Patient Characteristics (intention-to-treat [ITT] population)**

	Placebo (n = 134)	Escitalopram (n = 129)
Age (years), mean ± SD	68.5 ± 7.1	68.1 ± 6.7
Young-old: age <75 years, n (%)	101 (75)	105 (81)
Old-old: age ≥75 years, n (%)	33 (25)	24 (19)
Women, n (%)	80 (60)	76 (59)
White, n (%)	117 (87)	118 (92)
MADRS total score, mean ± SD	28.4 ± 3.6	29.4 ± 4.1

Two-way analysis of variance with treatment group and study center as factors for continuous variables; Cochran-Mantel-Haenszel test controlling for study center for categorical variables.

SD: standard deviation; MADRS: Montgomery-Asberg Depression Rating Scale.

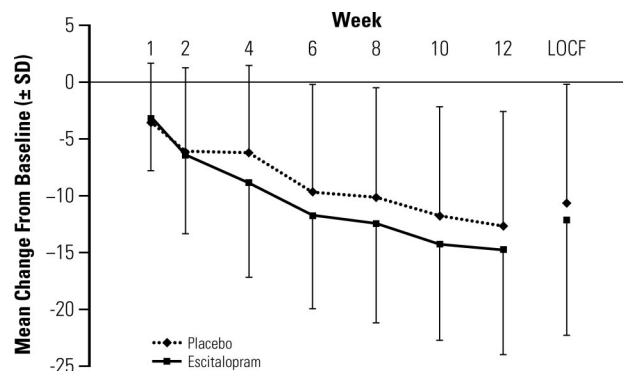
tics at baseline (Table 1). The mean baseline MADRS scores were 29.4 for the escitalopram group and 28.4 for the placebo group, indicative of a patient population with moderate-to-severe depressive symptomatology.

The overall mean daily dose was 1.5 tablets/day for the placebo group and 1.4 tablets/day (14 mg) for the escitalopram group. By the end of week 6, dose had been increased in approximately 80% of the placebo-treated patients and 60% of the escitalopram-treated patients.

### Efficacy

On the primary efficacy end point, mean change from baseline to week 12 in MADRS total score, escitalopram was not significantly different from placebo (least square mean difference, -1.34; 95% confidence interval, -3.84 to 1.15;  $t = 1.09$ ,  $df = 237$ ,  $p = 0.29$ ; LOCF) (Figure 2). Post hoc analysis based on the MMRM approach yielded an adjusted mean difference of -2.17 (95% confidence interval, -4.62 to 0.28) but failed to achieve statistical significance ( $t = 1.77$ ,  $df = 237$ ,  $p = 0.08$ ). The analyses of secondary outcomes demonstrated similar results (Table 2). There was no significant difference between escitalopram and placebo in rates of response or remission. The percentage of MADRS responders ( $\geq 50\%$  improvement) at week 12 (LOCF) in the escitalopram and placebo groups were 46% and 38%, respectively; remission rates (MADRS  $\leq 10$ ) at week 12 (LOCF) for escitalopram and placebo were 34% and 29%, respectively.

**FIGURE 2. Primary Efficacy End Point: Change From Baseline in Montgomery-Asberg Depression Rating Scale Scores (observed cases [OC] by week and last observation carried forward at end point, intention-to-treat [ITT] population)\***



\*ANCOVA with treatment group and study center as factors, and baseline score as covariate; SD, standard deviation

### Tolerability

Treatment-emergent adverse events occurring with an incidence of 10% or greater in either treatment group are presented in Table 3. The common treatment-emergent AEs in escitalopram-treated patients were headache, nausea, diarrhea, and dry mouth. Eight SAEs were reported in seven patients, one of which (syncope) occurred after the patient withdrew

**TABLE 2. Secondary Efficacy Parameters (intention-to-treat [ITT] population)**

Parameter	Time Point	Placebo (n = 134)	Escitalopram (n = 129)
		Mean ± SD	Mean ± SD
HAMD <sub>24</sub>	Baseline	24.3 ± 5.0	24.9 ± 5.5
	Change at week 12	-9.2 ± 9.1	-9.8 ± 9.3
HAMD <sub>17</sub>	Baseline	19.6 ± 3.9	20.3 ± 4.3
	Change at week 12	-7.1 ± 7.4	-7.5 ± 7.5
CGI-S	Baseline	4.2 ± 0.5	4.3 ± 0.5
	Change at week 12	-1.1 ± 1.3	-1.3 ± 1.3
CGI-I	Score at week 12	2.7 ± 1.2	2.6 ± 1.3

Analysis of covariance with treatment group and study center as factors and baseline score as covariate; for CGI-I, the baseline CGI-S score was used as covariate.

SD: standard deviation; HAMD<sub>24</sub> and HAMD<sub>17</sub>: Hamilton Depression Scale (24- and 17-item); CGI-S: Clinical Global Impressions-Severity Scale; CGI-I: Clinical Global Impressions-Improvement Scale.

**TABLE 3. Most Frequent Treatment-Emergent Adverse Events ( $\geq 10\%$  of patients in either treatment group; safety population)**

TEAE	Placebo (%; n = 134)	Escitalopram (%; n = 130)
Headache	9.7	19.2
Nausea	6.0	15.4
Diarrhea	3.7	14.6
Dry mouth	5.2	10.8
Insomnia	12.7	7.7
Upper respiratory tract infection	10.4	7.7

TEAE: treatment-emergent adverse events.

from the placebo lead-in period; the patient was not randomized and did not receive double-blind study medication. The SAEs in the remaining six patients included one placebo-treated patient with syncope and five escitalopram-treated patients with bowel obstruction, nausea, arrhythmia and respiratory arrest, retinal detachment, and chest pain. Two patients (one escitalopram-treated and one placebo-treated) were prematurely discontinued because of the SAEs (syncope and bowel obstruction). None of the SAEs were considered related to study medication by the investigator.

## DISCUSSION

In the present study, escitalopram treatment was not significantly different from placebo treatment in depressed patients aged 60 years and older on the primary efficacy end point of change from baseline at week 12 in MADRS score using the LOCF approach or the post hoc analysis using the MMRM approach.

Studies with other SRIs have reported acute antidepressant efficacy in elderly patients. In a pair of studies of 10 and 12 weeks' duration in patients aged 60 years or older, paroxetine controlled-release dosed from 12.5–50 mg/day was superior to placebo in change from baseline to end point on the HAMD<sub>17</sub> and on measures of response and remission.<sup>9,15</sup> A large placebo-controlled trial of 50–200 mg/day sertraline in depressed patients (N = 752) aged 60 years or older also reported a statistically significant drug effect after 8 weeks of treatment, although the drug-placebo difference at end point was relatively small

(HAMD<sub>17</sub> adjusted mean difference at end point: 1.5).<sup>10</sup> Finally, a pooled analysis of duloxetine (60 mg/day) treatment in older patients who were depressed reported significantly greater improvement than placebo on the HAMD<sub>17</sub> total score at end point (difference in mean change:  $-2.54$ ,  $p = 0.015$ ; MMRM).<sup>16</sup> However, it is notable that this was in a population of young-old patients defined as 55 years of age or older with a mean age of 63.3 years. In contrast to the results of the acute treatment trials in elderly patients, escitalopram continuation treatment in patients aged 65 years and older has demonstrated superior efficacy relative to placebo in relapse prevention of major depression.<sup>17</sup>

Conversely, a number of studies in elderly patients who were depressed have failed to differentiate between active treatment and placebo. Fluoxetine at a fixed dose of 20 mg/day in a pooled analysis of a pair of six-week studies produced greater response and remission versus placebo in patients aged greater than 60 years who were depressed (N = 671),<sup>18</sup> but there was no difference between fluoxetine and placebo in change from baseline to end point in HAMD<sub>17</sub> score ( $-8.1$  versus  $-6.4$ , respectively,  $p = 0.06$ ). Moreover, in one of the two studies from this pooled report, fluoxetine failed to separate from placebo on the primary efficacy parameter of HAMD response rate at end point (fluoxetine, 64%; placebo, 49%;  $p = 0.079$ ).<sup>19</sup> In a comparison of 75–225 mg/day venlafaxine and 20–60 mg/day fluoxetine versus placebo in elderly patients who were depressed (N = 300), neither active treatment was significantly different from placebo at end point on change in HAMD<sub>21</sub> scores, response, or remission rates.<sup>11</sup>

Interpretation of the results of this study is limited by several factors, including exclusion of patients with comorbid primary psychiatric diagnoses as well as exclusion of patients with clinically significant medical conditions judged to be severe or possibly unstable. The current exclusion criteria are typically used by most antidepressant trials, which make these results comparable to the existing literature. In addition, this study included outpatients and thus did not address treatment of elderly depressed patients in nursing homes or other long-term care facilities.

In conclusion, escitalopram treatment did not separate from placebo treatment in this acute study of patients aged 60 years or older. Treatment with

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10–20 mg/day escitalopram appeared to be well tolerated.

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