# Escitalopram Maintenance Treatment for Prevention of Recurrent Depression: A Randomized, Placebo-Controlled Trial

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***Background:*** Major depressive disorder is a recurrent illness that often requires maintenance antidepressant treatment. Escitalopram is a selective serotonin reuptake inhibitor (SSRI) that has shown efficacy in both acute and continuation treatment of major depressive disorder. The current trial examined the efficacy of maintenance escitalopram treatment in preventing depression recurrence in patients who responded to acute SSRI therapy.

***Method:*** Patients with recurrent DSM-IV–defined major depressive disorder (≥ 2 previous episodes; baseline Montgomery-Asberg Depression Rating Scale [MADRS] score ≥ 22) who had responded (MADRS score ≤ 12) to acute open-label treatment (8 weeks) with 1 of 4 SSRIs (fluoxetine, sertraline, paroxetine, or citalopram) received open-label, flexible-dose continuation treatment (16 weeks) with escitalopram (10–20 mg/day). At the end of continuation treatment, patients maintaining response criteria were randomly assigned to 52 weeks of double-blind, fixed-dose maintenance treatment with escitalopram (10 or 20 mg/day) or placebo. Recurrence was defined as a MADRS score ≥ 22 or insufficient therapeutic response during the double-blind phase. The study was conducted between October 16, 2000, and February 4, 2003.

***Results:*** A total of 234 patients who responded to acute open-label treatment with 1 of 4 SSRIs received at least 1 dose of open-label escitalopram continuation treatment. Of 164 patients who completed escitalopram continuation treatment, 139 were randomly assigned to double-blind maintenance treatment with escitalopram (N = 73) or placebo (N = 66). Mean baseline MADRS scores at the start of the maintenance phase were < 5 for both the placebo- and escitalopram-treatment groups. Time to recurrence was significantly longer in patients who received maintenance treatment with escitalopram compared with patients switched to placebo (hazard ratio = 0.26, 95% CI = 0.13 to 0.52, p < .001). Long-term escitalopram treatment was well tolerated.

***Conclusion:*** Maintenance treatment with escitalopram was well tolerated and significantly reduced the risk for recurrence of depression. Patients with few residual symptoms following continuation treatment with escitalopram experienced a high rate of depression recurrence when switched to placebo, demonstrating the need for maintenance therapy of recurrent major depressive disorder beyond 4 to 6 months of initial symptom resolution even if few residual symptoms are present.

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Major depressive disorder (MDD) is a highly recurrent condition and, for many, a potentially lifelong illness.[1,2] The National Institute of Mental Health Collaborative Program on Psychobiology of Depression, in a prospective, naturalistic, longitudinal investigation, found that after resolution of an index episode of unipolar depression, the cumulative probability of recurrence was approximately 30% at 6 months and nearly 40% at 12 months of follow-up.[3] A subsequent report from the National Institute of Mental Health Consensus Development Panel on Recurrent Mood Disorders indicated the need for long-term maintenance treatment planning, thus reinforcing evidence in support of the chronic and recurrent nature of mood disorders.[4] More recently, a 15-year follow-up of patients in the United States who had recov-

ered from a major depressive episode yielded a cumulative recurrence rate of 85%.[5] In patients who remained well for at least 5 years, the cumulative recurrence rate was 58%. However, reported rates of antidepressant treatment were low both for the index episode and during the well interval in this naturalistic setting, thus highlighting the need for adequate diagnosis and care.

The risk of depression recurrence is known to increase with the number of prior episodes and the duration of those episodes.[3,6,7] A more significant risk factor for depression recurrence is the presence of residual symptoms following the resolution of a depressive episode.[8,9] Therefore, the management of depression involves 2 primary challenges—to provide treatment that brings the patient to the well state and then to maintain the well state with long-term treatment. A number of antidepressant agents have demonstrated the prophylactic efficacy of maintenance therapy in studies of patients with recurrent depression, including tricyclics,[10] such as imipramine[11,12] and nortriptyline[13]; fluoxetine[14,15]; fluvoxamine[16]; paroxetine[17,18]; sertraline[19,20]; citalopram[21]; and venlafaxine.[22] Escitalopram, a single-isomer selective serotonin reuptake inhibitor (SSRI) antidepressant, was demonstrated to be an effective and well-tolerated treatment for major depression in several acute (8-week), placebo-controlled trials.[23–25] Continuation treatment with escitalopram has been shown to effectively prevent relapse of major depressive episodes.[26] In that trial, the effect of escitalopram in relapse prevention was independent of whether patients had initially responded to acute treatment with placebo, citalopram, or escitalopram.

The current trial examined the efficacy of maintenance treatment with escitalopram in preventing depression recurrence in patients who previously responded to treatment with another SSRI antidepressant. It was hypothesized that patients who received maintenance treatment with escitalopram would have a significantly longer time to depression recurrence and would be less likely to experience recurrence relative to patients in the placebo group. Notably, the study design utilized is unique for a recurrence trial in that the prophylactic effect of escitalopram maintenance treatment was examined in patients who had responded to treatment with another SSRI antidepressant and maintained that response when switched to escitalopram for continuation treatment. It is more typical of depression recurrence trials to select only patients who are responsive to the study medication in the acute phase for random assignment to the maintenance phase. However, it has been suggested that this type of study design introduces a selection bias that may limit the extrapolation of recurrence prevention results beyond the study population.[20] To examine the actual prophylactic efficacy of a medication in long-term maintenance, the study should include patients who were responders to other treatments in the acute phase.

## METHOD

The current trial was conducted in 3 parts: (1) an acute open-label phase followed by (2) an open-label continuation phase and, finally, (3) a randomized, double-blind, placebo-controlled maintenance phase. The study was conducted at 28 centers in the United States between October 16, 2000, and February 4, 2003. The study protocol was approved by the institutional review boards of all participating centers, and all subjects provided written informed consent.

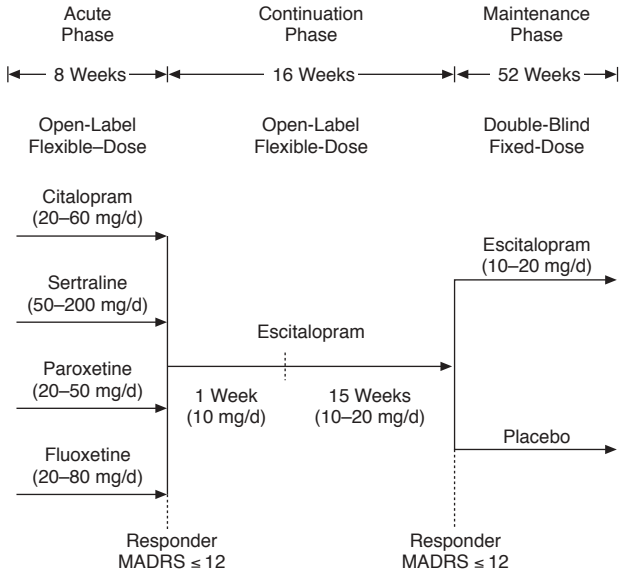
Patients entered the continuation phase of the trial following completion of 1 of 3 treatment paths originating from a single acute phase. The present report focuses only on patients from the primary treatment path, who were characterized as SSRI responders in the acute phase and directly entered the continuation phase. The other 2 treatment paths included patients who were nonresponders or did not tolerate initial SSRI therapy in the acute phase. Patients from the latter 2 treatment paths could qualify for the continuation phase by subsequently responding to and tolerating open-label escitalopram treatment; however, these patients were not included in the current analyses because the mixed treatment histories of the 3 paths would complicate interpretation of depression recurrence. The overall study results are available in the Forest Laboratories Clinical Trial Registry.[27]

### Patient Population

Subjects (male or female, aged 18–81 years) entering the acute phase met DSM-IV criteria for a current major depressive episode of at least 4 weeks' duration and had experienced at least 2 major depressive episodes before the index episode, with 1 of the episodes resolving within the previous 5 years. A Montgomery-Asberg Depression Rating Scale (MADRS)[28] total score ≥ 22 and a minimum score of 2 on item 1 of the Hamilton Rating Scale for Depression (HAM-D)[29] were also required both at screening and at baseline. Enrolled patients had normal or clinically insignificant findings on physical examination, laboratory tests, and 12-lead electrocardiogram at the screening visit.

Patients were excluded from the acute phase if they met DSM-IV criteria for bipolar disorder, schizophrenia or any psychotic disorder, obsessive-compulsive disorder, mental retardation, or any pervasive developmental or cognitive disorder. Patients were also excluded if they had a diagnosis of any Axis I disorder other than MDD (including dysthymic disorder), had a history of any psychotic disorder, exhibited any psychotic features, had a significant personality disorder, or had a history of substance abuse or dependence (other than nicotine) in the previous 6 months per DSM-IV criteria. In addition, patients were ineligible to enroll if they presented a suicide risk, had a score of at least 5 on MADRS item 10 (suicidality), or required concomitant psychotropic medication (other than zolpidem for

Figure 1. Study Design




Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

sleep). Women of childbearing potential were excluded if pregnant or nursing and were required to practice a reliable method of birth control.

### Study Design

In the acute phase, patients were randomly assigned to receive up to 8 weeks of open-label, flexible-dose treatment with citalopram (20–60 mg/day), fluoxetine (20–80 mg/day), paroxetine (20–50 mg/day), or sertraline (50–200 mg/day) (Figure 1).[30] Responders (MADRS score ≤ 12) to acute treatment with 1 of the SSRIs were eligible to directly enter the continuation phase of the trial.

In the continuation phase, patients who had responded to acute SSRI treatment received 16 weeks of open-label, flexible-dose escitalopram treatment initiated at a dosage of 10 mg/day, with the first dose administered within 72 hours of completing open-label treatment in the acute phase. Starting at the end of week 1, the dosage could be increased to 20 mg/day, based on the judgment of the investigator. At the end of the continuation phase, patients who continued to meet response criteria (MADRS score ≤ 12) were eligible to enter the 52-week, randomized, double-blind, placebo-controlled, parallel, fixed-dose maintenance phase. Patients who did not meet response criteria at the end of the continuation phase were classified as ineligible to continue and discontinued from the study.

Patients eligible to enter the maintenance phase were randomly assigned on a 1:1 ratio to double-blind treatment with either placebo or escitalopram. During the maintenance phase, patients were instructed to continue taking the same number of tablets daily that was administered at the end of continuation treatment. No dosage adjustments were permitted during the maintenance phase. Depression recurrence was defined as a MADRS score ≥ 22 or withdrawal from the study due to insufficient treatment response based on the judgment of the principal investigator. Patients meeting recurrence criteria at any visit during the maintenance phase were withdrawn from the study.

Study visits were conducted at the end of weeks 1, 2, 4, and 8 and every 4 weeks thereafter during the continuation phase and at the end of weeks 18 and 20 and every 4 weeks thereafter during the maintenance phase. Efficacy assessments at each study visit included the MADRS, the 24-item version of the HAM-D, and the Clinical Global Impressions-Improvement (CGI-I) and -Severity of Illness (CGI-S) scales.[31] Safety measures obtained at every study visit included vital signs and spontaneous adverse event monitoring. An adverse event occurring during the treatment period of each respective phase of the study was determined to be a treatment-emergent adverse event (TEAE) if it was not present at baseline of the phase or if it was present and increased in severity during the treatment period.

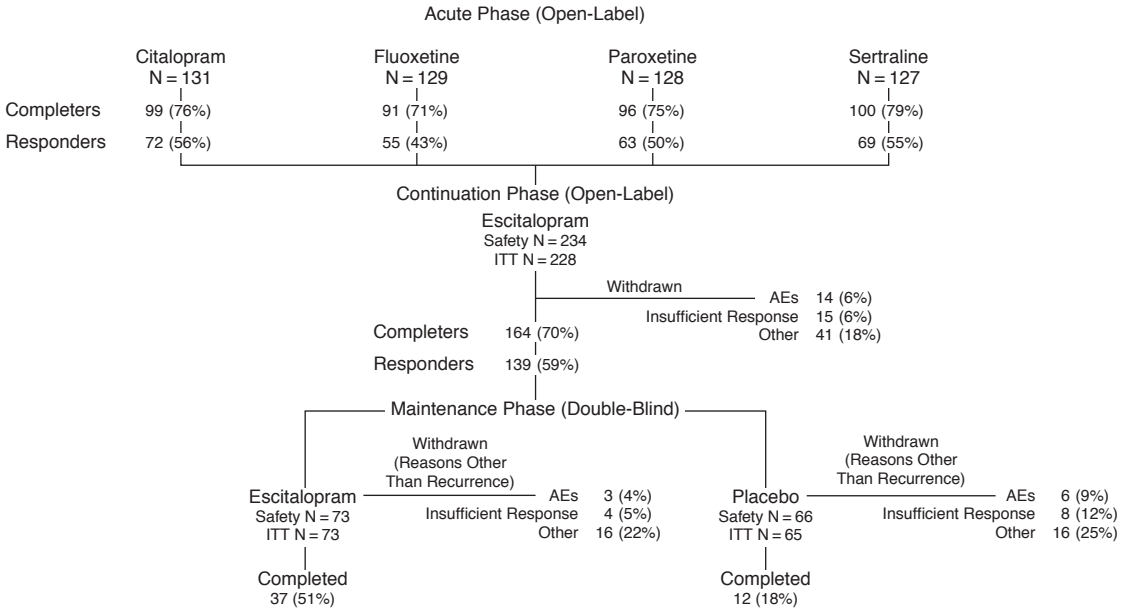
A serious adverse event (SAE) was one that resulted in death, was an immediate threat to life, required hospitalization, resulted in significant disability/incapacity, or was a congenital abnormality or birth defect. In addition, other important medical events were considered SAEs if, based upon appropriate 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.

Physical examinations and laboratory tests were performed at the baseline visit and at endpoint; laboratory evaluations were also performed at week 12 of the continuation phase. Electrocardiograms were performed at the end of 12 weeks of continuation treatment and at endpoint. All end of study safety and efficacy assessments were performed upon premature discontinuation.

### Statistical Methods

The safety population included all patients who received at least 1 dose of study medication in the continuation or maintenance phase. The intent-to-treat (ITT) population included all patients in the safety population who had at least 1 post-baseline MADRS assessment in the continuation phase or 1 post-randomization assessment in the maintenance phase. Baseline for the continuation phase was defined as the last assessment in the acute phase. Likewise, baseline for the maintenance phase was defined as the last assessment in the continuation phase. For the maintenance phase, a 2-way analysis of variance model with treatment and study center as factors was used

Figure 2. Patient Disposition (safety population)[a]




[a]Percentages are relative to the safety population.
Abbreviations: AEs = adverse events, ITT = intent to treat.

Table 1. Patient Demographics (safety population)

| Characteristic | Open-Label Continuation Phase, Escitalopram (N = 234) | Double-Blind Maintenance Phase | |
|---|---|---|---|
| | | Escitalopram (N = 73) | Placebo (N = 66) |
| Age, mean ± SD, y | 40.5 ± 11.6 | 42.0 ± 11.3 | 43.7 ± 12.4 |
| Female, N (%) | 175 (74.8) | 58 (79.5) | 52 (78.8) |
| White, N (%) | 196 (83.8) | 64 (87.7) | 57 (86.4) |
| Baseline MADRS score, mean ± SD | 6.6 ± 3.4 | 4.7 ± 4.0 | 4.9 ± 3.6 |
| No. of previous major depressive episodes, mean ± SD | 4.8 ± 3.9 | 4.7 ± 3.1 | 5.8 ± 6.0 |

Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

to test comparability of continuous variables between treatment groups at baseline; Cochran-Mantel-Haenszel tests were used for categorical variables.

The primary efficacy parameter was time to recurrence from the start of double-blind maintenance treatment. Equality of recurrence hazard for patients in the escitalopram- and placebo-treatment groups was tested using a Cox regression model with treatment group and baseline MADRS score as explanatory variables. Kaplan-Meier survival curves were estimated. Comparisons between double-blind escitalopram and placebo treatment with respect to efficacy parameters (change from baseline to endpoint) and safety parameters (treatment versus placebo) were performed using an additive analysis of covariance model with treatment group and center as factors and the baseline score as a covariate. For CGI-I, the baseline CGI-S score was used.

## RESULTS

### Patient Characteristics

A total of 515 patients with a mean MADRS score of 30.4 before initiation of treatment were enrolled in the acute open-label phase; 386 patients (75%) completed the acute phase, and 259 (50%) were treatment responders. A total of 234 patients who responded to open-label SSRI treatment in the acute phase received at least 1 dose of open-label escitalopram treatment in the continuation phase (Figure 2). From this total, 164 patients (70%) completed the continuation phase and 139 patients received at least 1 dose of double-blind study medication in the maintenance phase; 73 and 66 patients were randomly assigned to the escitalopram and placebo groups, respectively. These patients were included in the maintenance phase safety analyses. The maintenance phase ITT population consisted of 73 patients in the escitalopram treatment group and 65 in the placebo group. The 52-week maintenance phase was completed by a total of 49 patients (35%), 37 (51%) from the escitalopram treatment group and 12 (18%) from the placebo group.

There were no statistically or clinically significant differences in the demographic parameters of the 2 double-blind treatment groups (Table 1). The overall mean dose of escitalopram during the open-label con-

Table 2. Additional Efficacy Parameters: Open-Label Continuation Phase and Double-Blind Maintenance Phase (ITT population, OC)

| Efficacy Parameter | Open-Label Continuation Phase, Escitalopram (N = 228), Mean ± SD | Double-Blind Maintenance Phase | |
|---|---|---|---|
| | | Escitalopram (N = 73), Mean ± SD | Placebo (N = 65), Mean ± SD |
| MADRS | | | |
| Baseline | 6.6 ± 3.4 | 4.7 ± 4.0 | 4.9 ± 3.6 |
| Change at endpoint | –0.3 ± 0.49 | 0.1 ± 5.8 | –0.3 ± 3.0 |
| HAM-D | | | |
| Baseline | 7.2 ± 4.1 | 5.2 ± 4.0 | 5.2 ± 3.8 |
| Change at endpoint | –0.3 ± 0.48 | –0.5 ± 5.9 | –0.2 ± 3.6 |
| CGI-I | | | |
| Baseline | 1.4 ± 0.5 | 1.2 ± 0.5 | 1.2 ± 0.4 |
| Change at endpoint | 0.0 ± 0.8 | 0.0 ± 0.6 | –0.1 ± 0.3 |
| CGI-S | | | |
| Baseline | 1.9 ± 0.7 | 1.5 ± 0.6 | 1.6 ± 0.7 |
| Change at endpoint | 0.1 ± 1.2 | 0.0 ± 0.9 | 0.1 ± 0.3 |

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, ITT = intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale, OC = observed cases.

tinuation phase was 15.8 mg/day. In the double-blind maintenance phase, the overall mean dose for the escitalopram treatment group was 15.5 mg/day; the overall final escitalopram dose was 15.2 mg/day.

### Prevention of Depression Recurrence

The mean ± SD MADRS score was 6.6 ± 3.4 for all patients before the start of the continuation phase. At the start of the maintenance phase, the mean MADRS score was 4.9 ± 3.6 for patients randomly assigned to the placebo group and 4.7 ± 4.0 for patients randomly assigned to receive treatment with escitalopram. Baseline score and mean change from baseline at endpoint for MADRS and additional efficacy measures (HAM-D, CGI-I, and CGI-S) during the continuation and maintenance phases are presented in Table 2.

Time to recurrence was significantly longer for escitalopram-treated patients, mean ± SD of 252 ± 134 days and median of 357 days, compared with those patients receiving placebo treatment, mean ± SD of 130 ± 135 days and median of 58 days (hazard ratio [HR] = 0.26, 95% confidence interval [CI] = 0.13 to 0.52, $p < .001$) (Table 3). Furthermore, cumulative rates of recurrence were lower for escitalopram-treated patients compared with patients receiving placebo treatment (27% and 65%, respectively). The Kaplan-Meier curves for time to recurrence are presented in Figure 3. In addition, analyses were conducted after censoring all recurrence events occurring within 14 days of the start of double-blind treatment. The results remained statistically significant (HR = 0.29, $p < .001$) in favor of escitalopram treatment.

### Safety

Continuation and maintenance treatment with escitalopram was safe and well tolerated. In the continuation phase, the discontinuation rate due to adverse events (AEs) was 6% for patients receiving open-label escitalopram treatment. During the maintenance phase, the discontinuation rate due to AEs was 9% for patients switched to placebo and 4% for escitalopram-treated patients (Figure 2). The only TEAEs that occurred in at least 10% of patients receiving open-label escitalopram continuation treatment were headache and fatigue. During the double-blind maintenance phase, dizziness, influenza-like symptoms, upper respiratory tract infection, inflicted injury, rhinitis, and headache were reported by at least 10% of patients in either treatment group (Table 4).

During the first 14 days of maintenance treatment, which corresponds with the censoring period used in analyzing prevention of depression recurrence, the incidence of TEAEs was 41% in placebo-treated patients, compared with 21% in patients receiving escitalopram. Rates of individual TEAEs (overall incidence ≥ 10% during the maintenance phase) reported in the placebo and escitalopram treatment groups within the first 14 days of maintenance treatment are presented in Table 5. The incidence of dizziness, a common TEAE associated with acute SSRI discontinuation, was specifically examined during the first 14 days of maintenance treatment. In the placebo group, which was switched from open-label escitalopram treatment, 12 (18%) of 66 patients reported dizziness during the first 14 days of maintenance treatment. Notably, the majority of these patients (8 patients, 12% overall) were receiving an escitalopram dosage of 20 mg/day and were switched to placebo without down-taper. Following the first 14 days of maintenance treatment, the incidence of dizziness in the placebo group was approximately 2%. In the escitalopram group, no patients experienced dizziness during the first 14 days of maintenance treatment, whereas the incidence during the remainder of the double-blind phase was 3%.

No SAEs were reported during the continuation phase. A total of 4 SAEs were reported in 3 patients during the maintenance phase (1 placebo-treated patient—suicide attempt; 2 escitalopram-treated patients—1 hypotension, and 1 bladder and uterovaginal prolapse). However, no SAEs were classified as related to study medication by the investigator.

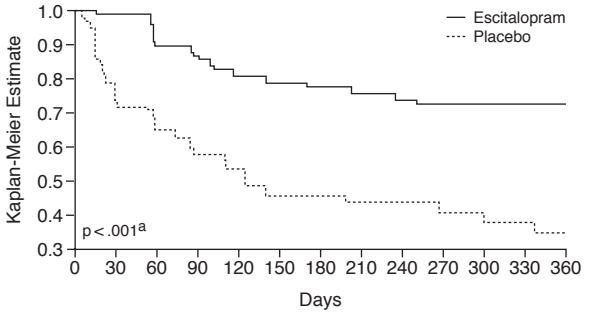
The suicide attempt occurred in a patient randomly assigned to placebo treatment during the maintenance phase and was categorized as possibly related to study medication by the investigator. The patient was a 56-year-old man with a history of suicide attempt who received open-label citalopram for 56 days in the acute phase, escitalopram for 16 weeks during the continuation phase, and double-blind placebo maintenance treatment for 44 weeks before withdrawal from the study (lost to follow-up).

**Table 3. Cumulative Rate of Depression Recurrence (ITT population)**

| Cumulative Recurrence Rate | Escitalopram (N = 73) | Placebo (N = 65) | Hazard Ratio | 95% CI | p Value |
|---|---|---|---|---|---|
| No censoring | 27% | 65% | 0.26 | 0.13 to 0.52 | < .001 |
| Censoring all recurrences within 14 days of double-blind treatment | 27% | 62% | 0.29 | 0.14 to 0.59 | < .001 |

Abbreviation: ITT = intent to treat.

**Figure 3. Survival Analysis: Time to Depression Recurrence During Double-Blind Maintenance Phase**




[a]Time to recurrence was significantly longer in patients who received maintenance treatment with escitalopram (hazard ratio = 0.26, 95% CI = 0.13 to 0.52, p < .001; intent-to-treat population). p Value is from Cox regression model.

**Table 4. Incidence of Patients With Most Frequent Treatment-Emergent Adverse Events During Double-Blind Maintenance Treatment (safety population), %[a]**

| Treatment-Emergent Adverse Event | Escitalopram (N = 73) | Placebo (N = 66) | p Value |
|---|---|---|---|
| Dizziness | 3 | 20 | .002 |
| Influenza-like symptoms | 16 | 2 | .003 |
| Upper respiratory tract infection | 16 | 12 | .629 |
| Inflicted injury | 12 | 5 | .135 |
| Rhinitis | 11 | 9 | .783 |
| Headache | 11 | 6 | .374 |

[a]Occurred in 10% or more of patients treated with escitalopram or placebo.

**Table 5. Incidence of Patients With Most Frequent Treatment-Emergent Adverse Events Occurring During the First 14 Days of Double-Blind Maintenance Treatment (safety population), %[a]**

| Treatment-Emergent Adverse Event | Escitalopram (N = 73) | Placebo (N = 66) |
|---|---|---|
| Dizziness | 0 | 18.2 |
| Rhinitis | 0 | 6.1 |
| Upper respiratory tract infection | 0 | 3.0 |
| Headache | 1.4 | 1.5 |
| Inflicted injury | 2.7 | 1.5 |
| Influenza-like symptoms | 1.4 | 0 |

[a]Occurred in 10% or more of patients treated with escitalopram or placebo.

**Table 6. Vital Signs and Weight During Double-Blind Maintenance Treatment (completers)**

| Measure | Escitalopram (N = 73), Mean ± SD | Placebo (N = 66), Mean ± SD | p Value |
|---|---|---|---|
| Systolic blood pressure, mm Hg | | | .509 |
| Baseline | 119.1 ± 14.5 | 118.3 ± 15.4 | |
| Change at endpoint | –1.3 ± 13.5 | 0.6 ± 13.1 | |
| Diastolic blood pressure, mm Hg | | | .133 |
| Baseline | 76.2 ± 8.7 | 75.4 ± 9.2 | |
| Change at endpoint | –0.7 ± 8.8 | 1.9 ± 8.3 | |
| Pulse rate, bpm | | | .948 |
| Baseline | 72.3 ± 8.4 | 71.3 ± 9.6 | |
| Change at endpoint | 1.0 ± 10.3 | 2.2 ± 9.1 | |
| Weight, lb | | | .366 |
| Baseline | 188.5 ± 54.2 | 177.4 ± 46.9 | |
| Change at endpoint | 2.9 ± 10.3 | 1.2 ± 10.2 | |

Abbreviation: bpm = beats per minute.

Approximately 1 month after the last reported dose of blinded placebo, the patient was hospitalized for attempted suicide by overdose. The lavage contents included escitalopram and acetaminophen. Since the patient received blinded placebo, it is likely that he had not fully complied with treatment during the open-label phase and had accumulated study medication.

Evaluation of escitalopram treatment during the maintenance phase in patients with measurements at baseline and study endpoint demonstrated a minimal impact on vital signs (i.e., systolic and diastolic blood pressure, pulse rate) that was not significantly different than placebo (Table 6). Furthermore, in patients who completed the maintenance phase, escitalopram and placebo treatment were similarly associated with minimal weight gain of 2.9 lb and 1.2 lb, respectively.

## DISCUSSION

This study demonstrates that maintenance treatment with escitalopram significantly reduces the risk of depression recurrence and is both safe and well tolerated. The time to depression recurrence was significantly longer and the cumulative recurrence rate was significantly lower for patients receiving maintenance escitalopram treatment compared with patients switched to placebo. During the 52-week double-blind maintenance phase, patients switched to placebo were nearly $2^1/_2$ times more likely to experience recurrence of depression compared with patients continuing escitalopram treatment; a cumulative recurrence rate of 65% was observed for patients who were switched to placebo, compared with 27% for patients maintained on escitalopram. Importantly, censor-

ing of all recurrence events occurring within 14 days of initiating double-blind treatment did not alter the primary finding of the trial. The 14-day censoring period was chosen to mirror the time course of a potential discontinuation reaction, which can emerge 24 to 72 hours following SSRI treatment discontinuation and is generally described as lasting an average of 7 to 14 days.[32] Thus, the prophylactic effects of escitalopram observed in this study cannot be attributed to withdrawal symptoms associated with discontinuation of medication from patients in the placebo group.

Escitalopram continuation treatment over a period of 36 weeks has been previously shown to prevent relapse of depression.[26] The current study extends those findings to demonstrate the efficacy of escitalopram in maintenance treatment. Efficacy in prevention of relapse and recurrence has been shown for many antidepressants, including monoamine oxidase inhibitors, tricyclics, SSRIs, and the serotonin-norepinephrine reuptake inhibitor venlafaxine.[22,33] In comparison with earlier trials, this study design was unique in that patients responded to treatment in the acute phase with a different antidepressant, albeit another SSRI, than was examined in the maintenance phase. This avoids the selection bias inherent in including only patients who previously responded to the same treatment in the acute phase. Therefore, the present study design allows for evaluation of prophylactic efficacy of maintenance treatment distinct from the ability of a drug to sustain its acute response. Nonetheless, only patients who continued to respond to 16 weeks of open-label escitalopram treatment following the switch from acute phase SSRI treatment were included in the maintenance phase. While this introduces a bias in selecting patients who continue to respond to and tolerate escitalopram treatment (i.e., the maintenance phase patient population may be enriched with escitalopram-responsive patients from the continuation phase), it also ensures that patients randomly assigned to the double-blind maintenance phase are stable responders. The latter issue is important in that a failure to achieve a stable treatment response may alternatively bias depression recurrence findings in the maintenance phase (i.e., patients switched to placebo in the maintenance phase may be more likely to experience depression recurrence if they did not achieve a stable response to the active medication). An analogous study design was employed by Lepine et al.[20] in a sertraline depression recurrence trial. In that study, a preventive effect for sertraline was similarly demonstrated in patients who attained remission with another antidepressant.

Current treatment guidelines indicate that patients should continue treatment for 14 to 20 weeks following remission in order to prevent relapse of a depressive episode.[34] Furthermore, the guidelines suggest that maintenance treatment be considered in patients at high risk for recurrence. In the present study, patients, on average, had previously experienced approximately 5 major depressive episodes. The most significant predictor of depression recurrence is the number of prior episodes; in patients with 3 or more prior episodes, the probability of recurrence is greater than 95%.[2] Therefore, in patients with a chronic or recurrent course of depression who have experienced 3 or more lifetime episodes, maintenance phase pharmacotherapy is recommended as prophylaxis against recurrence.[35] While guidelines do not provide specific recommendations for the type or duration of maintenance treatment, they do indicate that, in general, the treatment that was effective in the acute and continuation phases of treatment should be used in the maintenance phase at the same, full antidepressant dose. Notably, it has been reported that, even in patients with well-controlled symptoms, switching to half-dose maintenance treatment results in significantly poorer outcomes relative to patients maintained on full-dose therapy.[18,36]

The presence of residual symptoms that persist after a depressive episode has resolved is also a major known predictor of relapse or recurrence.[8,9,37] Before randomization, the patients in the present study had concluded 6 months of active treatment and had a mean MADRS score of < 5, which essentially represents complete symptom resolution.[38] Thus, our findings suggest that even in patients who have few residual symptoms, withdrawing active therapy entails a significant risk of depression recurrence. Maintenance therapy beyond 4 to 6 months of initial symptom resolution in patients with recurrent major depressive disorder is therefore recommended to prevent recurrence even for those with few residual symptoms.[39]

Limitations in the design of the current trial include the varied treatment paths patients could follow from the acute open-label phase to entry in the open-label continuation phase. To simplify interpretation of the results, only data from patients in the primary treatment path are presented here (i.e., responders from the acute phase who directly entered the continuation phase). For the overall study population, including all 3 possible treatment paths, the result for the primary efficacy parameter of time to recurrence was similarly statistically significant, with a longer time to recurrence and a lower risk of recurrence for escitalopram-treated patients.[27] A second potential concern is that in the acute phase patients were randomly assigned to 1 of 4 SSRI treatments, none of which were escitalopram. Patients who responded to acute treatment with another SSRI were then switched to open-label escitalopram in the continuation phase. It is notable that this does not represent best clinical practice, as well-controlled patients should continue therapy with the treatment that was effective in the acute phase. In addition, this may have resulted in an underestimation of the prophylactic efficacy of escitalopram compared to other maintenance studies, in that the study population was not

specifically selected for their response to and tolerability of escitalopram. Finally, a third limitation, which is common in this type of clinical study, was the exclusion of patients with either medical or psychiatric (i.e., Axis I, Axis II, or Axis III disorders) comorbidities from the study population.

Escitalopram treatment was well tolerated, and the majority of reported AEs were mild. Treatment-emergent adverse events observed with maintenance escitalopram treatment were consistent with previous reports of escitalopram continuation treatment in patients with major depression,[26] generalized anxiety disorder,[40,41] and social anxiety disorder.[42,43] In addition, the incidence of dizziness, a symptom associated with SSRI discontinuation, was examined in patients switched to placebo during the maintenance phase following open-label escitalopram continuation treatment. Although it is just one of a number of potential symptoms associated with SSRI discontinuation, the incidence of dizziness was used to assess the extent to which withdrawal contributed to the occurrence of AEs in patients switched from open-label escitalopram treatment to double-blind placebo in the maintenance phase. Initially, there was a higher incidence of dizziness in patients switched to placebo compared with patients who were randomly assigned to continue escitalopram treatment. However, the incidence of dizziness in the placebo group decreased from 18% during the first 14 days of maintenance treatment to 2% thereafter. This result is consistent with the duration of the censoring period used to limit the effect of withdrawal symptoms on depression recurrence results. Furthermore, the majority of patients who reported dizziness as a TEAE during the first 14 days of maintenance treatment were receiving escitalopram 20 mg/day, and treatment was discontinued without downward titration of the dosage. In usual clinical practice, patients would be tapered from a 20-mg/day to a 10-mg/day escitalopram dosage, and potentially a 5-mg/day escitalopram dosage, before treatment cessation.

A high rate of recurrence was observed in patients with well-controlled depression who exhibited few residual symptoms before switching to placebo. This finding clearly demonstrates the need for maintenance therapy of recurrent major depressive disorder beyond 4 to 6 months of initial symptom resolution, even in patients with few residual symptoms. Maintenance treatment with escitalopram was effective and well tolerated in the prevention of depression recurrence, thus extending previous results in relapse prevention and in the acute treatment of major depression.[23–26] In conclusion, these data suggest that escitalopram is an effective antidepressant for maintenance treatment in patients with recurrent major depressive disorder.

*Drug names:* citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), zolpidem (Ambien).

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