Escitalopram Continuation Treatment Prevents Relapse of Depressive Episodes

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Background: Current guidelines for antidepressant use recommend 4 to 6 months of continuation treatment to prevent relapse of depression following symptom resolution. This study evaluates the efficacy and safety of continuation escitalopram treatment.

Method: Outpatients diagnosed with DSM-IV major depressive disorder (male or female, aged 18 to 81 years) who had completed 8 weeks of randomized double-blind treatment with escitalopram, citalopram, or placebo entered an 8-week flexible-dose, open-label phase in which all patients received escitalopram (10–20 mg/day). This study was initiated November 3, 1999, and completed April 5, 2001. Patients who met responder criteria (score of ≤ 12 on the Montgomery-Asberg Depression Rating Scale [MADRS]) were randomly assigned in a 2:1 ratio to escitalopram (at the dose each patient was receiving at the end of the open-label phase) or placebo for 36 weeks of double-blind treatment. The primary efficacy variable was time to depression relapse (defined as MADRS score ≥ 22 or discontinuation due to an insufficient therapeutic response) from the start of the double-blind treatment phase.

Results: A total of 502 patients received open-label escitalopram treatment and had at least 1 MADRS assessment. A total of 274 evaluable subjects entered the double-blind treatment phase; 93 received placebo and 181 received escitalopram. Time to depression relapse was significantly longer ($p = .013$) and the cumulative rate of relapse was significantly lower in patients who received escitalopram (26% escitalopram vs. 40% placebo; hazard ratio = 0.56; $p = .01$). Escitalopram-treated subjects had significantly lower depression ratings than those of placebo-treated patients. Escitalopram continuation treatment was safe and well tolerated. Discontinuation rates due to adverse events were 7% for the placebo group and 4% for the escitalopram-treated group.

Conclusion: Continuation treatment with escitalopram is effective in preventing relapse into an episode of major depressive disorder.

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Major depression is a common but heterogeneous condition that is associated with considerable morbidity and mortality. The World Health Organization's Global Burden of Disease survey[1] estimates that depression is the leading cause worldwide of years lived with disability. Despite a plethora of available antidepressant medications, unmet treatment needs remain. Acute response rates to any antidepressant medication are only about 50% to 60%, and less than one third of those treated will achieve a full, sustained remission after an initial antidepressant trial.[2–4] Although most patients eventually will respond to some type of antidepressant treatment, at present it is not possible to determine a priori which medication will produce the best response in an individual patient. A second important consideration in the selection of antidepressant medication is its safety and tolerability. These concerns greatly influence a patient's decision to accept and continue with antidepressant treatment, which is a particular concern over the long term, as it is now clear that depression is a relapsing condition that requires a minimum of 4 to 6 months of treatment prolonged beyond initial symptom resolution.[5–10] Thus, new medications with the potential for enhanced effectiveness and/or improved tolerability are needed.

Escitalopram is a single isomer selective serotonin reuptake inhibitor (SSRI) antidepressant and the therapeutically active component of the racemic compound citalopram. The antidepressant efficacy of escitalopram has been demonstrated in acute (8-week) trials in which both escitalopram and citalopram were compared with placebo.[11–13] Burke and colleagues[11] noted that the magnitude of effect at endpoint of 10 mg/day of escitalopram in depressed patients was comparable to that of 40 mg/day of

citalopram. Post hoc analyses of pooled acute trial data suggest that there may be some efficacy advantages for escitalopram relative to citalopram in treating depression, at least in the more severely depressed patients.[14] These clinical observations are consistent with the theoretical advantages of single isomer compounds, in general, relative to racemic mixtures.[15,16] Pharmacologic findings are also consistent with an inhibitory effect of *R*-citalopram on the SSRI activity of escitalopram,[17–19] providing a potential mechanistic explanation for these clinical differences.

Citalopram has been shown to prevent depression relapse,[20] but to date the effects of continuation treatment with escitalopram have not been reported. On the basis of the results of continuation trials with racemic citalopram and the acute phase clinical trial experience with escitalopram, we hypothesized that continuation escitalopram treatment would significantly increase the time to relapse and lead to continued improvement in depression scores in patients who had responded to acute escitalopram treatment.

METHOD

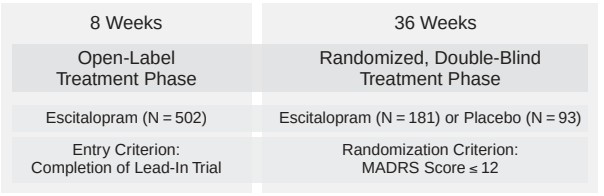
A total of 53 centers in the United States participated in this randomized, double-blind, placebo-controlled trial, conducted between November 3, 1999, and April 5, 2001. The study protocol was approved by the institutional review boards of all participating centers, and all subjects provided written informed consent.

Patient Population

Subjects (male or female, aged 18–81 years) had been diagnosed with major depressive disorder and had completed 8 weeks of randomized double-blind acute treatment with 10 to 20 mg/day of escitalopram, 20 to 40 mg/day of citalopram, or placebo. Patients entered the current continuation trial within 72 hours of completing one of the lead-in trials. To qualify for the lead-in trial, patients were required to have a minimum baseline Montgomery-Asberg Depression Rating Scale (MADRS)[21] score of 22 and to have met DSM-IV criteria for an ongoing major depressive episode of at least 4 weeks' duration. For both trials, the primary efficacy measure was the mean change from baseline to week 8 in MADRS score using the last observation carried forward (LOCF). One of the lead-in trials was a fixed-dose study in which both escitalopram and citalopram produced significant reductions in LOCF MADRS scores relative to placebo.[11] In the second trial, a flexible-dose study, escitalopram and citalopram both produced significant reductions versus placebo in MADRS scores at week 8 for the observed cases data set but not for the LOCF data set (data on file, Forest Laboratories, Inc., New York, N.Y.).

Exclusion criteria included any principal Axis I disorder other than major depressive disorder and a history of schizophrenia or any other psychotic disorder. In addition, patients who presented a suicide risk, scored at least 5 on MADRS item 10 (suicidality), or required concomitant psychotropic medication (with the exception of zolpidem for insomnia) were ineligible to enroll. Women of childbearing potential were not eligible if pregnant and were required to employ a reliable method of contraception.

Figure 1. Study Design



Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Study Design

This study consisted of 2 phases: an 8-week open-label, flexible-dose treatment phase followed by a 36-week randomized, double-blind, placebo-controlled, parallel, fixed-dose phase (Figure 1). Patients who had completed one of the lead-in studies received 8 weeks of open-label escitalopram treatment, starting at a dose of 10 mg/day. The dose of escitalopram could be increased to 20 mg/day for nonresponders (defined as MADRS score > 12) at the end of weeks 4 and 6 during the open-label phase. At the end of week 8, patients classified as responders (MADRS score of 12 or less) were randomly assigned to 36 weeks of double-blind treatment with either escitalopram or placebo in a 2:1 ratio; all other patients were discontinued from the trial. Any patient who met relapse criteria (MADRS score of 22 or greater) at any visit during the double-blind treatment phase was defined as having relapsed and was discontinued from the study. Patients who discontinued treatment because of an insufficient therapeutic response during double-blind treatment, as determined by the investigator, were also considered to have relapsed.

The final visit of the lead-in study served as the baseline visit of this study. Study visits were conducted at the end of weeks 1, 2, 4, 6, and 8 of the open-label treatment phase. During the double-blind phase, study visits were conducted at the end of weeks 2 and 4, and then every 4 weeks thereafter up to week 36 of the double-blind phase. Efficacy assessments at each study visit included the MADRS,[21] the 24-item version of the Hamilton Rating Scale for Depression (HAM-D),[22,23] and the Clinical Global Impressions-Improvement (CGI-I) and -Severity of Illness (CGI-S) scales.[24] Patients were evaluated for DSM-IV criteria for a major depressive episode at the

final visit of the open-label phase and upon completion of the double-blind phase.

Safety measures obtained at every study visit included vital signs and spontaneous adverse event monitoring. Physical examination and laboratory tests were performed at the baseline visit and at endpoint; laboratory evaluations were also performed at week 6 of the open-label phase and after 12 weeks of double-blind treatment. Electrocardiograms (ECGs) were performed at the end of 6 weeks of open-label treatment and at endpoint. All end-of-study safety and efficacy assessments were performed at the time of premature discontinuation.

Statistical Methods

The primary efficacy parameter was time to relapse from the start of the double-blind treatment. The log-rank test was used to test the equality of relapse hazard for patients in the escitalopram group relative to those in the placebo group. Kaplan-Meier survival curves were estimated. Exploratory investigations of the effects of sex, age, race, and depression history on the relapse rate were performed using Cox regression analyses, with these effects included as covariates in addition to the treatment effect.

Comparisons between escitalopram and placebo with respect to the change from baseline to endpoint in the efficacy parameters were performed using an additive analysis of covariance (ANCOVA) model, with treatment group and center as factors and the baseline score as a covariate. Baseline was defined as the last assessment in the open-label phase prior to randomization to double-blind medication.

Comparisons between escitalopram and placebo with respect to the number of patients meeting DSM-IV criteria for a major depressive episode during the double-blind phase were performed using the Mantel-Haenszel chi-square test.

RESULTS

Patient Characteristics

A total of 502 patients received at least 1 dose of open-label escitalopram treatment and had at least 1 post-baseline MADRS assessment. Three hundred seventy-seven patients (75%) completed the open-label phase. Of the open-label completers who were not subsequently randomized to double-blind treatment, most (83 patients) had a MADRS score > 12 and were therefore ineligible to continue in the double-blind phase. All 274 patients who received at least 1 dose of double-blind treatment (93 with placebo and 181 with escitalopram) had at least 1 post-randomization MADRS assessment.

There were no significant differences with regard to demographic parameters between the escitalopram and placebo treatment groups (Table 1). A total of 123 patients (45%) completed the 36-week double-blind phase; 31 (33%) from the placebo group and 92 (51%) from the escitalopram group. The most common reason for discontinuation was relapse (17% escitalopram, 24% placebo), followed by withdrawal of consent (11% escitalopram, 15% placebo), loss to follow-up (6% escitalopram, 9% placebo), insufficient therapeutic response (3% escitalopram, 8% placebo), and adverse events (4% escitalopram, 7% placebo).

Table 1. Baseline Patient Characteristics

Characteristic	Open-Label Phase Escitalopram (N = 502)	Double-Blind Phase Placebo (N = 93)	Double-Blind Phase Escitalopram (N = 181)
Age, mean ± SD, y	41.7 ± 11.9	41.8 ± 11.9	42.9 ± 11.6
Sex (% female)	61.9	62.4	60.2
Race (% white)	85.1	84.9	86.7
Disease course (% recurrent)	66	68	70

Efficacy

Open-label phase. The mean (SD) depression rating scale scores at the beginning of the open-label phase were MADRS = 14.9 (9.5) and HAM-D = 13.7 (8.4) (Table 2); 43% of patients had a MADRS score of 12 or less. In general, the patients who entered the open-label phase following active treatment with either escitalopram or citalopram in the lead-in study had milder symptoms than those who had received placebo treatment in the lead-in study. The mean (SD) baseline MADRS and HAM-D scores for patients treated previously with citalopram were 14.0 (10.2) and 12.8 (8.7), respectively, and for patients treated previously with escitalopram, these values were 13.8 (8.6) and 12.9 (7.9), respectively. For patients treated with placebo in the lead-in study, mean (SD) baseline scores were MADRS = 17.4 (9.7) and HAM-D = 15.7 (8.7) (Table 2).

Open-label escitalopram treatment led to further improvement in depressive symptoms. At the end of the open-label phase, the mean (SD) changes from baseline in MADRS and HAM-D scores were –3.8 (9.3) and –3.1 (8.0), respectively (LOCF values; Table 2). A total of 75% of patients who completed the open-label phase had a MADRS score of 12 or less; this proportion was similar for patients who had received active treatment in the lead-in trial and those who had received placebo during the lead-in studies.

Double-blind phase. Mean MADRS, HAM-D, and CGI-S scores at baseline for the double-blind phase indicated few residual depressive symptoms in either treatment group (Table 3).

The Kaplan-Meier curves for the time to relapse are presented in Figure 2. Time to relapse was significantly longer and the cumulative rate of relapse was significantly lower for patients who received continuation treat-

Table 2. Depression Scores for the Open-Label Phase (LOCF values; mean ± SD)

Efficacy Parameter	Lead-In Study Treatment Group: Placebo (N = 145)	Escitalopram (N = 219)	Citalopram (N = 138)	Total (N = 502)
Baseline				
MADRS	17.4 ± 9.7	13.8 ± 8.6	14.0 ± 10.2	14.9 ± 9.5
HAM-D	15.7 ± 8.7	12.9 ± 7.9	12.8 ± 8.7	13.7 ± 8.4
CGI-S	3.2 ± 1.1	2.7 ± 1.2	2.7 ± 1.3	2.8 ± 1.2
Endpoint (change from baseline)				
MADRS	–5.5 ± 10.9	–3.2 ± 8.5	–2.9 ± 8.6	–3.8 ± 9.3
HAM-D	–4.6 ± 9.4	–2.7 ± 7.0	–2.3 ± 7.6	–3.1 ± 8.0
CGI-S	–0.7 ± 1.0	–0.4 ± 1.0	–0.4 ± 0.9	–0.5 ± 1.0

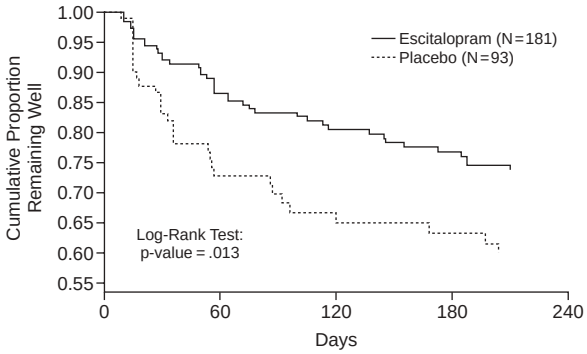
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 3. Depression Scores for the Double-Blind Phase (mean ± SD)

Efficacy Parameter	Placebo (N = 93)	Escitalopram (N = 181)
Baseline		
MADRS	6.2 ± 3.8	7.2 ± 4.0*
HAM-D	6.6 ± 4.6	7.7 ± 4.6*
CGI-S	1.7 ± 0.7	1.8 ± 0.8
Endpoint (change from baseline)		
MADRS	0.7 ± 4.2	–1.4 ± 4.8*
HAM-D	0.8 ± 4.1	–1.6 ± 4.6*
CGI-S	0.1 ± 0.8	–0.3 ± 0.9**

*$p \leq .05$.
**$p < .01$.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 2. Survival Analysis: Time to Relapse During Double-Blind Phase[a]



[a]Time to relapse was significantly longer and the cumulative rate of relapse was significantly lower in patients who received continuation treatment with escitalopram (26% escitalopram vs. 40% placebo; hazard ratio = 0.56, p = .013).

Table 4. Most Frequent (incidence > 5% in active group) Treatment-Emergent Adverse Events During Double-Blind Treatment, %

Adverse Event	Placebo (N = 93)	Escitalopram (N = 181)
Headache	8.6	8.8
Upper respiratory tract infection	10.8	8.8
Rhinitis	1.1	8.8
Sinusitis	4.3	7.2
Back pain	1.1	6.1
Influenza-like symptoms	1.1	6.1
Insomnia	7.5	5.5
Nausea	4.3	5.5

ment with escitalopram (26% escitalopram vs. 40% placebo; p = .01). The risk of relapse was 44% lower in escitalopram-treated patients than in placebo-treated patients (hazard ratio = 0.56). Time to relapse was not significantly affected by age, sex, race, or depression history. Continuing treatment with escitalopram also significantly decreased the percentage of patients meeting DSM-IV–defined criteria for a major depressive episode as compared with placebo (23% escitalopram vs. 35% placebo; p = .03, Mantel-Haenszel chi-square test).

Continuing treatment with escitalopram led to further, statistically significant, improvement in rating scale scores (Table 3). Analyses of changes from double-blind baseline in MADRS and HAM-D scores for patients completing the double-blind phase revealed both improvement for the escitalopram-treated group and worsening in the placebo-treated group. CGI scores at completion of the double-blind phase were consistent with the changes in MADRS and HAM-D scores. At endpoint, the mean (SD) CGI-I score was 1.3 (0.5) in the escitalopram treatment group versus 1.5 (0.6) in the placebo treatment group ($p < .01$).

Safety

Continuation treatment with escitalopram was safe and well tolerated (Table 4). No single adverse event was reported by greater than 10% of escitalopram-treated patients during the 36-week double-blind treatment period. Adverse events led to discontinuation in 7% of placebo-treated patients and 4% of escitalopram-treated patients. No adverse event was given as a reason for discontinuation by more than 2 patients in either double-blind treatment group. There were no clinically significant changes in ECG, vital sign, or laboratory values for either treatment group.

DISCUSSION

Current antidepressant treatment guidelines recommend 4 to 6 months of continuation treatment to prevent relapse into an episode of major depressive disorder.[5–7,9,10] This study demonstrates that continuation treatment with escitalopram significantly reduces the risk of depression relapse (23% vs. 35%, respectively; p = .03) and is safe and well tolerated. During the 36-week double-blind

phase, the time to relapse was significantly longer in the escitalopram group than the placebo group, and the cumulative relapse rate was significantly lower for the escitalopram-treated group than for the group randomized to placebo treatment (26% vs. 40%; hazard ratio = 0.56, p = .01).

The mean changes observed in clinical rating scores during double-blind treatment demonstrated a beneficial effect for continuation treatment with escitalopram. For patients who completed double-blind treatment, the mean changes from baseline to endpoint for MADRS, HAM-D, and CGI scores revealed significant differences between the escitalopram and placebo groups, reflecting both improvement in the escitalopram-treated group and worsening in the placebo-treated group.

Limitations of the present trial include the requirement that patients complete one trial and then agree to rerandomization in another trial. A further limitation is that patients presenting with comorbid primary Axis I diagnoses were excluded. The homogeneity of the patient sample, though useful for clinical trial analysis, may not reflect the full spectrum of patients encountered in routine practice. Another potential concern that must be addressed is the impact of lead-in treatment on subject outcomes observed in this study. Patients entering this trial had previously been assigned to 1 of 7 double-blind treatment groups in the 2 lead-in trials, and there were therefore 7 possible paths of patient flow. There was no significant effect of path on relapse hazard ratio (data not shown). This is consistent with the report of Geddes and colleagues,[10] who reported that antidepressant effect on relapse risk was similar across a wide variety of treatment regimens and patient groups.

Despite these caveats, the design of the present trial ensured a rigorous test of the relapse prevention efficacy of escitalopram. The extended duration of antidepressant treatment (up to 16 weeks) prior to randomization to double-blind treatment would be expected to enhance the consolidation of the acute response, reducing the risk of relapse for the patients switched to placebo treatment during the double-blind phase through the reduction of residual symptoms. This in turn would make it more difficult for escitalopram treatment to show a significant advantage.[5] Moreover, between-group differences in depression symptom severity at the start of the double-blind phase, though small in magnitude, also tended to favor the efficacy outcomes for the placebo-treated group. Significant differences in relapse probability favoring escitalopram were demonstrated despite these potential confounds.

Safety results with escitalopram during continuation treatment were consistent with the favorable safety profile described in the acute treatment trials.[25] In 2 fixed-dose acute (8-week) trials, discontinuations due to adverse events did not differ for escitalopram 10 mg/day or placebo.[12,26] The comprehensive acute trial experience with escitalopram, totaling 715 patients, revealed only 1 adverse event (nausea) to be reported by more than 10% of patients.[25] During the 36-week double-blind phase, no adverse event occurred in patients randomized to escitalopram with an incidence exceeding 10%. Comparisons of the adverse events reported during the double-blind phase of this study with those reported during acute trial experience[25] indicate that reports of common adverse events (such as nausea) decreased with long-term treatment. Furthermore, the adverse event profile (i.e., types of events) did not change during long-term escitalopram therapy by comparison with acute treatment.[25] Other measures (laboratory examinations, ECGs, and vital signs) also suggest that escitalopram is safe.

The present results extend previously reported observations from acute treatment trials[11–13,25,26] and suggest that continued treatment with escitalopram is safe and effective. In this trial, escitalopram treatment led to the consolidation of acute treatment response and the prevention of relapse of depressive episodes.

Drug names: citalopram (Celexa), escitalopram (Lexapro), zolpidem (Ambien).

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