Fixed-Dose Trial of the Single Isomer SSRI Escitalopram in Depressed Outpatients

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Background: Escitalopram is the single isomer responsible for the serotonin reuptake inhibition produced by the racemic antidepressant citalopram. The present randomized, double-blind, placebo-controlled, fixed-dose multicenter trial was designed to evaluate the efficacy and tolerability of escitalopram in the treatment of major depressive disorder.

Method: Outpatients with an ongoing DSM-IV major depressive episode (N = 491) were randomly assigned to placebo, escitalopram, 10 mg/day, escitalopram, 20 mg/day, or citalopram, 40 mg/day, and entered an 8-week double-blind treatment period following a 1-week single-blind placebo lead-in. Clinical response was evaluated by the Montgomery-Asberg Depression Rating Scale (MADRS), the 24-item Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impressions (CGI) scales, the Hamilton Rating Scale for Anxiety (HAM-A), and patient-rated quality-of-life scales.

Results: Escitalopram, at both doses, produced significant improvement at study endpoint relative to placebo on all measures of depression; significant separation of escitalopram from placebo was observed within 1 week of double-blind treatment. Citalopram treatment also significantly improved depressive symptomatology compared with placebo; however, escitalopram, 10 mg/day, was at least as effective as citalopram, 40 mg/day, at endpoint. Anxiety symptoms and quality of life were also significantly improved by escitalopram compared with placebo. The incidence of discontinuations due to adverse events for the escitalopram 10 mg/day group was not different from the placebo group (4.2% vs. 2.5%; p = .50), and not different for the escitalopram 20 mg/day group and the citalopram 40 mg/day group (10.4% vs. 8.8%; p = .83).

Conclusion: Escitalopram, a single isomer SSRI, is well-tolerated and has demonstrated antidepressant efficacy at a dose of 10 mg/day.

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The selective serotonin reuptake inhibitor (SSRI) antidepressants are recommended as first-line antidepressants, due mainly to their superior safety profile relative to their therapeutic predecessors, the tricyclic antidepressants.[1] Despite the well-known heterogeneity of the currently available SSRIs, and even some comparative trial data indicating differences in efficacy within the class,[2] no single SSRI is recognized as an obvious first-line choice. It has been suggested that some subsets of patients respond better to one SSRI than to another.[3–5]

Chirality potentially offers one method to improve upon the SSRI class: if all the serotonin reuptake inhibitory activity of a racemic SSRI antidepressant resides in one isomer, that single isomer would be expected to be more potent than the racemate, and it might also be more selective.[6,7] Thus, the clinical development of that single isomer could improve both risks and benefits over the original antidepressant compound.

Escitalopram is the *S*-enantiomer of the SSRI citalopram, a racemic compound that has been demonstrated to be effective in the treatment of depression, panic disorder, premenstrual dysphoric disorder, and obsessive-compulsive disorder.[8–10] Substantial evidence indicates that escitalopram is responsible for the therapeutic efficacy of the racemate. For example, in vitro pharmacologic studies have demonstrated that escitalopram is more selective than the available SSRIs.[11] Escitalopram is over 100 times more potent as a serotonin reuptake inhibitor than its stereoisomer, *R*-citalopram.[12,13] In vivo studies of antidepressant action also support this conclusion; escitalopram is as efficacious as citalopram in various animal models of depression.[12,14–16] In animal behavioral experiments, escitalopram exhibits at least twice the potency of citalopram.[14] There is also abundant clinical experience with escitalopram as a component of citalopram, which has been used in over 30 million patients with an excellent safety profile (data on file; Forest Laboratories, Inc., New York, N.Y.).

Escitalopram is therefore expected to offer several advantages over citalopram. Escitalopram theoretically should have at least twice the antidepressant potency of citalopram, since the therapeutic effects of citalopram are thought to be dependent upon serotonin reuptake inhibition and escitalopram appears to be responsible for virtually all of the serotonin reuptake inhibition produced by citalopram. Moreover, if any adverse effects of racemic citalopram are attributable to the *R*-enantiomer, they would be avoided in patients treated with the pure *S*-enantiomer. The investigation of the antidepressant effects of escitalopram has thus been pursued with the objective of developing a novel SSRI that might be more potent and/or better tolerated than currently available antidepressant medications. The current multicenter, placebo-controlled study, using citalopram as an active treatment control, examined the safety and efficacy of escitalopram at fixed doses of 10 and 20 mg/day in outpatients with major depressive disorder.

METHOD

A total of 35 centers in the United States participated in this randomized, double-blind, placebo-controlled, multicenter, parallel, fixed-dose study.

Patients

Eligible participants were male or female outpatients, 18 to 65 years of age, with DSM-IV[17] diagnosis of major depressive disorder. Patients were required to meet DSM-IV criteria for a major depressive episode, at least 4 weeks in duration, and to have a minimum score of 22 on the Montgomery-Asberg Depression Rating Scale (MADRS),[18] and a minimum score of 2 on item 1 (depressed mood) of the Hamilton Rating Scale for Depression (HAM-D).[19]

Patients were excluded if they had any DSM-IV Axis I disorder other than major depression, any personality disorder, a history of substance abuse, a suicide attempt within the past year, or evidence of active suicidal ideation (as indicated by a score of at least 5 on item 10 of the MADRS). Women of childbearing potential were included only if they agreed to use a medically acceptable method of contraception; pregnant or lactating women were excluded. No concomitant psychotropic medication was permitted, except zolpidem for insomnia (no more than 3 times per week). The study protocol was approved by the institutional review boards for all participating study centers, and all subjects provided written informed consent.

Study Design

Patients meeting eligibility criteria at a screening visit entered a 1-week, single-blind, placebo lead-in period (1 placebo capsule daily), returning for a baseline visit at the end of the lead-in period. Patients completing the placebo lead-in, who continued to meet all entry criteria, were then randomly assigned to receive 8 weeks of double-blind treatment (1 capsule per day) with placebo, escitalopram, 10 mg/day, escitalopram, 20 mg/day, or citalopram, 40 mg/day.

Throughout the 8-week double-blind treatment period, patients assigned to placebo or to escitalopram, 10 mg/day, received no adjustment of dosage. Patients in the escitalopram 20 mg/day group and in the citalopram group were titrated to their final dose after 1 week of treatment at half of their assigned dose. In order to maintain the blind, all double-blind study medication was administered as 1 capsule per day, regardless of dose or treatment group. No further adjustment of dosage was permitted.

Study visits were conducted after 1, 2, 4, 6, and 8 weeks of double-blind treatment, during which efficacy and safety evaluations were conducted. Efficacy assessments at each visit included the MADRS, the 24-item HAM-D, and the Clinical Global Impressions[20] Improvement and Severity scales (CGI-I and CGI-S). Anxiety symptoms were measured at baseline and at week 8 with the Hamilton Rating Scale for Anxiety (HAM-A).[21] Additionally, patient functioning was assessed at baseline and at week 8 with 2 patient-rated questionnaires: the Center for Epidemiological Studies-Depression Scale (CES-D)[22] and the Quality of Life Questionnaire (QOL), a 16-item instrument derived from the Quality of Life Enjoyment and Satisfaction Questionnaire.[23] For the QOL, higher positive numbers represent better quality of life. Safety measures obtained at every visit included vital signs (after 5 minutes of sitting), body weight, and adverse event monitoring. Electroencephalogram (ECG), physical examination, and laboratory tests were performed at screening and at the end of week 8. All end-of-study assessments were also performed for any patient who discontinued the study prematurely.

Statistical Analysis

The primary statistical approach was a comparison between treatment groups of the change from baseline using the last-observation-carried-forward (LOCF) approach that included all patients who received at least 1 dose of double-blind study medication and had at least 1 postbaseline MADRS assessment. An analysis of patients completing 8 weeks of treatment was also conducted. All presented data are LOCF analyses except where otherwise indicated.

An analysis of covariance (ANCOVA), including treatment, study center, and the treatment by center interaction as factors and the baseline score as covariate, was used for the comparison of the change from baseline to endpoint in all efficacy parameters. The interaction term was dropped from the model if it was not significant at the 10% level. Pairwise comparisons were carried out only if the overall p value (F test) was significant. For the CGI-I, an analysis of variance model (ANOVA) was used. Additional by-visit analyses were carried out for all efficacy parameters using an additive ANCOVA model (ANOVA for CGI-I). Incidence of treatment-emergent adverse events and rate of dis-

Table 1. Baseline Characteristics of Patients With DSM-IV Major Depressive Disorder[a]

Characteristic	Placebo (N = 119)	Citalopram 40 mg/d (N = 125)	Escitalopram 10 mg/d (N = 118)	Escitalopram 20 mg/d (N = 123)
Age, mean ± SD, y	40.1 ± 10.6	40.0 ± 11.5	40.7 ± 12.3	39.6 ± 12.0
Gender, % female	60	62	70	68
MADRS, mean ± SD	29.5 ± 5.0	29.2 ± 4.5	28.0 ± 4.9	28.9 ± 4.6
HAM-D, mean ± SD	25.8 ± 5.9	25.9 ± 5.9	24.3 ± 6.2	25.8 ± 5.7
CGI-S, mean ± SD	4.2 ± 0.5	4.3 ± 0.6	4.2 ± 0.5	4.3 ± 0.6
Disease course, % recurrent	69	70	69	73

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 2. Change From Baseline (mean ± SEM) Endpoint Values for Efficacy Variables[a]

Outcome Measure	Placebo (N = 119)	Citalopram 40 mg/d (N = 125)	Escitalopram 10 mg/d (N = 118)	Escitalopram 20 mg/d (N = 123)
MADRS	–9.4 ± 0.9	–12.0 ± 0.9*	–12.8 ± 0.8**	–13.9 ± 0.8**
HAM-D	–7.6 ± 0.8	–9.9 ± 0.9*	–10.2 ± 0.7*	–11.7 ± 0.8**
CGI-I[b]	3.0 ± 0.1	2.6 ± 0.1*	2.5 ± 0.1**	2.4 ± 0.1**
CGI-S	–0.8 ± 0.1	–1.2 ± 0.1*	–1.3 ± 0.1**	–1.4 ± 0.1**
HAM-D, depressed mood item	–0.9 ± 0.1	–1.4 ± 0.1**	–1.3 ± 0.1**	–1.4 ± 0.1*

[a]Abbreviations: CGI-I and CGI-S = Clinical Global Impressions-Improvement and -Severity scales, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.
[b]For CGI-I, values represent mean scores after 8 weeks of treatment.
*Significantly different from placebo, $p \leq .05$.
**Significantly different from placebo, $p < .01$.

continuation due to adverse events were analyzed using Fisher exact test. All statistical tests were 2-sided and used a 5% significance level.

The primary outcome measure was the change from baseline in the MADRS total score at week 8. Secondary outcome measures included the change from baseline in the MADRS total score at weeks 1, 2, 4, and 6; the change from baseline in the HAM-D and CGI-S at all visits; and the CGI-I score at weeks 1, 2, 4, 6, and 8. Additional analyses included the change from baseline in the HAM-D depressed mood item at weeks 1, 2, 4, 6, and 8 and the change from baseline in the HAM-A, QOL, and CES-D at week 8.

RESULTS

Patient Characteristics

A total of 491 patients entered the double-blind treatment period: 119 in the escitalopram 10 mg/day group, 125 in the escitalopram 20 mg/day group, 125 in the citalopram 40 mg/day group, and 122 in the placebo group. These patients were included in all safety analyses. Efficacy was assessed in the intent-to-treat (ITT) population, which included all patients who had received at least 1 dose of double-blind study medication and had at least 1 postbaseline MADRS assessment. The ITT population consisted of 118 patients in the escitalopram 10 mg/day group, 123 in the escitalopram 20 mg/day group, 125 in the citalopram 40 mg/day group, and 119 in the placebo group.

Following randomization, there were no clinically meaningful differences between treatment groups on the basis of demography or disease severity, course, or duration at baseline (Table 1). The mean baseline scores across treatment groups are indicative of a patient sample with moderate-to-severe depressive symptomatology.

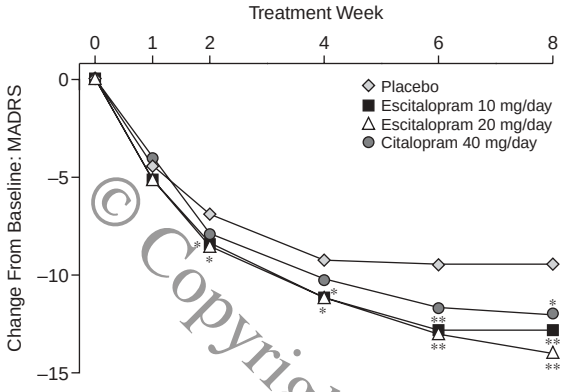
Efficacy

At study endpoint (week 8), the decreases from baseline in the MADRS, HAM-D, HAM-D depressed mood item, and CGI-S and the effect on the CGI-I for escitalopram, 10 mg/day, and escitalopram, 20 mg/day, were statistically significantly superior to those observed for placebo treatment. Citalopram, the active treatment control group, also produced significant improvement compared with placebo in all major efficacy variables (Table 2). Mean changes from baseline for the MADRS total score were –9.4, –12.8, –13.9, and –12.0 for the placebo, escitalopram 10 mg/day, escitalopram 20 mg/day, and citalopram groups, respectively. The change from baseline in MADRS total score was significantly associated with baseline MADRS score. Mean changes from baseline in the HAM-D total score were –7.6, –10.2, –11.7, and –9.9 for the placebo, escitalopram 10 mg/day, escitalopram 20 mg/day, and citalopram groups, respectively. It was of note that at least half of the patients in both the escitalopram 10 mg/day (50%) and escitalopram 20 mg/day (51.2%) treatment groups satisfied prospectively defined criteria for response to treatment (50% improvement in MADRS from baseline). The response rate in the citalopram 40 mg/day treatment group was 45.6%, and each of the 3 active treatment groups had statistically significantly greater response rates than placebo treatment (27.7%; $p < .01$, Cochran-Mantel-Haenszel test). Differences in response rate between each of the escitalopram dosage groups and the citalopram group were not significant.

There were no significant differences in the mean change from baseline to endpoint between the escitalopram 20 mg/day and citalopram 40 mg/day groups on the MADRS ($p = .09$) and the CGI-S ($p = .09$). It was of note that citalopram, 40 mg/day, was not more effective than escitalopram, 10 mg/day, on the majority of the major efficacy outcome variables at study endpoint, including MADRS, HAM-D, CGI-I, and CGI-S (Table 2).

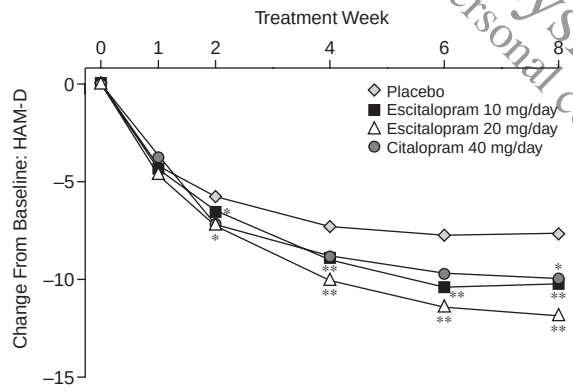
Analyses of patients completing 8 weeks of treatment (observed cases) were consistent with those for the LOCF analyses. At endpoint, the mean changes from baseline for the MADRS total score were –10.0, –14.0, –16.1, and –13.5 for the placebo, escitalopram 10 mg/day, escitalopram 20 mg/day, and citalopram groups, respectively. For the HAM-D total score, the mean changes at endpoint from

Figure 1. Mean Change From Baseline on the Montgomery-Asberg Depression Rating Scale in Depressed Patients Treated With Escitalopram (10 or 20 mg/day), Citalopram, or Placebo



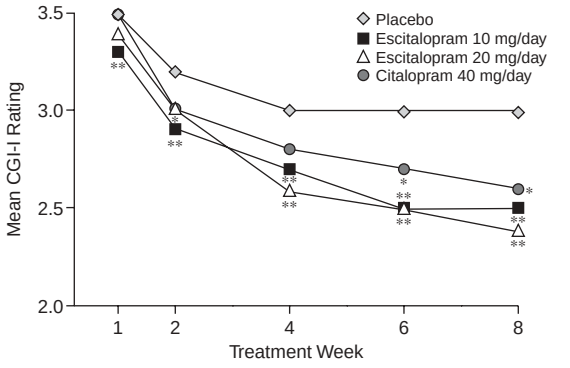
*p ≤ .05, compared with placebo.
**p < .01, compared with placebo.

Figure 2. Mean Change From Baseline on the Hamilton Rating Scale for Depression in Depressed Patients Treated With Escitalopram (10 or 20 mg/day), Citalopram, or Placebo



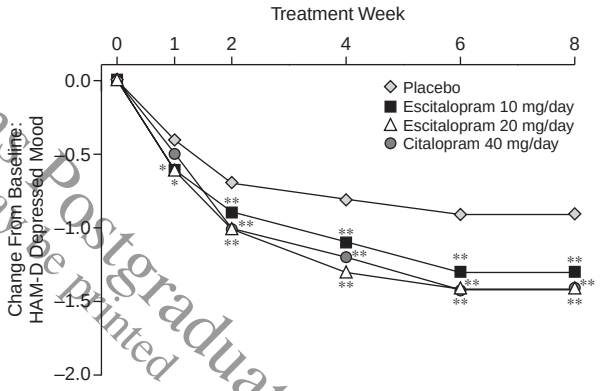
*p ≤ .05, compared with placebo.
**p < .01, compared with placebo.

Figure 3. Mean Clinical Global Impressions of Improvement Scores in Depressed Patients Treated With Escitalopram (10 or 20 mg/day), Citalopram, or Placebo



*p ≤ .05, compared with placebo.
**p < .01, compared with placebo.

Figure 4. Mean Change From Baseline on the Depressed Mood Item of the Hamilton Rating Scale for Depression in Depressed Patients Treated With Escitalopram (10 or 20 mg/day), Citalopram, or Placebo



*p ≤ .05, compared with placebo.
**p ≤ .01, compared with placebo.

baseline were –8.2, –10.9, –13.3, and –11.0 for the placebo, escitalopram 10 mg/day, escitalopram 20 mg/day, and citalopram groups, respectively. For patients completing 8 weeks of treatment, each active treatment group was significantly different from placebo at endpoint. Differences between escitalopram 20 mg/day treatment and citalopram 40 mg/day treatment were not statistically significant on the observed cases analyses of either the MADRS total score (p = .07) or the HAM-D total score (p = .06).

A summary of efficacy results by study visit on the MADRS, HAM-D, CGI-I, and HAM-D depressed mood item is shown in Figures 1–4, respectively. On the MADRS (Figure 1) and HAM-D outcomes (Figure 2), statistically significant improvement compared with placebo treatment was observed with both escitalopram doses beginning 2 weeks after initiation of active treatment and continuing through every study visit to endpoint. On the CGI-I (Figure 3) and the HAM-D depressed mood item (Figure 4), escitalopram treatment significantly separated from placebo treatment after 1 week of double-blind treatment (immediately prior to up-titration in the escitalopram 20 mg/day group). These effects were maintained throughout the treatment period as well.

Additional analyses indicated that escitalopram effectively improved other aspects of depressive disorder. Anxiety symptoms, as measured with the HAM-A, were significantly reduced by escitalopram at endpoint. For the HAM-A, the difference in the mean change from baseline for escitalopram versus placebo treatment was –1.1 for the 10-mg/day group (p = .04) and –2.6 for the 20-mg/day

Table 3. Most Frequent Adverse Events (% of patients)[a]

Adverse Event	Placebo (N = 122)	Citalopram 40 mg/d (N = 125)	Escitalopram 10 mg/d (N = 119)	Escitalopram 20 mg/d (N = 125)
Nausea	6	22	21	14
Diarrhea	7	11	10	14
Insomnia	3	11	10	14
Dry mouth	7	10	10	9
Ejaculatory disorder[b]	0	4	9	12

[a]Listed are those adverse events that occurred in at least 10% of patients in any active treatment group and were more prevalent than in the placebo treatment group.
[b]As a percentage of male patients; number of reports ranged from 2–5 per active treatment group.

group ($p < .01$). Both doses of escitalopram significantly improved scores on both patient-rated questionnaires used in this study. For the QOLS, the difference in the mean change from baseline for escitalopram versus placebo treatment was 2.4 for the 10-mg/day group ($p = .04$) and 4.8 for the 20-mg/day group ($p < .01$). For the CES-D, the difference in the mean change from baseline for escitalopram versus placebo treatment was –2.7 for the 10-mg/day group ($p = .02$) and –6.8 for the 20-mg/day group ($p < .01$).

Six (4.9%) patients discontinued from the placebo treatment group for lack of efficacy, while only 3 (2.5%), 0, and 1 (0.8%) patients from the escitalopram 10 mg/day, escitalopram 20 mg/day, and citalopram treatment groups, respectively, discontinued for this reason.

Safety

Overall, 76% of patients completed the study. Completion rates were similar across all groups ($p = .73$, chi-square test).

Escitalopram was well tolerated in this study at both doses. Discontinuations due to adverse events occurred in 2.5% of placebo patients, 4.2% of escitalopram 10 mg/day patients, 10.4% of escitalopram 20 mg/day patients, and 8.8% of citalopram patients. There was no significant difference in the discontinuation rates due to adverse events between the escitalopram 10 mg/day group and the placebo group, but the differences were significant for both escitalopram, 20 mg/day, and citalopram, 40 mg/day ($p \leq .05$).

The rate of adverse events overall during the double-blind treatment period (treatment-emergent adverse events) did not differ between the escitalopram 10 mg/day group and the placebo group (79.0% vs. 70.5%; $p = .14$), although the rate of treatment-emergent adverse events was significantly different from placebo for both the escitalopram 20 mg/day group (85.6%; $p < .01$) and the citalopram 40 mg/day group (86.4%; $p < .01$).

The adverse events that occurred in at least 10% of patients in any active treatment group and were more prevalent than in the placebo treatment group were nausea, diarrhea, insomnia, dry mouth, and ejaculatory disorder (Table 3). The majority of these events were mild in severity. Noticeably absent from this list is somnolence, as well as symptoms of general activation (such as nervousness or anxiety), a finding that is consistent with previous clinical experience with the racemate.[10] Furthermore, reporting of sexual adverse events was low, with only ejaculatory disorder exceeding 10% in any active treatment group (Table 3). For example, anorgasmia was reported by 1% to 2% of patients in any group, and loss of libido was reported in 2% to 3% of patients in any active treatment group.

Analysis of laboratory, vital sign, body weight, and ECG parameters revealed no clinically remarkable changes from baseline.

DISCUSSION

This study provides strong clinical support for the antidepressant efficacy and tolerability of escitalopram at doses of 10 mg/day or higher. Furthermore, these results suggest that escitalopram within the doses studied may be more potent and better tolerated when administered as a single isomer than as a component of racemic citalopram.

Significant improvement relative to placebo treatment was observed in escitalopram-treated patients beginning in the first week of double-blind treatment, with significant differences being observed on the CGI-I and the HAM-D depressed mood item. By week 2, both escitalopram dose groups had significantly separated from placebo treatment on the MADRS and HAM-D. Although this study was not designed to evaluate the time to response, the rapidity with which escitalopram produced significant responses on all major efficacy parameters is consistent with its rapid onset of action in animal models.[14,16,24]

In addition to improving core depressive symptomatology, escitalopram treatment led to improvements over placebo in other aspects of depressive disorder, including anxiety, social functioning, and overall quality of life. The latter is of particular interest, since quality of life issues such as poor social functioning are often the impetus for depressed persons to seek treatment.[25] Anxiety is a common symptom in depression, affecting up to about 70% of depressed patients.[26] Comorbid anxiety is associated with increased disease severity.[9] In this regard, it is noteworthy that escitalopram significantly improved HAM-A scores as well.

Escitalopram was well tolerated; the rate of discontinuations for adverse events did not differ for the escitalopram 10 mg/day group and for placebo treatment (4.2% vs. 2.5%), and also did not differ for the escitalopram 20 mg/day group versus the citalopram 40 mg/day group (10.4% vs. 8.8%). Furthermore, the overall incidence of adverse events occurring during the double-blind treatment period did not differ between the escitalopram 10 mg/day group compared with placebo treatment (79.0% vs. 70.5%) and also did not differ for the escitalopram 20 mg/day group compared with the citalopram 40 mg/day group (85.6% vs. 86.4%). No adverse events occurred during escitalopram

treatment that were unexpected, given what is known from extensive clinical experience with citalopram.

There are a number of theoretical advantages to the development of single isomers of already approved racemic medications. Often the isomer that does not contribute to the therapeutic effects of the racemate nevertheless complicates the clinical response to the racemate.[6] Twice as much escitalopram is administered daily in the 40-mg/day citalopram dose than is administered in the 10-mg/day escitalopram dose, and one might expect from this that citalopram, 40 mg/day, would be more effective than escitalopram, 10 mg/day. This was not the case, however, since actual treatment with escitalopram, 10 mg/day, was at least as effective as citalopram, 40 mg/day, on the major efficacy outcome variables (MADRS, HAM-D, CGI-I, and CGI-S), as well as the MADRS response rate. These results raise the possibility that the presence of the *R*-enantiomer as a constituent of citalopram has a negative effect on the clinical efficacy seen with the racemate.

Another theoretical rationale for the clinical development of single isomer compounds is the avoidance of side effects associated with the opposite isomer. In comparison to 40 mg/day of citalopram, 10 mg/day of escitalopram was at least as well tolerated, in terms of individual adverse event rates, overall rates of treatment-emergent adverse events, and rates of discontinuation due to adverse events. In this study, therefore, escitalopram, 10 mg/day, provided at least as much antidepressant efficacy as citalopram, 40 mg/day, and with at least as favorable a tolerability profile. Since citalopram, 40 mg/day, is itself a routinely effective dose in clinical practice,[27] escitalopram, 10 mg/day, may be an adequate dose for routine practice as well.

Treatment with escitalopram, 20 mg/day, yielded further improvements in MADRS and HAM-D scores, but the differences relative to escitalopram, 10 mg/day, or citalopram, 40 mg/day, were not statistically significant. As this study was not designed to test differences between active treatment groups, it is not possible to draw firm conclusions; however, these results are certainly most encouraging and provide strong stimulus for further work to test the hypothesis that escitalopram provides greater antidepressant efficacy than citalopram.

These observations emphasize that an existing antidepressant compound can be improved upon by taking advantage of its chiral properties. In conclusion, escitalopram is a new, well-tolerated SSRI with antidepressant efficacy at the lowest tested dose of 10 mg/day.

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

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