DOUBLE-BLIND COMPARISON OF CITALOPRAM AND PLACEBO IN DEPRESSED OUTPATIENTS WITH MELANCHOLIA

Joseph Mendels, M.D.,* Ari Kiev, M.D., J.D.,2 and Louis F. Fabre, M.D., Ph.D.3

This multicenter study compared the efficacy and safety of citalopram and placebo in a population of moderately to severely depressed patients with melancholia. This randomized, double-blind, parallel-group study compared citalopram (flexible dose; 20–80 mg/day) with placebo in 180 psychiatric outpatients with a DSM-III diagnosis of major depression or bipolar disorder, depressed, who also met DSM-III criteria for melancholia. Following a 1-week placebo washout period, patients meeting study entry criteria were randomized to 4 weeks of double-blind treatment with either citalopram or placebo. Efficacy measures included the Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impressions (CGI) Scale, and the Zung Self-Rating Depression Scale. Patients treated with citalopram showed significantly greater improvement at endpoint than placebo patients on the HAM-D, CGI, and Zung scales. On the HAM-D, citalopram patients exhibited significantly greater improvement than placebo patients after 1 week of double-blind treatment and at all subsequent study visits. Endpoint analyses of the HAM-D subscales demonstrated that citalopram produced significant improvement of the psychomotor retardation, cognitive disturbance, sleep disturbance, and melancholia symptom clusters. Nausea, dry mouth, somnolence, dizziness, and increased sweating were reported at higher rates by citalopram-treated patients than by placebo-treated patients, but there were no significant citalopram-placebo differences in the incidence of activation (e.g., anxiety, nervousness, insomnia) or sexual dysfunction. Analysis of electrocardiograms, vital signs, and laboratory tests did not reveal any clinically significant effects of citalopram treatment. The results of this study indicate that citalopram is safe and effective in the treatment of depressed patients with melancholia, and is associated with a favorable side effect profile and a potentially rapid onset of action.


Key words: citalopram; depression; serotonin; selective serotonin reuptake inhibitors; melancholia

INTRODUCTION

Citalopram hydrobromide was first identified as a molecule for clinical development in the early 1970s. Citalopram is a highly selective serotonin reuptake inhibitor (SSRI), with only very weak effects on norepinephrine and dopamine reuptake [Hyttel, 1982, 1994]. In fact, citalopram is the most selective SSRI in clinical use today based on its preferential inhibition of serotonin reuptake relative to other biogenic amines [Hyttel, 1994]. Citalopram has little or no affinity for a variety of receptor types [Hyttel, 1994], rendering it relatively free of anticholinergic and cardiovascular side effects, properties that have limited the usefulness of the tricyclic antidepressants [Dencker and Hopfner Petersen, 1989]. Furthermore, citalopram does not impair cognition or psychomotor performance, and does not potentiate the depressant effect of ethanol [Lader et al., 1986].

Citalopram has an elimination half-life of 1.5 days, which allows for once-daily dosing and facilitates dos-
ing compliance; steady state is achieved after 1 week of dosing. Citalopram is metabolized by the liver and is predominantly (~75%) eliminated as unchanged drug or as metabolites in the urine [Baumann and Larsen, 1995; Oyehung et al., 1984]. Its principal metabolites occur in low concentrations and do not substantially contribute to citalopram’s overall clinical activity. By comparison, the primary metabolite of fluoxetine, norfluoxetine, is as potent as the parent in regard to serotonin reuptake inhibition.

The pharmacokinetic profile of citalopram distinguishes it in a number of respects from other antidepressants. Citalopram is approximately 80% absorbed after oral administration, does not undergo extensive first-pass metabolism, and is unaffected by the presence of food. It displays linear, dose-proportional pharmacokinetics [Baumann and Larsen, 1995; Overø, 1982; Fredricson Overø et al., 1985] unlike other antidepressants with nonlinear kinetics due to saturable and inhibitory metabolic pathways [Preskorn et al., 1993]. This property of citalopram allows for more rapid and controlled dosage adjustments. Citalopram is not extensively protein bound, making it an unlikely candidate for potential drug-drug displacement interactions [Fredricson Overø et al., 1985].

The efficacy of citalopram as an antidepressant has been demonstrated in numerous controlled clinical trials, in comparison with placebo as well as reference antidepressant drugs [De Wilde et al., 1985; Gravem et al., 1987; Bouchard et al., 1987; Montgomery et al., 1992]. It is being used for the treatment of depression in 64 countries and, in seven countries, for the treatment of panic disorder as well.

The depression symptoms that are most commonly identified as diagnostic features of melancholia include lack of reactivity, anhedonia, psychomotor retardation or agitation, late insomnia; weight loss, diurnal variation, distinct quality of mood, and guilt [Rush and Weissenburger, 1994]. The mood disturbance in patients with melancholia has been generally characterized as more severe and more biologically based, or “endogenous,” than in other types of depressed patients. It has also been suggested that tricyclic antidepressants may be more effective than SSRIs as pharmacotherapy for depressed patients with melancholia [Danish University Antidepressant Group, 1986, 1990; Roose et al., 1994; Perry, 1996]. The present study adopted a rapid, semiforced, upward titration regimen to provide a convincing test of citalopram’s efficacy and onset of activity in a depression subpopulation that is thought by some to be relatively unresponsive to treatment with an SSRI.

**MATERIALS AND METHODS**

**SUBJECTS**

Patients were recruited and screened by investigators at three study centers in the United States. Standardized DSM-III diagnostic assessment interviews were conducted at the end of the washout period to identify patients who were eligible for continuing in the study. Outpatients between the ages of 18 and 65 years who met DSM-III criteria for melancholia and DSM-III criteria for major depression or bipolar disorder, depressed, were eligible for participation. Women of childbearing potential were not included. To qualify for random assignment to double-blind therapy at the end of the washout period, patients were required to meet the following criteria: (1) have a minimum score of 25 or more on the 24-item HAM-D; (2) have normal baseline clinical laboratory values or abnormal values that were judged to be clinically insignificant; and (3) have discontinued all other psychoactive medications before the start of the study. Patients with dysthymic disorder or with psychotic features were excluded from study participation, as were patients with a history of schizophrenia, substance abuse (within the past 6 months), or organic brain syndrome. Patients with a history or evidence of significant medical conditions were also excluded.

**STUDY DESIGN**

This was a randomized, double-blind, parallel-group, flexible-dose, multicenter study designed to compare the efficacy and safety of citalopram with placebo when administered to psychiatric outpatients with major depression or bipolar disorder, depressed, with melancholia. The study protocol and patient informed consent forms were reviewed and approved by an appropriately constituted Institutional Review Board at each of the three centers. After giving written informed consent, eligible patients entered a 1-week, single-blind, placebo washout period that was designed to eliminate placebo responders and to wash out any previous antidepressant or psychotropic medications. During this period, patients received one placebo tablet daily. At the end of the washout period, patients meeting study entry criteria: DSM-III criteria [American Psychiatric Association, 1980] for major depression or bipolar disorder, depressed, and DSM-III criteria for melancholia, with a minimum score of 25 or more on the 24-item Hamilton Rating Scale for Depression (HAM-D), were randomly assigned, in equal numbers, to receive either citalopram or placebo during the 4-week, double-blind, flexible-dose treatment period. The duration of double-blind treatment was limited to 4 weeks because of the relatively severe patient population under study in this first placebo-controlled trial of citalopram conducted in the United States. All patients were started with one tablet per day (20 mg citalopram or placebo) in the evening; the once-daily dose was increased in 20 mg increments up to the maximum tolerated dose, with a maximum of four tablets per day (80 mg). Dose titration was restricted to the first 2 weeks of the double-blind treatment period, after which dosage adjustment was only permitted because of dose-limiting adverse events. Concomitant medications with psychoactive properties (except chloral hydrate for

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EVALUATION OF EFFICACY

Clinical efficacy evaluations were made at baseline (the end of washout), and at the end of weeks 1, 2, 3, and 4 of the double-blind treatment period. The final evaluation of efficacy was completed at the end of week 4 or at the time that the patient was withdrawn from the study. Efficacy was assessed with the following three rating scales: (1) HAM-D (24-item); (2) Clinical Global Impressions (CGI), including Severity of Illness and Improvement; and (3) Zung Self-Rating Depression Scale. All of the scales, except the Zung Self-Rating Depression Scale, were completed by a trained clinician. The 17-item HAM-D score was also derived from the 24-item HAM-D scale. In addition, scores on the HAM-D depressed mood item and on the HAM-D subscales measuring cognitive disturbance, psychomotor retardation, sleep disturbance, anxiety/somatization, and melancholia were examined individually.

EVALUATION OF SAFETY

Safety assessments were performed during the washout period, at the end of washout, and at the end of each study week during the double-blind treatment period, and consisted of reports or observations of adverse events, vital sign measurements, 12-lead electrocardiograms (ECGs), physical examinations, and clinical laboratory assessments (clinical chemistry, hematology, and urinalysis). Adverse events (observed, spontaneously reported, or elicited by general questioning but not a checklist or questionnaire) were classified according to the World Health Organization (WHO) Adverse Reaction Terminology dictionary.

STATISTICAL METHODS

Statistical analyses of safety data were conducted on all patients randomized to double-blind treatment who took at least one dose of study medication. Efficacy analyses included all patients randomized to double-blind treatment who took at least one dose of study medication and had at least one follow-up evaluation of efficacy. The comparability of the treatment groups at baseline was tested using analysis of variance (ANOVA) models for continuous data and chi-square tests for discrete data. Efficacy analyses examined the change from baseline at each study visit and at endpoint (last observation carried forward; LOCF).

Between-group effects were tested using analysis of covariance (ANCOVA) models with baseline value as a covariate and including the treatment and center main effects, and the treatment and center interaction effect. Efficacy comparisons between the treatment groups were performed at each of the 4 weeks during the double-blind treatment period and at endpoint (LOCF). For the CGI Improvement scale, categorical data at each visit were analyzed using the Cochran-Mantel-Haenszel chi-square test, stratified for center.

Patients were classified as responders based on a CGI Improvement rating of 1 (very much improved) or 2 (much improved).

All statistical analyses were performed using the General Linear Model (PROC GLM) procedure of Statistical Analysis System (SAS), version 6.09 (SAS Institute, Cary, N.C.). All statistical tests were two-sided with a $P$ value of $\leq .05$ regarded as statistically significant.

RESULTS

A total of 180 patients were randomized, 89 to citalopram and 91 to placebo. The baseline demographics of the two groups (Table 1) were similar with respect to gender, age, race, body weight, height, vital signs, marital status, educational level, general occupational category, and primary diagnosis. The majority of patients in both treatment groups were white (citalopram, 84%; placebo, 89%). The study population was predominately male (about two-thirds of each treatment group) because of the exclusion of females of childbearing potential.

The mean duration of the patients’ current depressive episode was approximately 11 months in both groups. Nearly all of the patients met DSM-III criteria for Major Depression, with only four or five cases of bipolar disorder in each treatment group. Although the study protocol restricted the population to depressed patients with melancholic features, approximately 15% of the patients in each treatment group did not meet DSM-III criteria for melancholia.

Efficacy

Baseline comparison. Comparison of the baseline scores on all outcome measures (Table 2) failed to reveal any significant differences in severity of depression between the two treatment groups. Mean baseline scores of approximately 34 on the 24-item HAM-D are indicative of a patient population with moderately severe depressive symptomatology.

Discontinuations for lack of efficacy. As illustrated in Figure 1, the percentage of patients who discontinued prematurely because of an insufficient therapeutic response was significantly higher ($P < .05$) in the placebo group (23/91, 25%) than in the citalopram group (6/89, 7%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Citalopram (n=89)</th>
<th>Placebo (n=91)</th>
</tr>
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<tbody>
<tr>
<td>Gender (% female)</td>
<td>35%</td>
<td>32%</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>84%</td>
<td>89%</td>
</tr>
<tr>
<td>Age (mean yr)</td>
<td>43.3</td>
<td>42.7</td>
</tr>
<tr>
<td>Weight (mean kg)</td>
<td>74.1</td>
<td>74.4</td>
</tr>
<tr>
<td>Duration of current episode (mean mo)</td>
<td>11.3</td>
<td>10.9</td>
</tr>
<tr>
<td>Principal diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression (n)</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Bipolar disorder (n)</td>
<td>4</td>
<td>5</td>
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HAM-D. As illustrated in Figure 2, the citalopram group exhibited significantly greater improvement ($P < .05$) than the placebo group on the 24-item HAM-D at every study visit beginning at 1 week of double-blind treatment as well as in the endpoint analysis. Analysis of the derived 17-item HAM-D score and of the HAM-D depressed mood item yielded the same results, a significantly greater decrease ($P < .05$) from baseline in the citalopram patients compared with the placebo patients at every study visit and at endpoint. In the endpoint analysis, the mean change from baseline in the 17-item HAM-D in the citalopram group was -9.43 points as compared to -6.95 points in the placebo group. Analysis of individual HAM-D subfactors revealed significantly greater improvement ($P < .05$) and endpoint in the citalopram group relative to the placebo group with respect to cognitive disturbance, psychomotor retardation, sleep disturbance, and melancholia but not the anxiety/somatization factor.

CGI. On the CGI Severity scale, the citalopram group exhibited a significantly greater reduction ($P < .005$) from baseline to endpoint than the placebo group. Significant citalopram-placebo differences were apparent beginning at the end of week 2. Results from the CGI Improvement scale are presented in Figure 3. Responders on the CGI Improvement scale were defined as patients with a score of “1” or “2” (very much or much improved). The responder rate on the CGI Improvement scale was significantly higher ($P < .05$) in the citalopram group than in the placebo group at endpoint and from week 2 onwards. The responder rate among patients completing the study was 81% in the citalopram group and 47% in the placebo group.

Zung. As illustrated in Figure 4, the patients’ subjective ratings of the severity of their depressive symptomatology showed a significantly greater reduction ($P < .05$) in the citalopram group than in the placebo group at endpoint and at every study visit. In the subgroup of patients with bipolar disorder, three of four citalopram patients (75%) were classified as responders at study endpoint, as compared to one of five placebo patients (20%).

SAFETY

Discontinuations. Among the 180 patients randomized, 83 discontinued prematurely, 43 (48%) in the citalopram group and 40 (44%) in the placebo group. Discontinuations because of adverse events occurred significantly ($P < .005$) more frequently in the citalopram group (22/89, 25%) than in the placebo group (7/91, 8%). As described above, 25% of placebo patients and 7% of citalopram patients were discontinued for lack of efficacy. In addition, 10% of placebo patients and 19% of citalopram patients discontinued treatment because of administrative reasons, with-

TABLE 2. Baseline efficacy measures

<table>
<thead>
<tr>
<th>Efficacy scale</th>
<th>Citalopram (n=89)</th>
<th>Placebo (n=91)</th>
</tr>
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<tbody>
<tr>
<td>24-item HAM-D</td>
<td>33.6 ± 4.4</td>
<td>33.9 ± 5.0</td>
</tr>
<tr>
<td>17-item HAM-D</td>
<td>23.9 ± 3.2</td>
<td>24.1 ± 3.5</td>
</tr>
<tr>
<td>CGI-Sex</td>
<td>4.6 ± 0.8</td>
<td>4.7 ± 0.7</td>
</tr>
<tr>
<td>Zung</td>
<td>65.8 ± 9.8</td>
<td>67.2 ± 10.5</td>
</tr>
</tbody>
</table>

*a* HAM-D, Hamilton Rating Scale for Depression.  
*b* CGI, Clinical Global Impressions Scale.
Dosage. The mean daily dose at endpoint for patients receiving citalopram was 52 mg/day.

Serious adverse events. Three patients experienced a serious adverse event. Two citalopram patients had concurrent illnesses of doubtful relationship to study drug: prostatic hypertrophy in one and bronchitis in the other. One placebo patient, a 40-year-old white male with a baseline 24-item HAM-D total score of 42, committed suicide during the first week of double-blind treatment.

Adverse events. The adverse events most frequently reported in both treatment groups were gastrointestinal complaints, psychiatric signs and symptoms, and nervous system disorders. Table 3 presents the treatment-emergent adverse events that occurred in citalopram patients at an incidence at least 5% greater than in the placebo group: nausea, dry mouth, somnolence, dizziness, and increased sweating. Noticeably absent from the list are a number of activating side effects (e.g., nervousness, anxiety, agitation, insomnia, tremor) and symptoms of sexual dysfunction (e.g., decreased libido, ejaculation failure, impotence). Furthermore, other than nausea, a number of gastrointestinal symptoms commonly related to SSRI treatment (e.g., diarrhea, anorexia, constipation) occurred with a similar frequency in citalopram and placebo patients.

Laboratory tests. There were no significant differences between the citalopram and placebo groups in the incidence of potentially clinically significant abnormalities in urinalysis, hematology, or serum chemistry values with the exception of glucose and bicarbonate levels. Elevations in nonfasting glucose levels occurred in 11 citalopram patients and three placebo patients, none of which were associated with adverse events. Mean glucose levels decreased from baseline by 0.79 mg/dL in the citalopram group. Abnormal decreases in bicarbonate levels occurred in 10 citalopram patients and three placebo patients, although the abnormalities were thought to be unrelated to study medication. Mean bicarbonate values increased from baseline by 0.16 mEq/L in the citalopram group. Relative to the placebo group, the citalopram group showed no mean decrease from baseline in serum uric acid and no mean increases in liver function tests. One citalopram patient, however, exhibited marked elevations in SGOT, SGPT, and gamma-GT, and was subsequently diagnosed with hepatitis A.

Electrocardiograms. The incidence of abnormal ECG diagnoses that were not present at baseline did not differ in the citalopram and placebo groups. There were no clinically significant changes in PQ or QRS interval, although one placebo patient and no citalopram patients had a prolongation of the QTc interval > 0.50 sec.

Vital signs. Patients in the citalopram group experienced a mean decrease from baseline in systolic blood pressure of almost 5 mm Hg in comparison to a decrease of approximately 1 mm Hg in the placebo group. No individual patient showed a decrease in systolic blood pressure below 90 mm Hg. Mean standing heart rate decreased by 2.3 beats per minute in citalopram patients, but no individual pulse readings below 50 beats per minute were recorded. No citalopram-placebo differences in diastolic blood pressure or respiration rate were observed.

Body weight. At study endpoint, the citalopram group showed a mean decrease from baseline body weight of 0.3 pounds. None of the body weights of citalopram patients recorded during the study differed from baseline by more than 7%.

DISCUSSION

In this 180-patient, multicenter, randomized, double-blind trial, the SSRI citalopram was demonstrated to be significantly more effective than placebo in the treatment of depressed patients with melancholia. Citalopram patients exhibited significantly greater improvement than placebo patients on all efficacy measures: the HAM-D, the CGI, and the self-rated Zung Scale. Significant differences from placebo were observed on the HAM-D after 1 week of treatment and throughout the double-blind treatment period, indicating that citalopram had a rapid onset of action and produced a sustained therapeutic effect. Significantly more placebo patients than citalopram patients were discontinued for lack of efficacy and, after 4 weeks of double-blind treatment, 81% of the citalopram patients were classified as responders (much or very

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**TABLE 3. Treatment-emergent adverse events**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Citalopram (n=89)</th>
<th>Placebo (n=91)</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>23.6%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>21.4%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>16.9%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13.5%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Increased sweating</td>
<td>6.7%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

*Citalopram incidence at least 5% greater than placebo incidence.*
much improved) on the CGI Improvement Scale. The melancholia subscore of the HAM-D also revealed significantly greater improvement in citalopram patients as compared to placebo patients. In addition, citalopram produced significant improvement relative to placebo on the HAM-D depressed mood item as well as the cognitive disturbance, psychomotor retardation, and insomnia subscales. Citalopram treatment also appeared to provide a therapeutic benefit relative to placebo in a small subset of patients with a diagnosis of bipolar disorder, depressed. The generalizability of the study findings is partly limited by the exclusion from the trial of women of childbearing potential, which resulted in a predominantly male patient sample.

The robust efficacy of citalopram demonstrated in this study, in particular the significant improvement observed on the HAM-D melancholia subscale, to some extent contradicts a number of reports that SSRIs may be less effective than tricyclic antidepressants (especially clomipramine) in the treatment of depressed patients with melancholia [Danish University Antidepressant Group, 1986, 1990; Roose et al., 1994; Perry, 1996]. One possible reason for this apparently differential response is that a number of the side effects associated with some of the SSRIs, psychomotor agitation, insomnia, anorexia, and weight loss, are also common melancholic features. None of these adverse events appeared to be associated with citalopram treatment in the present study. Furthermore, other studies have also failed to suggest such an advantage for the tricyclic antidepressants [Stuppaeck et al., 1994], and clomipramine is the most potent serotonin reuptake inhibitor among the tricyclic antidepressants.

The safety profile of citalopram in this study was generally comparable to what has been reported for other SSRIs. Citalopram was well tolerated in spite of a rapid, semiforced titration regimen that resulted in a mean final dose of 52 mg/day. The adverse events that appeared to be associated with citalopram treatment included nausea, dry mouth, somnolence, dizziness, and increased sweating. The only serious adverse events that occurred in citalopram patients (one case of bronchitis and one case of prostatic hypertrophy) were not likely to be related to drug therapy. Citalopram treatment did not appear to be associated with any clinically important laboratory test findings. Assessment of electrocardiographic and vital sign recordings revealed only a slight decrease in systolic blood pressure and standing heart rate.

The results of this study suggest that citalopram may have some therapeutic advantages over other members of the SSRI class with respect to both safety and efficacy. An onset of antidepressant action during the first week of treatment has not been previously reported for any of the SSRIs. In partial support of this finding, a recent citalopram-fluoxetine comparative study in depressed patients revealed a significantly higher response rate in the citalopram group after only 2 weeks of treatment [Patris et al., 1996]. With regard to side effect profile, citalopram appears to be potentially distinguishable from other SSRIs by its lack of activating side effects (e.g., anxiety, nervousness, agitation, tremor, insomnia), lack of sexual dysfunction, and limited gastrointestinal effects. This favorable side effect profile could be linked to citalopram's greater serotonin selectivity as a reuptake inhibitor. The low rate of adverse events related to sexual function could be underestimates, however, since they were not elicited by a symptom checklist. In contrast to effects occasionally observed with other SSRIs, this study failed to demonstrate increased liver function tests, increased cholesterol levels, decreased serum uric acid, decreased body weight, or increased body weight in association with citalopram treatment.

In summary, the results of this study support the following conclusions: (1) that citalopram is effective in the treatment of major depression with melancholia; (2) that citalopram may have a rapid onset of therapeutic activity, with an antidepressant effect demonstrable during the first week of treatment; and (3) that citalopram's safety profile presents a number of potential therapeutic advantages.

**Drug names.** citalopram (Celexa™, Cipramil®, Cipram®, Seropram®); clomipramine (Anaframil), fluoxetine (Prozac®).

**Acknowledgments.** This study was supported in part by Pfizer, Inc. The data in this article have been presented as a poster at the American Psychiatric Association meeting held May 17–22, 1997, in San Diego, California, and the National Institute of Mental Health (NIMH)-sponsored New Clinical Drug Evaluation Unit (NCDEU) Program held May 27–30, 1997, in Boca Raton, Florida.

**REFERENCES**


