Multicenter, Placebo-Controlled, Fixed-Dose Study of Citalopram in Moderate-to-Severe Depression

John P. Feighner, M.D., and Kerstin Overø, D.Sc.Pharm.

Background: Citalopram, the most selective serotonin reuptake inhibitor (SSRI), is a bicyclic phthalane derivative with a chemical structure that is unrelated to that of other SSRIs and available antidepressants. The drug is approved for use in 69 countries. This 6-week, fixed-dose, placebo-controlled, parallel-arm, multicenter trial was performed to confirm its efficacy and safety in treatment of outpatients with major depression in the United States.

Method: Six hundred and fifty adult outpatients with moderate-to-severe major depression (DSM-III-R) were randomly assigned to receive citalopram at doses of 10 mg (N = 131), 20 mg (N = 130), 40 mg (N = 131), or 60 mg (N = 129) or placebo (N = 129) once daily. Outcome assessments were the 21-item Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions scale.

Results: Between-group comparisons of the change from baseline to endpoint revealed significantly greater improvement in the citalopram patients relative to the placebo patients on all 3 efficacy measures. Patients randomly assigned to 40 mg/day and 60 mg/day of citalopram showed significantly greater improvement than placebo on all efficacy measures, as well as on the HAM-D symptom clusters measuring depressed mood, melancholia, cognitive disturbance, and psychomotor retardation. Patients who received 10 mg/day and 20 mg/day of citalopram also showed consistent improvement relative to placebo on all efficacy ratings, with statistical significance demonstrated in the MADRS response rate, the HAM-D depressed mood item, and the HAM-D melancholia subscale. Citalopram was well tolerated, with only 15% of patients discontinuing for adverse events. The side effects most commonly associated with citalopram treatment were nausea, dry mouth, somnolence, insomnia, and increased sweating.

Conclusion: Citalopram was significantly more effective than placebo in the treatment of moderate-to-severe major depression, especially symptoms of depressed mood and melancholia, with particularly robust effects shown at doses of 40 and 60 mg/day. Citalopram was well tolerated in spite of forced upward titration to fixed-dose levels, with a low incidence of anxiety, agitation, and nervousness.

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Reprint requests to: John P. Feighner, M.D., 5375 Mira Sorrento Pl., Suite 210, San Diego, CA 92121.

Citalopram is a potent and selective inhibitor of neuronal serotonin (5-HT) reuptake[1] that is currently approved in 69 countries for the treatment of depression. Extensive animal pharmacology and toxicology studies as well as clinical studies provide evidence that citalopram is an effective and safe antidepressant agent.[2–4] Serotonin reuptake inhibitors are of particular interest because of the wide recognition and acceptance of central serotonergic dysfunction in the etiology of depressive disorders.[5] Citalopram is the most selective antidepressant currently available in inhibiting serotonin reuptake and has at least 3400 times more potency in the inhibition of serotonin than norepinephrine or dopamine.[6]

The efficacy and safety of citalopram have been documented in numerous clinical trials, largely conducted in Europe, that have included more than 15,000 depressed patients. In fact, citalopram is the most widely used antidepressant in many European countries.[7] Additional placebo-controlled studies support the effectiveness of citalopram as a treatment for panic disorder,[8,9] alcohol abuse,[10] premenstrual dysphoric disorder,[11] obsessive-compulsive disorder,[12] and pain.[13] Such studies have also demonstrated improvement in affective disturbances of patients with schizophrenia,[14] stroke,[15] and Alzheimer's disease.[16] As of September 1999, it is estimated that 16 million patients have been treated with this antidepressant drug (data on file, H. Lundbeck A/S, Copenhagen, Denmark, 1999).

Citalopram has a low potential for drug interactions, which may be due to its relatively low (80%) protein binding and minimal inhibitory effects on the cytochrome oxidase P450 (CYP) enzyme system, including CYP1A2, CYP2C9, CYP2C19, CYP2E1, CYP3A4, and CYP2D6.[17,18]

Citalopram is readily absorbed, with an absolute bioavailability of 80% and a half-life of 35 hours, consistent

with a once-daily dosing regimen.[17] Steady-state plasma levels are achieved after 1 week. Unlike the pharmacokinetics of most selective serotonin reuptake inhibitors (SSRIs),[19–22] steady-state concentrations of citalopram show a linear relationship with dose.[17] This results in predictable, proportional changes in plasma levels as the dose is adjusted.

The present study is the largest placebo-controlled trial of citalopram to date. Although citalopram is usually administered in single, daily doses of either 20 mg or, less commonly, 40 mg, the present study utilized a parallel-group, fixed-dose design to explore a broader range of doses, from 10 mg/day to 60 mg/day.

METHOD

Patients

Male and female outpatients, 18 to 65 years of age, were eligible for participation if they satisfied the following criteria: (1) DSM-III-R criteria[23] for major depression, with symptoms present for a minimum of 4 weeks; (2) minimum total score of 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D)[24]; (3) a score of 2 or greater on HAM-D item 1; and (4) a Raskin Depression Rating Scale score that exceeded the Covi Anxiety Scale score at screen. Patients who showed an improvement of 20% or greater on the HAM-D during the 1-week, single-blind, placebo lead-in were not randomly assigned to double-blind treatment.

Patients with any DSM-III-R Axis I disorder other than major depression were excluded from participation in the study, as were patients with a history of substance abuse or suicide attempt within the past year. Patients considered to have active suicidal ideation (score ≥ 5 on item 10 of the Montgomery-Asberg Depression Rating Scale [MADRS])[25] were also excluded.

Women who were pregnant or lactating were excluded. Women of childbearing potential were included only if they were using a medically acceptable method of contraception. Patients with clinically significant medical conditions, including uncontrolled hypertension, hypothyroidism, insulin-dependent diabetes, and a history of cancer, myocardial infarction, or seizure disorder, were excluded.

Patients who, during the past 3 years, had failed to respond to treatment with either 3 antidepressant agents or 1 SSRI and 1 other antidepressant were excluded. Patients could not enter the study until a minimum of 2 weeks after receiving any antidepressant (4 weeks for fluoxetine) and 3 months after receiving electroconvulsive therapy. No concomitant psychotropic medication was permitted, with the exception of chloral hydrate (maximum dose = 1000 mg/day), which was allowed until the end of the first week of double-blind treatment. The study protocol was approved by the institutional review boards for all participating study centers, and all subjects provided written informed consent.

Study Design

Prospective patients entered a 1-week, single-blind, placebo lead-in period, during which a physical examination was conducted, medical and psychiatric histories were obtained, and psychiatric rating scales, including the Raskin Depression Rating Scale and Covi Anxiety Scale, were administered. Routine laboratory tests were performed, including hematology, serum chemistry, urinalysis, and a thyroid panel, along with standard electrocardiograms (ECGs). Patients received 1 placebo tablet daily for 1 week. Eligible patients then entered the 6-week, double-blind treatment period. Patients were randomly assigned to receive either 10, 20, 40, or 60 mg/day of citalopram or placebo given as a single, oral tablet. The placebo and citalopram tablets were identical in appearance. Patients in the placebo, 10-mg, and 20-mg dosage groups received their assigned dose from the first day of double-blind treatment. The dose was titrated in the 40 and 60 mg/day groups as follows: patients received 20 mg/day on days 1 to 3, 40 mg/day beginning on day 4, and, in the high-dose group only, 60 mg/day beginning on day 8. Downward titration because of adverse events or any other adjustment of dose was not permitted, and patients with dose-limiting adverse events were discontinued.

Patients were evaluated at baseline (the end of the 1-week placebo lead-in) and at weekly clinic visits. Efficacy assessments administered at each visit included the 21-item HAM-D,[24] the MADRS,[25] and the Clinical Global Impressions (CGI)[26]-Severity scale. The CGI-Improvement scale was administered at all visits after baseline. Safety measures obtained at every visit included vital signs (after 5 minutes of sitting), body weight, and adverse events. ECG and laboratory tests were performed at the end of weeks 2 and 6, physical examination was performed at the end of week 6, and all assessments were performed upon early discontinuation.

Statistical Methodology

Demographic and background information was summarized using descriptive techniques. The Kruskal-Wallis[27] and chi-square[28] tests were used to analyze baseline differences between treatment groups for continuous data and categorical data, respectively. The Fisher exact test[28] was used for categorical data where the cell numbers were small.

Efficacy was assessed primarily on the basis of the results from the HAM-D, MADRS, and CGI scales, with change from baseline in the HAM-D identified as the primary outcome measure. For the HAM-D, in addition to the total score, the depressed mood item and the scores on the melancholia, psychomotor retardation, cognitive dis-

Table 1. Baseline Characteristics of the Study Population

Characteristic	Placebo (N = 129)	Citalopram 10 mg/day (N = 131)	Citalopram 20 mg/day (N = 130)	Citalopram 40 mg/day (N = 131)	Citalopram 60 mg/day (N = 129)	Citalopram All Citalopram (N = 521)
Sex, % female	55	63	66	60	53	61
Race, % white	84	87	92	90	90	90
Age, mean, y	38	38	39	39	38	39
Weight, mean, lb (kg)	167 (76)	170 (77)	166 (75)	170 (77)	177 (80)	171 (78)
Previous depressive episode, %	46	51	56	47	52	51
Previous antidepressant treatment, %	42	44	51	44	38	44
Raskin Depression Rating Scale, mean score	10.5	10.6	10.6	10.8	10.4	10.6
Covi Anxiety Scale, mean score	6.6	6.7	6.8	6.7`	6.5	6.7

turbance, anxiety/somatization, and sleep disturbance subscales were also analyzed.

Outcome measures were analyzed using the intent-to-treat, last-observation-carried-forward (LOCF) method for all patients randomly assigned to study medication. Observed case analyses by study visit were also conducted as a secondary analysis. Change from baseline was examined using analysis of covariance with treatment and center as factors and baseline score as covariate. For the CGI-Improvement scale, an analysis of variance was conducted with baseline excluded, since change from baseline is inherent in the improvement rating. The change from baseline in the citalopram patients was compared with the change from baseline in the placebo group using the F test. In addition, F tests[28] using the overall mean square error from the 5-group analysis of variance as an error term were used to test for differences (contrasts) between each of the 4 individual citalopram dose group means and the placebo group mean. On the MADRS, the percentage of responders (patients with a ≥ 50% decrease from baseline to endpoint) in each citalopram dosage group was compared with that in the placebo group using the Fisher exact test.

The statistical software used was SAS version 6. Hypothesis testing was 2-sided and conducted at the 5% level of significance.

RESULTS

Patient Characteristics

Of 650 patients enrolled in the study, 521 were randomly assigned to receive citalopram and 129 to receive placebo (Table 1). Among the 521 citalopram patients, 131 were in the 10-mg/day group, 130 were in the 20-mg/day group, 131 were in the 40-mg/day group, and 129 were in the 60-mg/day group.

No statistically significant overall differences were detected among treatment groups in demographic characteristics or in the patients' psychiatric history (see Table 1). Approximately 60% of the patients were women and 89% were white, and the mean age in all treatment groups was 38 to 39 years old. About half the patients had experienced a previous major depressive episode and 44% had received previous antidepressant treatment. The patients in the 20-mg group had the highest incidence of previous depressive episodes (56%) and previous antidepressant treatment (51%).

No between-group differences in baseline disease severity were found. At screening, the mean Raskin Depression Rating Scale score was 10.6 and the mean Covi Anxiety Scale score was 6.7. The mean baseline 21-item HAM-D scores ranged from 24.4 to 25.1 in the 5 treatment groups, and more than 95% of the patients were rated as "moderately ill" or "markedly ill" on the CGI-Severity scale.

Efficacy

Table 2 presents the change from baseline in the placebo group and the pooled citalopram group for all efficacy variables. In the endpoint analysis, citalopram-treated patients exhibited significantly greater improvement than the placebo-treated patients on the HAM-D, MADRS, and CGI-Severity and Improvement scales. Analysis of individual symptom clusters on the HAM-D revealed significantly greater improvement in citalopram patients relative to placebo patients on the depressed mood item (Figure 1), the melancholia subscale, the psychomotor retardation subscale, and the cognitive disturbance subscale. Citalopram-placebo differences on the sleep disturbance and anxiety/somatization subfactors were nonsignificant.

Pairwise comparisons between the individual citalopram dosage groups and the placebo group revealed that all doses produced significantly greater improvement than placebo in the MADRS response rate (Figure 2), the HAM-D depressed mood item (Figure 3), and the HAM-D melancholia subscale. For the HAM-D total score, greater mean improvement versus placebo was observed in each of the citalopram dosage groups, with significant differences apparent in the 40-mg/day and 60-mg/day dosage groups (Figure 4).

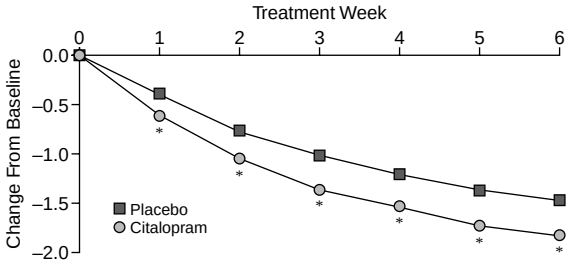
The rates of discontinuation for lack of efficacy in each treatment group also provided evidence of the effectiveness of citalopram treatment relative to placebo. The percentage of patients who dropped out because of an insufficient therapeutic response was 9% in the placebo group,

Table 2. Efficacy Results[a]

Outcome Measure	Placebo Baseline	Placebo Change From Baseline	Citalopram Baseline	Citalopram Change From Baseline	F Value*	p Value*
HAM-D						
Total score	24.6	–9.3	24.6	–11.2	6.28	.0124
Depressed mood item	2.8	–1.0	2.9	–1.5	21.10	.0001
Melancholia subscale	12.3	–4.2	12.3	–5.9	15.91	.0001
Psychomotor retardation subscale	8.0	–2.8	8.0	–3.8	11.78	.0006
Cognitive disturbance subscale	5.4	–2.4	5.3	–2.9	6.97	.0085
Sleep disturbance subscale	3.2	–1.4	3.3	–1.4	0.04	.8501
Anxiety/somatization subscale	6.7	–2.3	6.8	–2.7	2.07	.1510
MADRS total score	27.1	–9.4	27.5	–12.7	10.51	.0013
CGI						
Severity	4.3	–1.1	4.3	–1.4	4.07	.0441
Improvement[b]		2.6		2.3	7.30	.0071

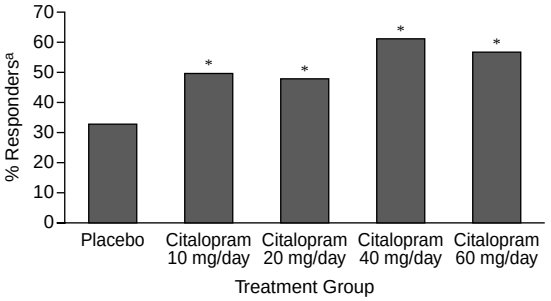
[a]Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.
[b]Mean score, rated as change from baseline.
*F values and p values were derived from a 2-group analysis of covariance including treatment and center as factors, with the baseline values as covariate. CGI-Improvement was compared between groups by analysis of variance.

Figure 1. Mean Change From Baseline in the HAM-D Depressed Mood Item Among Citalopram and Placebo Patients[a]



[a]Significantly greater improvement ($p < .05$) was observed in the citalopram group relative to the placebo group at each week of double-blind treatment based on an analysis of covariance of observed cases with treatment and center as factors and baseline score as covariate.
*Significantly different from placebo, $p < .05$.

Figure 2. Percentage of Responders on the MADRS in Each Treatment Group at Endpoint (last observation carried forward)[a]



[a]Responders were defined as patients with a ≥ 50% decrease from baseline on the MADRS. The rate of response to treatment in each citalopram dosage group was significantly higher ($p < .05$) than in the placebo group based on the Fisher exact test.
*Significantly different from placebo, $p < .05$.

7% in the 10-mg/day citalopram group, 2% in the 20-mg/day citalopram group, 2% in the 40-mg/day citalopram group, 3% in the 60-mg/day citalopram group, and 4% among all citalopram patients.

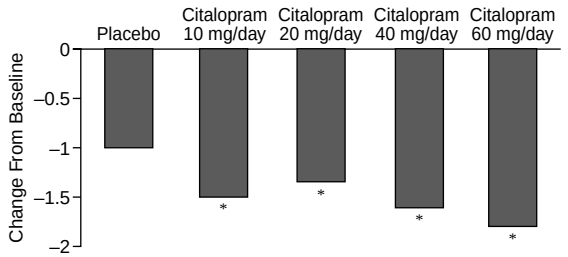
Adverse Effects

Table 3 presents the incidence of all treatment-emergent adverse events that occurred in 10% or more patients in any treatment group. Among these adverse events, the side effects that occurred with a 5% higher incidence in citalopram patients as compared with placebo patients were nausea, dry mouth, somnolence, insomnia, and increased sweating. Although the incidence of increased sweating, fatigue, and insomnia each showed monotonic increases in association with increasing citalopram doses, other events such as nausea and dry mouth occurred at similar incidences at all dose levels.

All central nervous system (CNS) stimulant side effects other than insomnia, including agitation, anxiety, nervousness, and tremor, were reported by less than 5% of citalopram patients. Sexual side effects such as delayed ejaculation, anorgasmia, and decreased libido likewise occurred in fewer than 5% of citalopram patients of either sex.

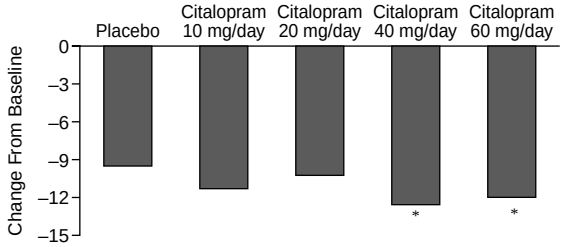
The rate of discontinuation for adverse events was 6% in the placebo group and 15% in the pooled citalopram group: 8% in the 10-mg/day citalopram group and 16% to 18% in the 20-, 40-, and 60-mg/day groups. Overall, 67% of both the placebo and citalopram patients completed the 6-week study, including 72%, 68%, 69%, and 60% of the patients in the 10-, 20-, 40-, and 60-mg/day groups, respectively. One patient in each treatment group, except the 40-mg/day citalopram group, was discontinued for lack of compliance. In addition, 18%, 12%, 12%, 11%,

Figure 3. Decrease From Baseline to Endpoint (last observation carried forward) in the HAM-D Depressed Mood Item in Each Treatment Group[a]



[a]Each of the citalopram dosage groups exhibited significantly greater improvement ($p < .01$) than the placebo group based on an analysis of covariance with treatment and center as factors and baseline score as covariate.
*Significantly different from placebo, $p < .01$.

Figure 4. Decrease From Baseline to Endpoint (last observation carried forward) in the HAM-D Total Score in Each Treatment Group[a]



[a]The overall 5-group analysis of covariance, including treatment and center as factors and baseline score as a covariate, revealed a statistically significant treatment effect ($p < .01$). Greater mean improvement than in the placebo group was exhibited by each of the citalopram treatment groups, with significant differences versus placebo ($p < .01$) in the 40-mg/day and 60-mg/day citalopram groups.
*Significantly different from placebo, $p < .01$.

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

		Citalopram				
Adverse Event	Placebo (N = 129)	10 mg/day (N = 131)	20 mg/day (N = 130)	40 mg/day (N = 131)	60 mg/day (N = 129)	All Citalopram (N = 521)
Headache	33	35	36	40	23	34
Nausea	11	19	28*	23*	22*	23*
Insomnia	11	13	15	21*	24*	18*
Dry mouth	6	15*	18*	13	18*	16*
Somnolence	4	9	13*	22*	19*	16*
Diarrhea	11	13	11	16	16	14
Rhinitis	9	9	6	8	12	9
Dizziness	5	5	11	10	9	9
URI	10	11	8	11	9	9
Increased sweating	2	2	8	11*	12*	8*
Fatigue	5	3	4	8	16*	7

[a]Incidence ≥ 10% in any treatment group. Abbreviation: URI = upper respiratory tract infection.
*Significantly different from placebo ($p < .05$) using Fisher exact test.

and 18% of the patients in the placebo and 10-, 20-, 40-, and 60-mg/day citalopram groups, respectively, discontinued for other miscellaneous reasons, including administrative reasons and patients lost to follow-up.

The serious adverse events that occurred in the citalopram-treated and placebo patients did not appear to be related to the study medication or the dose of study medication administered. Serious adverse events occurred in 8 citalopram patients, including 3 suicide attempts, a miscarriage, intestinal flu symptoms, chest pain and dizziness unaccompanied by ECG abnormalities, a severe thinking abnormality, and an allergic reaction.

Laboratory, Vital Sign, and ECG Findings

Examination of the change from baseline in laboratory parameters (hematology, biochemistry, and urinalysis), vital signs (pulse rate and systolic and diastolic blood pressure), and ECG variables (PQ interval, QRS duration, and QTc) revealed no significant differences between the citalopram and placebo groups with the exception of a clinically important 2 or 3 beat per minute decrease in pulse rate ($p < .05$) in the citalopram patients.

DISCUSSION

The results from this placebo-controlled, multicenter, fixed-dose study in 650 outpatients provide convincing evidence of the effectiveness of citalopram in the treatment of depression. Citalopram patients showed significantly greater improvement than placebo patients on each of the clinician rating scales—HAM-D, MADRS, and CGI—and on the HAM-D symptom clusters measuring depressed mood, melancholia, cognitive disturbance, and psychomotor retardation. Patients randomly assigned to receive 40 mg/day of citalopram or 60 mg/day of citalopram showed significant improvement on all of these outcome measures. Patients who received 10 mg/day or 20 mg/day of citalopram showed consistent improvement

relative to placebo on all measures and statistically significant improvement for some of the measures.

Citalopram was well tolerated; only 15% of the patients discontinued citalopram because of adverse events in spite of the rapid forced titration regimen received by many of the patients. The most frequent adverse events occurring with a higher incidence in citalopram patients versus placebo patients were nausea, somnolence, dry mouth, insomnia, and increased sweating. This side effect profile is similar to that reported in previous citalopram studies,[29–31] although increased insomnia relative to placebo is not usually observed. This observation may have been related to the protocol requirement that chloral hydrate use for sleep disturbances be withdrawn after the first week of double-blind treatment. Other activating side effects and symptoms of sexual dysfunction occurred with a low incidence in citalopram-treated patients. However, sexual side effects were not elicited by direct inquiry or a symptom checklist. The incidence of adverse events did not appear to be markedly dose dependent. Changes in laboratory, vital sign, and ECG parameters were similar in the citalopram and placebo groups.

The study results suggest that depression can be safely and effectively treated with citalopram by using a starting dose of 20 mg once daily with flexible upward titration to a maximum dose of 60 mg once daily if clinically indicated. In this study, the demonstration of efficacy in patients receiving 20 mg/day of citalopram was not as robust as in patients assigned to 40 mg/day or 60 mg/day of citalopram. A dose of 20 mg/day of citalopram has been previously found to be effective in the prevention of depression relapse[32] and to produce numerically higher response rates than 20 mg/day of fluoxetine.[33] Surveys of historical prescription data from the estimated 16 million patients who have received citalopram therapy indicate that about 70% of patients were treated with a dose of 20 mg/day.[34]

Citalopram both at the fixed dose of 20 mg/day and after upward titration in 20-mg increments at intervals of 3 or 4 days was well tolerated in the present study. It is likely that tolerability could be optimized by titrating patients only when clinically necessary and with a more gradual, flexible titration regimen.

Citalopram is known to offer advantages over other antidepressants, including the greatest specificity for serotonin of existing SSRIs, a side effect profile superior to that seen in tricyclic and related antidepressants,[30] and a favorable drug-interaction profile. Citalopram is also well tolerated in the geriatric population.[35] The results of this fixed-dose, placebo-controlled study support and extend previous studies demonstrating that citalopram is a safe and effective SSRI antidepressant.

Drug names: citalopram (Celexa), fluoxetine (Prozac).

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