Two-Year Maintenance Treatment With Citalopram, 20 mg, in Unipolar Subjects With High Recurrence Rate

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Background: The efficacy of citalopram, 20 to 60 mg/day, in relapse prevention in major depression was demonstrated in 6-month placebo-controlled studies. The authors tested the efficacy of citalopram, 40 mg/day, in relapse prevention over a 4-month period and citalopram, 20 mg/day, in recurrence prevention over a 24-month period.

Method: Fifty inpatients with recurrent major depressive disorder (DSM-IV criteria) who had had at least one depressive episode during the 18 months preceding the index episode were openly treated with citalopram, 40 mg/day. Thirty-six subjects had a stable response to citalopram and remained in the continuation treatment with citalopram, 40 mg/day, for 4 months as outpatients. At the time of recovery, 32 patients gave their written informed consent before entering the 24-month maintenance period with citalopram, 20 mg/day. They were evaluated monthly by trained psychiatrists on the basis of the 21-item Hamilton Rating Scale for Depression. Every 3 months, patients were given the Sheehan Disability Scale, a self-rating instrument, to assess their psychosocial adjustment.

Results: No relapse was observed in the 4-month continuation period. Sixteen (50%) of 32 patients who entered the 24-month maintenance period had a new recurrence. Patients with recurrence showed a persistent moderate disability on Sheehan Disability Scale score, while no further differences were highlighted in clinical and demographic characteristics between patients with and without recurrence.

Conclusion: In agreement with previous findings, these data suggest that a full dose of antidepressant is strongly recommended in prophylactic therapy of patients with recurrent major depression. Moreover, it appears that psychosocial impairment may increase the risk of recurrence, thus conditioning a poor outcome.

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Relapse or recurrence is frequent in major depressive disorder and is associated with considerable disability and impairment.[1] Thus, prophylactic therapy is strongly recommended, particularly in those patients with frequent and disabling recurrences.[2–4] In particular, the superiority of an antidepressant, such as imipramine, over a mood-stabilizing agent, such as lithium carbonate, has been suggested in the preventive treatment of recurrent unipolar depression characterized by severe and/or frequent episodes.[5] The preventive efficacy of imipramine in the treatment of recurrent unipolar depression has been confirmed in subsequent placebo-controlled studies.[6,7] Moreover, full doses of imipramine (200 mg daily) have been compared in long-term treatment with lower doses of imipramine (100 mg daily), and a similar rate of treatment failure was observed with the lower imipramine dose as with placebo.[8]

During the last decade, the benefits of selective serotonin reuptake inhibitors (SSRIs) in the long-term treatment of depression have also been demonstrated in several controlled studies.[9–14] Nevertheless, few data are available regarding the dosing regimen during prophylaxis. In a clinical setting, the dose required for acute efficacy is usually continued during maintenance treatment. In recent years, some SSRIs, such as paroxetine, fluvoxamine, and sertraline, have shown good efficacy in preventing recurrences at doses lower than those used to treat the acute episode.[11–13] The efficacy of citalopram in doses of 20 to 60 mg/day in the prevention of relapses of major depression has been demonstrated in 6-month placebo-controlled studies,[15–17] but to date, no data are available about its preventive efficacy for recurrences.

The current investigation was designed to test the prophylactic effectiveness of citalopram, 20 mg/day, for recurrence in a population of unipolar patients with a high rate of recurrence in whom citalopram, 40 mg/day, had led to remission and recovery of the index depressive episode. Given the increasing recognition of the need to consider the recovery of depressed patients in broader terms than merely an improvement in symptoms, we assessed the level of disability experienced by patients in work, family, and social functioning over the long-term treatment.

METHOD

Sample

Patients consecutively hospitalized in the Research Center for Mood Disorder of the San Raffaele Hospital in Milan, Italy, for a recurrent, major depressive episode without psychotic symptoms (DSM-IV criteria)[18] were screened for the absence of manic or hypomanic previous episodes, other Axis I diagnoses, clinically important physical illness, a history of low compliance to past treatments, mania or hypomania in first- and second-degree relatives, and prior long-term maintenance treatments and for the presence of at least one depressive episode during the 18 months preceding the index episode. Patients with longer recurrence cycles were excluded to allow a meaningful comparison of the preventive efficacy of the maintenance treatments within our 24-month follow-up time limit. All patients had to have a score of 18 or more on the 21-item Hamilton Rating Scale for Depression (HAM-D).[19]

Study Design

Fifty inpatients were openly treated with citalopram, titrated up to 40 mg/day, for 6 weeks. Patients were considered to be stabilized at whatever point in the acute treatment regimen they maintained a HAM-D score ≤ 8 for 3 consecutive weeks. According to this requirement, 36 subjects (72%) remained in continuation treatment as outpatients for an additional 4-month period. Over this time, the dosage of citalopram remained unchanged (40 mg/day). At the time of recovery (4 months of remission confirmed by the absence of depressive symptoms according to DSM-IV criteria, absence of functional impairment, and stable 21-HAM-D score ≤ 8), 32 patients (7 men and 25 women) gave their written informed consent before entering the 24-month maintenance period. From this time on, a half-dose regimen of citalopram (20 mg/day) was administered. During the continuation as well as the maintenance period, patients were evaluated monthly. Whenever a patient presented signs of clinical worsening and functional impairment and had a HAM-D score > 15, the treating clinician, a psychiatrist, called an independent trained psychiatrist. The patient was recognized as having a relapse (any depressive episode during the 4-month continuation therapy) or a recurrence (any depressive episode during the 24-month maintenance therapy) whenever both the independent clinical evaluator and the treating clinician judged that the patient met DSM-IV criteria for a major depressive episode and had a HAM-D score > 15.

Side effects were recorded monthly by using Dosage Records and Treatment Emergent Symptom Scale (DOTES).[20] Moreover, every 3 months patients were given the Sheehan Disability Scale,[21] a self-rating instrument, to assess their global psychosocial adjustment. Each item (work, family, and social functioning) is rated on a 1- to 5-point scale, with 1 indicating absence of disability and 5, incapacitating symptoms.

Table 1. Baseline Clinical and Demographic Characteristics of Patients Who Entered 24-Month Continuation Therapy With Citalopram (N = 32)[a]

Variable	Value
Gender, F/M, N	25/7
Socioeconomic status, N	
Employed	25
Unemployed	7
Current age, y	50.8 ± 10.3
Marital status, N	
Single	10
Widowed	3
Married	19
Age at onset, y	39.8 ± 12.8
No. of previous episodes	5.6 ± 3.5
Duration of index episode, wk	16.8 ± 3.6
HAM-D score at index episode	27.7 ± 3.3

[a]Data expressed as mean ± SD unless specified otherwise.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Statistical Analysis

Clinical and demographic characteristics between patients with and without recurrence were compared by using chi-square or t tests as appropriate. To determine if the Sheehan Disability Scale discriminated between subgroups of patients with and without recurrence, a discriminant function analysis was carried out including recurrence/nonrecurrence as the grouping variable and 3-monthly mean Sheehan Disability Scale scores (i.e., the mean for all patients in each group after 3, 6, and 9 months of follow-up) as the independent variable. Computerized analyses were performed with a commercially available statistical package.[22]

RESULTS

Fifty inpatients completed the acute open treatment phase, and 36 (72%) had a stable response (score of 8 or less on the 21-item HAM-D). All 36 patients who entered the 4-month continuation period maintained a full-dose regimen of citalopram (40 mg/day). Over this time, no relapse was observed. Four patients did not give informed consent to enter 24-month maintenance therapy in the half-dose regimen of citalopram (20 mg/day). Table 1 shows the baseline clinical and demographic characteristics of the 32 patients who entered the long-term treatment phase. All patients completed this phase. No polarity switches or dropouts due to unpleasant side effects were observed.

At the end of the 24-month maintenance phase, 16 (50.0%) of 32 patients showed a single recurrence. Figure 1 shows the survival curve of subjects over this period. The cumulative probability of having no recurrence was 84.4% (27/32) at month 9, 78.1% (25/32) at month 12, 53.1% (17/32) at month 13, and 50% from month 18 to month 24.

Figure 1. Rate of Survivors During Maintenance Phase

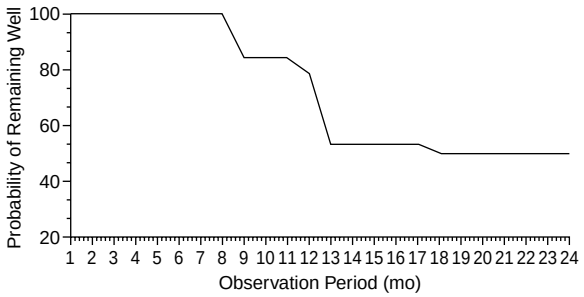

Table 2. Clinical and Demographic Characteristics of Patients With and Without Recurrence of Depression[a]

Variable	With Recurrence (N = 16)	Without Recurrence (N = 16)
Gender, F/M, N	12/4	13/3
Current age, y	48.8 ± 10.9	52.8 ± 9.5
Age at onset, y	38.8 ± 12.6	40.7 ± 13.2
No. of previous episodes	3.4 ± 1.6	4.2 ± 1.2
HAM-D score at index episode	28.4 ± 3.1	27.3 ± 3.3
Duration of index episode, wk	9.5 ± 4.8	9.3 ± 4.3

[a]Data expressed as mean ± standard deviation unless specified otherwise. No significant differences were found between patients with and without recurrence of depression.

Table 2 shows the demographic and clinical variables of patients with and without recurrence. No difference in gender, current age, age at onset, presence/absence of Axis II diagnosis, number of previous depressive episodes, or duration of the index acute depressive episode (i.e., the length of time required to treat the index episode) was observed between the 2 groups. Specifically, mean ± SD baseline HAM-D scores at the index episode before preventive treatment were 27.3 ± 3.3 and 28.4 ± 3.1 for patients with or without recurrence, respectively.

Moreover, recurrences observed during maintenance therapy were less severe and shorter in duration than index episodes. In fact, the intensity of new episodes (determined by mean ± SD HAM-D scores) of patients on citalopram treatment decreased from 27.3 ± 3.3 to 25.2 ± 2.3 ($t = 2.1$, $df = 30$, $p = .007$), and their duration decreased from 9.3 ± 4.3 to 6.4 ± 2.2 ($t = 2.4$, $df = 30$, $p = .006$).

Table 3 shows the results of the discriminant function analysis performed on the whole sample using mean scores of 3-monthly Sheehan Disability Scale obtained before recurrences. A total of 87.5% of patients with recurrence and 81.2% of patients without recurrence were correctly classified (Wilks $\lambda = 0.45$; $F = 35.243$; $p = .0001$) on the basis of the Sheehan Disability Scale scores. In fact, considering the mean Sheehan Disability Scale scores retrospectively, patients with recurrence showed higher mean ± SD scores than patients without recurrence: 3.94 ± 0.44 versus 2.56 ± 0.81 ($t = 5.94$, $df = 30$, $p = .00001$). Few patients reported the presence of mild or moderate side effects: headache N = 2 (6.2%), nausea N = 2 (6.2%), and loss of energy N = 1 (3.1%). These side effects disappeared spontaneously and occurred only during acute or continuation treatment.

Table 3. Discriminant Analysis: Observed and Predicted Classification of Patients With and Without Recurrence According to Mean Sheehan Disability Scale Scores[a]

		Predicted Classification	
Observed Classification	% Correct	Without Recurrence	With Recurrence
Without Recurrence	81.25	13	3
With Recurrence	87.50	2	14
Total	84.38	15	17

[a]Wilks $\lambda = 0.46$, $F = 35.243$, $p = .0001$.

DISCUSSION

The current investigation was designed to test the effectiveness of citalopram, 40 mg/day in relapse prevention and 20 mg/day (half the dose of citalopram the patients had responded to during the acute treatment phase and that was continued for 4 months) in the prophylaxis of recurrent depression.

Previous placebo-controlled studies have demonstrated the effectiveness of citalopram in preventing relapses in major depression.[15–17] In line with those findings, citalopram in our study proved effective in consolidating the response to acute treatment in that no relapse was observed in the 4-month continuation phase. The lack of relapses may be explained by the fact that, in assessing the clinical response to acute treatment, we used a more stringent criterion than a 50% reduction in baseline HAM-D score; only patients who had a HAM-D score lower than 8 for 3 consecutive weeks entered the continuation phase. Supporting this view, it has been reported that patients who had a HAM-D score > 8 after acute treatment experienced higher relapse rates.[23]

During the 24-month maintenance period, patients showed a high recurrence rate (50%), which was similar to those reported in the absence of a medication or with placebo as maintenance treatment.[24] In this regard, it has been reported that after recovery from a major depressive episode, there is a 50% probability that subjects will experience a new episode within 2 years,[25] and the study by Frank et al.[6] showed that approximately 74% of recurrences in the placebo-treated group occurred within 2 years of maintenance treatment. One limitation of our study is the lack of a placebo control group, which was a necessary choice and in accordance with the guidelines of the ethical committee of our hospital because of the entrance into the study of depressed patients with a high risk of recurrence. Thus, we cannot exclude that, in our

sample, a higher percentage of patients would have had a recurrence if no active medication had been administered.

Moreover, since doses lower than 40 mg/day have not been tested in acute patients, it is possible that 20 mg/day of citalopram may be an effective maintenance dose in patients whose depression responds to 20 mg/day during acute treatment. Similarly, it is likely that not reducing the dose regimen of citalopram during the maintenance treatment would have led to a better outcome. In agreement with this, we have recently demonstrated that paroxetine, 40 mg/day, is more effective than paroxetine, 20 mg/day, in long-term treatment of patients with high risk of recurrence who had previously responded to 40 mg/day in the acute phase.[14] Moreover, Frank and colleagues[8] reported that the hazard of recurrence while receiving half a dose of imipramine was 3.3 times greater than while receiving a full dose.

All patients recruited in our study assessed their psychosocial adjustment by using a self-rating instrument (Sheehan Disability Scale), and patients with recurrence experienced a more severe psychosocial disability compared with those without recurrence. Subjects with severe episodes of depression (hospitalized during the acute phase) and repeated episodes of illness have a major risk of disability that could also be due to the continuous care intervention needed.[26] Moreover, it has been reported that subjects with subthreshold depressive symptoms may have changes in global functioning over time.[1] Most of the residual symptoms of depression may be prodromal symptoms of relapse or recurrence.[23,27] According to these observations, many literature data[6,26–31] suggest that a combined (pharmacologic, interpersonal, or cognitive-behavioral) treatment may act on the disability related to this lifelong condition and on those residual symptoms of major depression that prove to be prodromal symptoms of relapse or recurrence. In fact, depression is a long-term problem, and it is important for psychiatrists to teach their patients how to recognize the early symptoms, encouraging them to seek help at the earliest signs of clinical change. In this sense, the identification and the use of a rating instrument assessing functional impairment, in addition to the recording of some psychiatric symptoms not identified with a depression rating scale, could allow a more timely and structured clinical intervention, thus improving the outcome and the quality of life of patients.

In conclusion, citalopram, 40 mg/day, is an effective means to prevent relapses in patients with unipolar depression with high probability of recurrence. The half-dose reduction (20 mg/day) during the maintenance phase appears to be linked with a decrease in citalopram's preventive action. This latter conclusion should be accepted with caution, given the lack of controls and a comparison group in our study. Citalopram was well tolerated during the duration of the study in that no patient reported side effects that affected global functioning. Psychosocial impairment may increase the risk of recurrence, thus conditioning a poor outcome.

Drug names: citalopram (Celexa), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft).

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