Dose-Response Efficacy of Paroxetine in Preventing Depressive Recurrences: A Randomized, Double-Blind Study

Linda Franchini, M.D.; Mariangela Gasperini, M.D.; Jorge Perez, M.D., Ph.D.; Enrico Smeraldi, M.D.; and Raffaella Zanardi, M.D.

Background: The authors evaluated and compared the efficacy of 20 mg versus 40 mg of paroxetine in a randomized, double-blind, parallel-group study during a maintenance period of 28 months.

Method: Ninety-nine inpatients with recurrent, unipolar depression (DSM-IV criteria) who had at least 1 depressive episode during the 18 months preceding the index episode were openly treated with paroxetine 40 mg/day. Seventy-two subjects had a stable response (Hamilton Rating Scale for Depression score < 8) to paroxetine treatment and remained in the continuation treatment as outpatients for 4 months. At the time of recovery, 68 patients were randomly assigned to 1 of the 2 maintenance treatment groups: paroxetine 20 mg or paroxetine 40 mg daily.

Results: Sixty-seven patients completed the 28-month follow-up period. Seventeen (51.5%) of 33 patients in the 20-mg paroxetine regimen had a single recurrence compared with 8 (23.5%) of 34 subjects in the 40-mg dose regimen ($\chi^2 = 5.56$, $p = .018$).

Conclusion: These data suggest that a full dose of paroxetine is recommended in unipolar patients who are at high risk for recurrent depressive episodes.

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Reprint requests to: Raffaella Zanardi, M.D., Istituto Scientifico H. San Raffaele, Department of Neuropsychiatric Sciences, University of Milan, Via Luigi Prinetti, 29, 20127 Milan, Italy (e-mail: zanardi.raffaella@hsr.it).

Major depression is a common (1-year and lifetime prevalences of 5% to 10% and 15% to 20%, respectively) and disabling illness.[1] It is well recognized that of subjects who recover from an initial episode of depression, at least half will experience 1 or more recurrences.[2] Moreover, there is a higher risk of recurrence for patients with a history of 2 or more episodes.[3] On these bases, an extended course of maintenance pharmacotherapy has been recommended to keep patients with recurrent depression well.[4]

Serotonin selective reuptake inhibitors (SSRIs) are effective in the treatment of depression,[5] and over the past 10 years, particular attention has been paid to define the ability of these medications in preventing new episodes in patients suffering from recurrent depression.[6] The prophylactic efficacy of fluoxetine was demonstrated in a 1-year placebo-controlled study.[7] Additionally, successful results in recurrence prevention have also been reported with sertraline,[8] paroxetine,[9–12] and fluvoxamine.[13,14] Overall, these findings strongly suggest that SSRIs are effective prophylactic treatments.

To date, there is only 1 randomized clinical trial[15] in which the efficacy of higher and lower doses of the tricyclic antidepressant imipramine was compared. Although the small size of the sample precluded any firm conclusion, the authors have suggested that the full dose of imipramine was more effective than the half dose in preventing recurrences.

The most beneficial dosage of an SSRI that should be used during maintenance treatment has yet to be studied. To further this research, we carried out a randomized, double-blind trial comparing 20 mg versus 40 mg of paroxetine over a 28-month maintenance period in a population of unipolar patients with a high probability of recurring depressive episodes.

METHOD

Sample

Inpatients consecutively hospitalized in the Research Center for Mood Disorder of the S. Raffaele Hospital in Milan for a recurrent, major depressive episode without psychotic symptoms (DSM-IV criteria[16]) were screened for the absence of other Axis I diagnoses, 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 the presence of at least 1 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 28-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.[17]

Study Design

Ninety-nine patients were openly treated with paroxetine for 6 weeks: 20 mg daily during the first week, 30 or 40 mg daily in the second week, and 40 mg thereafter. Patients were considered to be stabilized at whatever point in this acute treatment regimen the patient had maintained a HAM-D score less than or equal to 8 for 3 consecutive weeks. According to this requirement, 72 subjects (72.7%) remained in continuation treatment as outpatients for an additional 4 months. During this time, patients maintained the full dosage (40 mg/day) of paroxetine. If a patient presented signs of clinical worsening and functional impairment, the treating clinician called an independent trained psychiatrist. The patient was observed and evaluated by the trained psychiatrist. Relapse was defined if both the independent clinical evaluator and the treating clinician judged that the patient met the DSM-IV criteria for a major depressive disorder and the independent evaluator rated the patient as having a HAM-D score > 15.

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 HAM-D-21 score < 8), 68 patients (24 men and 44 women) gave their written informed consent before entering the follow-up period of 28 months. Patients were randomly assigned to 1 of 2 maintenance treatment groups: paroxetine 20 mg/day was administered to 34 subjects, while 34 patients received paroxetine 40 mg/day. The blind was maintained by providing patients with capsules identical in external appearance, containing 20 mg or 40 mg of paroxetine. Capsules were administered in the morning. During this period, patients were evaluated monthly by trained psychiatrists who were blinded to the treatment option. If a patient presented a major depressive episode (DSM-IV criteria and HAM-D-21 score > 15), they were recognized as having a recurrence, and additional treatment was prescribed, according to clinical judgment.

Moreover, to verify an adequate compliance with the maintenance treatment, plasma paroxetine levels were randomly monitored in each patient at various times during treatment.

Statistical Analyses

Demographic and clinical characteristics of the sample were examined using t test and chi-square analyses.

The Mantel-Cox statistic was used to compare the cumulative probability of survival in the full- and half-dose condition. The Cox proportional hazard model[18] was used to calculate the hazard of recurrence.

Table 1. Baseline Clinical and Demographic Characteristics of the 2 Therapy Groups*

	Paroxetine 20 mg (N = 34)		Paroxetine 40 mg (N = 34)	
Characteristic	Mean	SD	Mean	SD
Current age (y)	46.5	6.6	47.5	10.9
Age at onset (y)	40.1	6.6	40.0	8.6
Number of episodes	6.1	2.3	6.7	2.6
HAM-D score at index episode	26.9	1.8	26.6	1.4
Duration of index episode (wk)	8.5	2.7	8.4	2.4

*Abbreviation: HAM-D = 21-item Hamilton Rating Scale for Depression. Male/female ratios: paroxetine 20 mg = 13/21, paroxetine 40 mg = 11/23. No statistical difference was found between groups (chi-square test for sex; Student t test for other variables).

RESULTS

Ninety-nine patients completed the acute open treatment phase, and 72 (72.7%) were responders (score of 8 or less on 21-item HAM-D). During the continuation phase, 3 (4.2%) of 72 patients suffered a relapse, and they were excluded from the maintenance period. One patient did not give his informed consent to entering the 28-month follow-up study. Randomization resulted in 34 patients who received paroxetine 20 mg/day and 34 patients who received paroxetine 40 mg/day.

Demographic and clinical characteristics of the 68 patients who entered the maintenance phase are given in Table 1. No statistically significant difference was found when these variables were compared between the 2 treatment groups.

Within the first month of treatment, 1 patient in the 20-mg/day group was excluded because of lack of compliance to the treatment. At the end of the 28-month follow-up trial, 17 (51.5%) of 33 patients in the half-dose condition had a single recurrence as compared with 8 (23.5%) of 34 subjects in the full-dose regimen. The Mantel-Cox survival analysis demonstrated a significant advantage for 40 mg of paroxetine compared with 20 mg of paroxetine ($\chi^2 = 5.56$, $p = .018$). Figure 1 shows the survival curves of subjects treated with the 2 different paroxetine doses. Among patients treated with paroxetine 20 mg, the cumulative probability of having no recurrence was 91.9% at month 5, 81.8% at month 10, 78.8% at month 11, 69.6% at month 12, 66.6% at month 13, 63.6% at month 17, 60.6% at month 18, 57.5% at month 20, 54.5% at month 21, and 48.5% at month 25. In the group of patients treated with 40 mg of paroxetine, the cumulative probability of remaining well was 96.8% at month 6, 93.7% at month 11, 91% at month 15, and 76.5% from month 17 to month 28.

No difference in sex, current age, age at onset, number of previous depressive episodes and duration of the index depressive episode was observed between subjects who suffered a recurrence and those who did not (Table 2).

Patients reported the presence of side effects only during the acute phase of treatment: abnormal ejaculation, 8%

Figure 1. Survival Curves of Subjects Treated With Either of 2 Paroxetine Doses: Cumulative Probability of Having No Single Recurrence

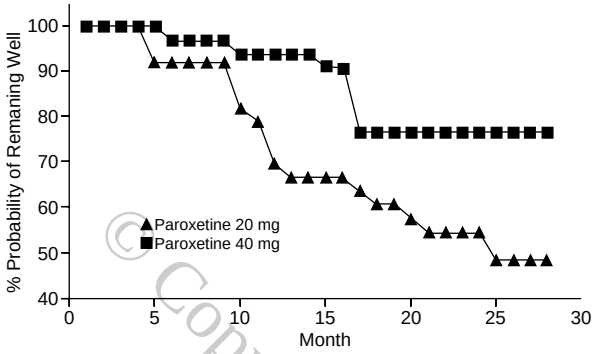

Table 2. Comparison of Clinical Characteristics Between Patients Who Suffered a Recurrence and Those Who Did Not During the 28-Month Follow-Up Period of Paroxetine Treatment*

	Recurred (N = 25)		Nonrecurred (N = 42)	
Characteristic	Mean	SD	Mean	SD
Current age (y)	44.6	7.6	48.4	9.7
Age at onset (y)	38.4	7.0	40.9	7.9
Number of episodes	5.7	2.6	6.7	2.4
HAM-D score at index episode	26.9	1.8	26.6	1.4
Duration of index episode (wk)	8.0	2.5	8.8	2.6

*Male/female ratios: recurred = 8/17, nonrecurred = 15/27. No statistical difference was found between groups (chi-square test for sex; Student t test for other variables). One patient was excluded within the first month because of lack of compliance.

(percentage corrected for gender); headache, 7%; anxiety, 4%; somnolence, 4%; and sweating 3.5%. These side effects were of moderate or mild intensity and disappeared spontaneously during the acute or the continuation treatment phase.

DISCUSSION

Previous investigations have already demonstrated the efficacy of paroxetine in preventing relapses and/or recurrences when compared with placebo.[10,12] It has also been reported that paroxetine is comparably effective, but more easily tolerated than the reference comparator imipramine in the long-term treatment of depression.[9,10]

The current investigation was designed to test the efficacy of different therapeutic doses of paroxetine in preventing recurrence in those patients whose paroxetine treatment led to remission and to recovery of the initial episode of depression.

All the patients included in this study were hospitalized during the acute phase because of the severity of the depressive episode. Considering that severely depressed patients may need a higher antidepressant dose to achieve response and that a more pronounced therapeutic effect was obtained with doses of paroxetine higher than the standard 20 mg,[19,20] we chose a paroxetine regimen reaching 40 mg within 2 weeks.

In our study design, the response criterion needed to be maintained during the 4-month continuation period before the start of the test of prophylactic efficacy. Paroxetine proved to be effective in consolidating the response to acute treatment. In fact, the number of relapses (3 [4.2%] of 72 patients) compares favorably with that obtained by Montgomery and Dunbar[12] in a placebo-controlled study (3% for paroxetine and 19% for placebo). During the further 28 months (maintenance period), we found that paroxetine 40 mg was highly efficacious in preventing recurrences, while patients treated with paroxetine 20 mg showed a higher recurrence rate. The better outcome of patients treated with paroxetine 40 mg compared with paroxetine 20 mg agrees with early reports showing greater efficacy of higher doses of antidepressants.[15,21–23]

There is evidence suggesting that the same dose of antidepressant that the patients responded to in the acute treatment phase should be continued long term.[6] In the open part of this study, all patients achieved 40 mg of paroxetine. Since lower doses have not been tested in acute patients, it is possible that 20 mg of paroxetine may be an effective maintenance dose in patients whose depression responds to 20 mg. On the other hand, in our study, it appears that the response to long-term treatment is strictly related to the dose of the prophylactic agent administered since, later in the study, the regimen of paroxetine 20 mg continued to be associated with a poor outcome, and paroxetine 40 mg continued to be efficacious in the longer term.

It has been reported that some SSRIs are efficacious in preventing recurrences at a dose lower than that used to treat the acute episode.[12–14,24] Considering our results, which suggest that paroxetine 40 mg is more effective than paroxetine 20 mg to treat patients who have a high risk of recurrence of depressive episodes, we can say with confidence that prophylactic efficacy should be examined on an individual basis rather than assumed as a class effect.

Drug names: fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), paroxetine (Paxil), sertraline (Zoloft).

REFERENCES

1. Judd LL. Mood disorders in the general population represent an important and worldwide public health problem. Int Clin Psychopharmacol 1995; 10(4, suppl):5–10
2. Thase ME. Long-term treatments of recurrent depressive disorders. J Clin Psychiatry 1992;53(9, suppl):32–44
3. Keller MB, Lavori PW, Lewis CE, et al. Predictors of relapse in major depressive disorders. JAMA 1983;250:3299–3304
4. Prien RF, Kocsis JH. Long-term treatment of mood disorders. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995:1067–1079
5. Anderson A, Tomenson BM. The efficacy of selective serotonin reuptake

inhibitors in depression: a meta-analysis of studies against tricyclic antidepressants. J Psychopharmacol (Oxf) 1994;8:238–249
6. Montgomery SA. Efficacy in long-term treatment of depression. J Clin Psychiatry 1996;57(2, suppl):24–30
7. Montgomery SA, Dufour H, Brion S, et al. The prophylactic efficacy of fluoxetine in unipolar depression. Br J Psychiatry 1988;153(3, suppl): 69–76
8. Doogan DP, Caillard V. Sertraline in the prevention of depression. Br J Psychiatry 1992;160:217–222
9. Christiansen PE. Paroxetine and imipramine in the treatment of depressed patients in psychiatric specialist practice. Nord J Psychiatry 1992;46(27, suppl):33–39
10. Claghorn JL, Feighner JP. A double-blind comparison of paroxetine with imipramine in the long-term treatment of depression. J Clin Psychopharmacol 1993;13(2, suppl):23–27
11. Duboff EA. Long-term treatment of major depressive disorder with paroxetine. J Clin Psychopharmacol 1993;13(2, suppl):28–33
12. Montgomery SA, Dunbar G. Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. Int Clin Psychopharmacol 1993;8:189–195
13. Franchini L, Zanardi R, Gasperini M, et al. Fluvoxamine and lithium in long-term treatment of unipolar subjects with high recurrence rate. J Affect Disord 1996;38:67–69
14. Franchini L, Gasperini M, Perez J, et al. A double-blind study of long-term treatment with sertraline or fluvoxamine for prevention of highly recurrent unipolar depression. J Clin Psychiatry 1997;58:104–107
15. Frank E, Kupfer DJ, Perel JM, et al. Comparison of full-dose versus half-dose pharmacotherapy in the maintenance treatment of recurrent depression. J Affect Disord 1993;27:139–145
16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
17. Hamilton MA. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
18. Cox DR. Regression models and life-tables. Journal of the Royal Statistical Society 1981;34:187–220
19. Montgomery SA. The advantages of paroxetine in different subgroups of depression. Int Clin Psychopharmacol 1992;6(4, suppl):91–100
20. Tignol J, Stoker MJ, Dunbar GC. Paroxetine in the treatment of melancholia and severe depression. Int Clin Psychopharmacol 1992;7:91–94
21. Rouillon F, Serrurier D, Miller HD, et al. Prophylactic efficacy of maprotiline on unipolar depression relapse. J Clin Psychiatry 1991;52:423–431
22. Peselow ED, Difiglia C, Fieve RR. Relationship of dose to antidepressant prophylactic efficacy. Acta Psychiatr Scand 1991;84:571–574
23. Robinson DS, Lerfald SC, Bennett B, et al. Continuation and maintenance treatment of major depression with the monoamine oxidase inhibitor phenelzine: a double-blind placebo controlled discontinuation study. Psychopharmacol Bull 1991;27:31–39
24. Terra JL, Noel F. Fluvoxamine effective in preventing recurrence of major depression [abstract]. Eur Neuropsychopharmacol 1996;6(4, suppl):65