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ORIGINAL PAPER

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Fluoxetine once every third day in the treatment of major depressive disorder

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Abstract *Objective* Fluoxetine and its active metabolite norfluoxetine have long half-lives. We postulate that, owing to the long elimination half-life and the time to reach steady-state level in plasma is nearly four weeks, patients diagnosed with major depressive disorder might be treated with fluoxetine taken once every third day, after being treated initially during 4 weeks with daily doses of fluoxetine. *Methods* In this open label, 12-weeks, randomized, prospective study, patients diagnosed with DSM-IV major depressive disorder were randomly assigned into 1 of 3 treatment groups. Thirty-four patients took 20 mg and 32 patients took 40 mg of fluoxetine daily throughout the study. Twenty-nine patients had been taking 20 mg of fluoxetine daily for 4 weeks of the study initially, and then were switched to 20 mg fluoxetine once every third day regime. The severity of depression was assessed by Hamilton Depression Rating Scale (HDRS) and Clinical Global Impressions-Severity Scale (CGI-S). Response was defined as a 50 % or greater reduction of the baseline HDRS total score. After defining a strict criterion of relapse, time to relapse was estimated using survival analyses (Kaplan-Meier method). *Results* The repeated measures analysis of variance (ANOVA) of HDRS found a significant time effect ($F = 464.04$, $df = 1.00$, $p < 0.001$), but no significant group effects ($F = 0.84$, $df = 2.00$, $p = 0.433$) from baseline through week 12. The proportion of responders was not significantly different between the treatment groups at the endpoint. Survival analyses showed, however, a significant delayed mean time to relapse in patients treated with 40 mg of fluoxetine daily compared to either patients treated with 20 mg of fluoxetine daily or 20 mg fluoxetine once every third day. The mean times to relapse were 79.8, 70.8, and 70.5 days, respectively. Fluoxetine was associated with some adverse events in 46.3 % of patients. The most frequently occurring adverse event was insomnia. *Conclusion* It is proposed that either every third day or daily dosing with the same dose of fluoxetine could treat the patients with major depressive disorder during the acute and continuation period of treatment. Nevertheless, higher daily dose of fluoxetine has a reduced relapse rate compared to that of the lower daily dose.

Key words depression · fluoxetine · once every third day · interrupted dosing · less frequent dosing

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Introduction

Fluoxetine may allow for less frequent than once daily dosing because of the long elimination half-lives of fluoxetine and norfluoxetine [1]. Its major metabolite, norfluoxetine, possesses fluoxetine's antidepressant efficacy and a half-life of 7 to 15 days, suggesting the possibility of non-standard dosing strategies. Norfluoxetine demonstrates approximately near equal selective uptake inhibition of both serotonin and noradrenaline [22]. With this point of view, several different dosage regimes have been tested in the treatment of depression with fluoxetine. Rickels et al. reported that there was no difference between a once daily and a twice daily dosage regime with fluoxetine [20]. Moreover, no significant relationship was found between response and plasma levels of fluoxetine [18] or between HDRS scores and serum concentrations of fluoxetine, norfluoxetine or fluoxetine + norfluoxetine [5]. Interestingly, the results of a study which compared a once a week dosage regime of fluoxetine with a daily regime found that the weekly treatment was apparently effective [18]. Montgomery et al. reported in this study that the plasma levels of nor-

fluoxetine achieved in the intermittent once-weekly dosage regimen group were obtained in the same range as the responders in the daily regimen group. Therefore, the authors emphasized that the apparent efficacy of the once-weekly dosage regime with very low levels of fluoxetine suggests that fluoxetine contributed very little to response and that the active pharmacological agent is norfluoxetine [18]. Recently, the results from double-blind, placebo controlled and randomized studies in depressed patients who had previously responded to fluoxetine 20 mg daily for short-term treatment supported the hypothesis that the antidepressant effect of fluoxetine might be maintained during weekly dosing and could be comparable to that observed during continuation treatment with fluoxetine taken daily [6, 21]. Open-labeled studies demonstrated that patients with depression who were symptomatic but who had not previously received antidepressants [13] or who had begun antidepressant treatment de novo, also benefited from once weekly treatment with enteric-coated fluoxetine [4]. Other studies have suggested that the weekly or interrupted dosing regimes might be suitable for the treatment of different psychiatric disorders. For example, in a double-blind study with a large sample, enteric-coated fluoxetine 90 mg given twice weekly was found to be effective for the treatment of premenstrual dysphoric disorder [17], and in a study including ten patients, it was reported that the once weekly regimen with fluoxetine serves an alternative method for maintenance treatment of panic disorder [8]. A twice weekly regime with fluoxetine for management of antidepressant-induced mania in bipolar depression was also reported in a case report [15].

On the other hand, compliance plays a permissive role in the success or failure of any treatment, for it is a necessary, although not sufficient condition for therapeutic success. Despite the efficacy of many antidepressant medications, it has been observed that patients commonly do not take antidepressants for an adequate length of time. One factor contributing to undertreatment is non-adherence to the recommended treatment regimen, including both missed doses and early discontinuation of medication [14, 16]. It was reported that the compliance to once weekly fluoxetine treatment was higher than compliance to once daily fluoxetine (85.9 % vs. 79.4 %, respectively) [7]. Moreover, while compliance declined significantly in the once daily fluoxetine group, group compliance remained unchanged from baseline in the patients treated with fluoxetine once weekly.

It is also clear that a once weekly or a less than daily dosing regimen may allow for considerable cost savings. Across 5 years of treatment, it has been estimated that cost savings with a once weekly 60 mg dose in comparison with daily 20 mg of fluoxetine approaches $2,700 [5]. Taken together, use of fluoxetine on a less than daily dosing schedule is of importance both from a patient compliance and acceptance standpoint and from a cost standpoint.

As the elimination half-life of fluoxetine is 1 to 3 days [22] and the time to reach steady state in blood is minimally four weeks [12], it would appear that clinical efficacy could be achieved with once every third day dosing after 4 weeks of once daily fluoxetine treatment. The aim of this study was to compare the antidepressant efficacy of standard dose (20 mg daily), dose optimization (40 mg daily), and once every third day of fluoxetine 20 mg regimes in the both acute and continuation phase of treatment.

Methods

Subjects

Included in the study sample were psychiatric outpatients of either sex, aged between 18 and 60 years. One hundred and twenty patients (60 male and 60 female) with a diagnosis of unipolar major depressive disorder [3], but without a psychotic features or a comorbid axis I disorder as assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders [10] by the clinicians were studied. The study was performed with patients who applied to psychiatric outpatient clinics for the treatment. After complete description of the study to the subjects, written informed consent was obtained. The subjects had been medication free for at least 10 days and had undergone a thorough medical examination to rule out other illnesses. Patients were given a physical examination, laboratory tests and ECG examination and patients with any physical condition that could pose as a risk were excluded. Other exclusion criteria included medical or neurological illnesses, pregnancy, breastfeeding, and substance abuse within 1 year, lifetime history of substance dependence (other than nicotine), comorbid current psychiatric disorder, and those with a clear suicide risk.

Treatment

This 12-week, randomized and open-label study was designed to compare the efficacy and safety of different doses of fluoxetine (20 or 40 mg daily) treatment and fluoxetine 20 mg once every third day. Patients meeting the entry criteria were then randomly assigned to 1 of 3 treatment groups. The study consisted of 2 periods. The first period was a four weeks open-label acute treatment phase in which patients received 20 (Group A and B) or 40 (Group C) mg of fluoxetine daily. After 4 weeks, patients receiving 20 mg of fluoxetine daily (Group A) received 20 mg of fluoxetine once every third day until the end of study in open-label design (Study period II, Fig. 1). Nevertheless, the dosage regimes of other treatment groups (B and C) were unchanged and continued to receive their medication during period II. For all treatment groups, fluoxetine was given as a single dose in the morning.

Each subject was aware of her/his specific treatment and expected side effects. At each assessment, adverse events were recorded (including onset, duration, and severity). These were detected by observation, examination or could be reported by the patient either spontaneously or in response to the open question, "Do you feel different in any way since starting the treatment or since the last visit?" Multiple episodes of the same complaint were counted only once, although rated at the greatest level of severity. Additional psychotropic medication or treatment was prohibited, but the use of alprazolam at night for sleeping was allowed if needed. Patients received no electroconvulsive therapy or structured psychotherapy during the study period. No dietary restrictions were imposed.

Assessments were performed at the end of weeks 2, 4, 6, 8, and 12 using the HDRS, 17-item version [11], and adverse events section of the form. Severity of major depressive disorder was measured with HDRS. CGI-S [19] was performed at the end of the week 4, 8, and 12. Clinicians rated global severity by means of the CGI-S, ranging from 1 (not at all ill) to 7 (extremely ill).

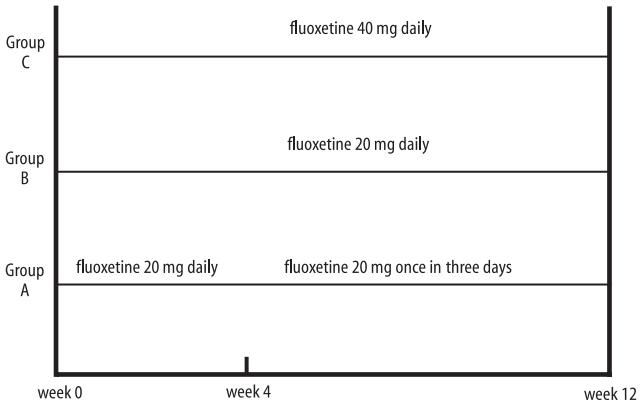

Fig. 1 Study design

A response to treatment was defined in two items: 1) a reduction in score equal to or greater than 50 % on the HDRS, or 2) a CGI-S scale rating of 1 (not at all ill) or 2 (borderline illness).

Additionally, we defined a strict relapse criterion, which was used by survival analysis, for comparing and assessing the efficacy of the treatments. Only the patients who had had sustained response (according to item 1) during the study period II were accepted as non-relapsed. Patients who met the criterion of response according to item 1 at the end of the study period I (week 4), and then if he or she did not meet such a response at any assessment during study period II (from week 4 to 12), even the patients who showed a response on all remaining assessments were considered to have experienced a relapse.

Analyses

Primary efficacy measures were the changes in the HDRS score with treatment and the response at the endpoint. After Mauchly's test of sphericity, a repeated-measures ANOVA with time as the covariate, was performed on HDRS score. The lower-bound epsilon value was used for multiplying the numerator and denominator degrees of freedom in the F test. The time to relapse was tested over the period II using survival analysis (Kaplan-Meier method). Equality of survival distributions and mean times to relapse among the treatment groups were compared with the Breslow test. Differences between continuous variables were assessed using the One Way ANOVA test. Those between categorical variables were assessed using Pearson chi-square test or Fisher's exact test. The Kruskal-Wallis One Way ANOVA test was used for assessing non-parametric data. All *P* values are 2-tailed, and statistical significance was set at the 5 % level ($p \leq 0.05$).

Results

Demographics

A total of 120 patients were enrolled; 25 patients dropped out within the first 2 weeks of the study due to adverse events. Of the 120 patients entering the 12-week treatment period, 72.5 % of the fluoxetine 20 mg once every third day patients (Group A), 85 % of the fluoxetine 20 mg daily patients (Group B), and 80 % of the fluoxetine 40 mg daily patients (Group C) completed the whole 12-week treatment period. There was no drop out after the first two weeks of study. Therefore, for all statistical analyses, the remaining 95 patients (50 females, 45 males, with a mean age of 34.8 ± 8.5) were evaluated in this study. There were no significant differences on baseline demographic measures or on baseline HDRS or CGI-S scores among the 3 randomized groups as seen in Table 1.

Efficacy of the treatments

The repeated measures ANOVA for HDRS during period I identified no significant group effects ($F = 1.30$, $df = 2.00$, $p = 0.276$). However, a significant time effect (from baseline visit through week 4) was observed on HDRS score ($F = 69.27$, $df = 1.00$, $p < 0.001$). For period II, the repeated measures ANOVA identified no significant group effects for HDRS scores ($F = 0.76$, $df = 2.00$, $p = 0.470$). Again, a significant time effect was found on HDRS score ($F = 440.45$, $df = 1.00$, $p < 0.001$) at period II as seen in Fig. 2. As a whole, repeated measures ANOVA found significant reduction in the HDRS scores throughout the study ($F = 464.04$, $df = 1.00$, $p < 0.001$), but no group effect ($F = 0.84$, $df = 2.00$, $p = 0.433$).

The response rates of treatment groups were not significantly different in both parameters of efficacy (percentage of 50 % reduction of HDRS score and CGI-S score 2 or lower) at the endpoint of study. Statistical assessments and the percentages of responders are given in Table 2.

Table 1 Baseline analyses

Variable	20 mg of fluoxetine every third day	20 mg of fluoxetine daily	40 mg of fluoxetine daily	Total	Statistic and *P* Value
No. of subjects	29	34	32	95	–
Female sex, %	55.2	50	53.1	52.6	$\chi^2 = 0.173$, df 2, $p = 0.917$[a]
Age, mean (SD), y	34.3 (9.4)	35.6 (7.7)	34.5 (8.6)	34.8 (8.5)	$F = 0.219$, df 2, $p = 0.804$[b]
Currently married, %	55.2	55.9	59.4	56.8	$\chi^2 = 0.129$, df 2, $p = 0.937$[a]
HDRS score, mean (SD)	20.6 (7.1)	23.4 (7.5)	20.7 (6.8)	21.6 (7.2)	$F = 1.678$, df 2, $p = 0.192$[b]
CGI-S score, mean (SD)	4.5 (1.1)	4.6 (0.9)	4.4 (1.0)	4.5 (1.0)	$\chi^2 = 0.631$, df 2, $p = 0.730$[c]
No. of previous episodes, mean (SD)	2.1 (0.9)	2.0 (0.9)	1.8 (0.9)	2.0 (0.9)	$\chi^2 = 3.155$, df 2, $p = 0.206$[c]
No. of first episode patients (%)	6 (20.7)	11 (32.4)	14 (43.8)	31 (32.6)	$\chi^2 = 3.682$, df 2, $p = 0.159$[a]

[a] P values were obtained with Pearson Chi-Square Tests; [b] P values were obtained with One-Way Analysis of Variance; [c] P values were obtained with Kruskal-Wallis Tests

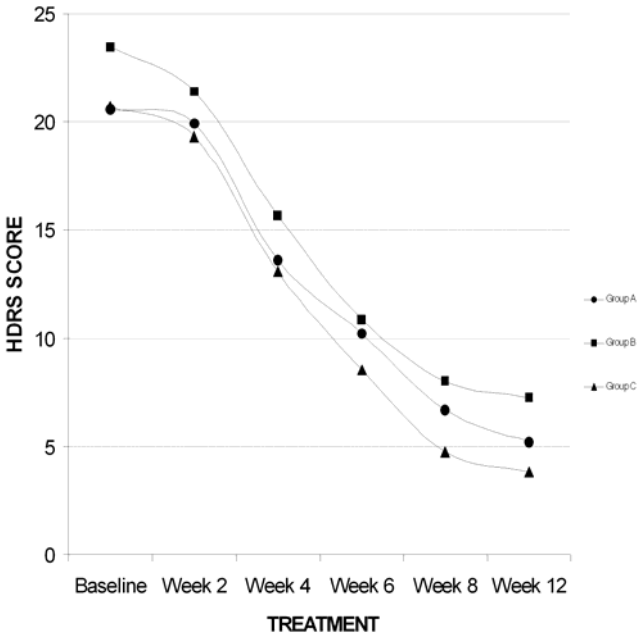

Fig. 2 Changes in HDRS scores throughout the study. **Group A:** 20 mg of fluoxetine once every third day; **Group B:** 20 mg of fluoxetine daily; **Group C:** 40 mg of fluoxetine daily

The mean times to relapse of the treatments were as follows: 79.8 days for the fluoxetine 40 mg daily group, 70.8 days for the fluoxetine 20 mg daily group, 70.5 days for the fluoxetine 20 mg once every third day. Comparisons revealed that the 40 mg fluoxetine daily treated patients were less likely to relapse than either the 20 mg fluoxetine daily or the 20 mg fluoxetine once every third day treated patients (Table 3). Cumulative relapse rates are also shown in Table 3. The difference between the percentages of patients relapsing for the 20 mg fluoxetine daily group compared with the 20 mg fluoxetine once every third day was not statistically significant (Breslow test 0.00, df = 1, p = 0.951).

Adverse events

Frequency of any emergent adverse events (any adverse events which started on or after the first day of study medication, but present any time after the 4th week – period II) reported by the patient or detected by the observer were as follows: for Group A 44.8 % (N = 13), Group B 44.1 % (N = 15), Group C 50 % (N = 16). This difference between groups was not found to be statistically significant ($\chi^2 = 0.267$, df = 2, p = 0.875). In total, 46.3 % of the patients experienced at least one treatment emergent adverse event during period II. The most frequently occurring treatment emergent adverse events were insomnia (23.2 %), nausea (20 %), sweating (16.8 %) in the whole group of patients. There were no significant differences in the proportions of these adverse events among the treatment groups. Most patients reported multiple adverse events, most being rated as of mild or moderate severity. No serious adverse effects such as central serotonin syndrome were observed throughout the study. Nevertheless, the comparisons which were made by 2 x 2 tables revealed that the rate of restlessness in the fluoxetine 40 mg daily group (25 %) significantly exceeded that of the fluoxetine 20 mg daily group (2.9 %) and that of the fluoxetine 20 mg once every third day (3.4 %) in period II (Fischer's exact test p = 0.012 and p = 0.028, respectively). Vomiting is significantly more

Table 2 Percentage of responders

	Week 4	Week 12
HDRS	Percentage of patients with at least 50 % reduction from baseline	Percentage of patients with at least 50 % reduction from baseline
Fluoxetine 20 mg once every third day, % (N)	96.6 % (28)	89.7 % (26)
Fluoxetine 20 mg daily, % (N)	100 % (34)	82.4 % (28)
Fluoxetine 40 mg daily, % (N)	93.8 % (30)	93.8 % (30)
p value[a]	NA	0.341
CGI-S	Percentage of patients with at least score of 2 on CGI-S scale	Percentage of patients with at least score of 2 on CGI-S scale
Fluoxetine 20 mg once every third day, % (N)	65.5 % (19)	86.2 % (25)
Fluoxetine 20 mg daily, % (N)	44.1 % (15)	79.4 % (27)
Fluoxetine 40 mg daily, % (N)	59.4 % (19)	93.8 % (30)
p value[a]	0.206	0.238

[a] *P* values were obtained with Pearson Chi-Square Tests. *NA* Not Applicable

Table 3 Mean time for relapse[1]

	Mean time to relapse (day)	Cumulative relapse rate (%, N)	20 mg fluoxetine once every third day	20 mg fluoxetine daily	40 mg fluoxetine daily
20 mg fluoxetine once every third day	70.50	31.03 (9)	NA	p = 0.951	p = 0.039
20 mg fluoxetine daily	70.82	32.35 (11)	p = 0.951	NA	p = 0.035
40 mg fluoxetine daily	79.80	9.37 (3)	p = 0.039	p = 0.035	NA

[1] The mean times to relapse and cumulative relapse rates estimated by Kaplan-Meier Survival Analysis. P values were obtained with Breslow test, which was used to test the equality of the survival distributions and mean times to relapse among the treatment groups. *NA* Not applicable

frequent in the fluoxetine 40 mg daily group (12.5 %) than the fluoxetine 20 mg daily group (0 %) (Fischer's exact test p = 0.05). There were no significant differences in the other adverse events (such as insomnia, nausea, sweating, sexual dysfunction, trembling, decreased appetite, skin eruptions, palpitation, diarrhea, and headache) among the treatment groups as assessed by 2 x 2 comparisons at period II.

Discussion

All three treatments led to a significant improvement in depression severity assessed by HDRS and CGI-S, throughout the study. Furthermore, the statistically significant increase in the number of responders among the three treatment groups over the 12-week study period indicated their antidepressant efficacy. The results of this study also demonstrate that treatment with fluoxetine 40 mg daily has a lower relapse rate than either fluoxetine 20 mg daily or fluoxetine 20 mg once every third day. However, it is important that there were no significant differences between continuous treatment with 20 mg of fluoxetine daily and interrupted treatment with 20 mg of fluoxetine once every third day regime after being initially treated with 20 mg of fluoxetine daily for 4 weeks, in improvement of depression severity, response, and relapse rates.

The results of the present study may also most likely be related to the unique pharmacokinetic profile of fluoxetine. In 1990, Montgomery et al. provided the initial demonstration that weekly dosing of fluoxetine might be an effective strategy for treatment of major depression [18]. In that study, Montgomery et al. found that 80 mg of fluoxetine once a week was effective for the acute treatment of major depression. This finding has been supported with double-blind, placebo controlled studies [6, 21] as well as recent open label studies [4, 13]. The present study corroborates that fluoxetine may allow for less frequent than once daily dosing, which is concordant with previous studies [4, 6, 13, 18, 21], although enteric-coated formulation [4, 13, 21] and higher doses of fluoxetine were used in the mentioned studies [4, 6, 13, 18, 21]. Establishing the correct or optimal dose for an antidepressant with a long half-life is an important but difficult task. Data suggest strongly 20 mg of fluoxetine a day as the optimal dose in the treatment of depression [2, 9, 23]. However, in a fixed dose study, which included 363 patients, assessed response to dosages 5 mg, 20 mg and 40 mg of fluoxetine compared to placebo found that the response in all three-treatment groups was not significantly different [24]. In other words, this study failed to find a lower limit for efficacy. This may be related to pharmacokinetics of fluoxetine, however, the mentioned study had been carried out only for six weeks, and neither fluoxetine nor norfluoxetine blood levels were obtained. Concordant with this result, a later study reported that no significant correlations have been observed between HDRS scores and serum concentrations of fluoxetine, norfluoxetine or fluoxetine + norfluoxetine [5].

The long half-lives of both fluoxetine and norfluoxetine may be seen as an advantage for four reasons: 1) interrupted dosage regimes such as once or twice weekly, 2) improved compliance, 3) withdrawal symptoms are lessened, and 4) the treatment costs are lower.

A less frequent than the once daily dosing strategy of fluoxetine (once or twice weekly) may have the potential of minimizing drug interactions. Fluoxetine has strong inhibitor effects on several hepatic enzymes such as P450 2D6, 1A2 and 3A4 [1, 12]. These enzymes are responsible for metabolizing a number of drugs such as tricyclic antidepressants, alprazolam, carbamazepine and phenytoin. This inhibition may cause increased side effects, intoxication, dangerous drug-drug interactions and psychomotor decrement [12]. Since the inhibitor effect of fluoxetine on the hepatic enzymes is dose related; presumably, the smaller dose of fluoxetine in a once or twice weekly dosing strategy would diminish the chance of such interactions. At least, it would diminish the serious adverse reactions or drug-drug interactions. Furthermore, a clinician may expect a significant decrease in the frequencies of adverse events compared to those associated with the once daily dosing strategy, in particular gastrointestinal intolerance might be lessened. Nevertheless, we did not observe such a significant difference in any adverse effect between the 20 mg of fluoxetine daily and once every third day regime. The usage of the immediate release (currently marketed) formulation of fluoxetine in the present study may be a reason for obtaining the similar rates of gastrointestinal adverse effects in patients treated with both 20 mg of flu-

oxetine given once every third day and daily. Also, it was not surprising that the treatment emergent adverse event of restlessness was found significantly higher in the 40 mg of fluoxetine daily group than both the 20 mg of the fluoxetine daily group and the 20 mg of the fluoxetine once every third day.

The findings of this study accord with pharmacokinetics of fluoxetine generally. The new proposed dosing regimen in the present study seems to have a pharmacokinetic base. To our knowledge, this is the first study that examines the efficacy of fluoxetine 20 mg once every third day. Although our experience reported here with short-term treatment of patients using fluoxetine 20 mg once every third day has been positive, the results of the present study should be interpreted with caution since we could not control the compliance and antidepressant plasma levels. Moreover, the study is not blinded, raising the possibility of measurement bias which may contribute to both "group" and "time" effects of the study. Short duration of follow-up and non-standard methods of adverse event recording may also weaken the study's ability to evaluate effectiveness of the treatments. Meanwhile, it should be noted as revealed in the present study that the higher daily dose has a reduced relapse rate than that of lower daily dose of fluoxetine (40 mg versus 20 mg). For this reason, it would also be useful to include patients taking 40 mg fluoxetine every third day as a control group to reveal the less frequent than daily dosing and improvement relation. However, this study clearly demonstrated that the same amount of fluoxetine can be administered either daily or every third day. The results of this study suggest that the 20 mg of fluoxetine once every third day dosing regime may be an option, which is effective, safe and economic, in both acute and continuation treatment of depression after four weeks of primary treatment with 20 mg of fluoxetine daily. However, further studies are needed to confirm the findings.

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