Exploring Treatment Alternatives: Weekly Dosing of Fluoxetine for the Continuation Phase of Major Depressive Disorder

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Antidepressant medications are typically taken on a daily basis owing to both tradition and the pharmacokinetics of these agents. Because fluoxetine and its primary metabolite norfluoxetine have long half-lives and flat dose-response curves, we examined the tolerability of a weekly dose and its equivalence to daily dosing during the continuation phase of treatment for major depressive disorder (MDD). Open-label treatment with 20 mg of fluoxetine daily for 7 weeks began with 114 subjects. Subsequently, 70 subjects who met criteria for response were randomly assigned in a double-blind design to 1 of 3 treatment groups (20 mg of fluoxetine daily [N = 21], 60 mg of fluoxetine weekly [N = 28], or placebo [N = 21]) and followed for 7 weeks. No statistically significant differences were observed in several clinical measures. Tolerability in the 3 groups was similar; there was no difference in dropout rates or adverse events. Hence, weekly dosing of fluoxetine appears to be well tolerated and possibly as effective as daily dosing in the treatment of MDD. It is proposed that less frequent dosing could potentially benefit patients by enhancing adherence and minimizing the risk of side effects and drug-drug interactions.
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Depression is very often a chronic, recurrent illness. As in many chronic illnesses, adherence to long-term treatment can be problematic. Consider these examples from other areas of medicine. Patient A is diagnosed with a duodenal ulcer and is prescribed a course of therapy. He completes several weeks of treatment but stops upon symptomatic recovery. The end result is often relapsing of symptoms. If disease recurs, treatment is reinitiated, usually with good response. Patient B is treated for active pulmonary tuberculosis and is given a course of acute treatment for symptom relief followed by ongoing treatment to prevent recurrence of the illness. The patient feels better after a few months and adherence to therapy gradually declines. The symptoms recur and now are potentially worsened by the selection of a more resistant strain of organism. Now consider Patient C with major depression. She is expertly diagnosed by her primary care physician and receives an appropriate medication at an appropriate dose. The patient has a complete response to treatment and after refilling the prescription once, she stops the medication on her own. Patient C experiences a relapse, possibly one of many to come.

These clinical scenarios are familiar to all who practice medicine and are the source of great frustration and consternation. As recently as a decade ago, one of the greatest problems in treating depression was lack of recognition of the disorder. However, as both recognition and treatment of depression have improved, the problem of long-term adherence to treatment has emerged as a serious threat to the well-being of depressed persons. These individuals frequently resemble the ulcer patient who interrupts therapy prematurely and subsequently experiences a flare-up in symptoms. Many times the treatment can be reinstated, often with the originally effective drug. However, major depression too often behaves as in the scenario of the tuberculosis patient. The relapsed patient resumes treatment, but the original robust response is not seen and other treatments must be considered. A golden opportunity to optimally treat the depression for an adequate duration has been lost.

One potential way to improve long-term adherence in major depression is to present alternative, staged treatment methods. Long-term compliance with a daily medication regimen is difficult to maintain, particularly in those con-

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ditions that, when well treated, are asymptomatic. Sustained long-term treatment in schizophrenia is often facilitated with a depot formulation of a neuroleptic. Unfortunately, no "depot" antidepressant has been available. However, norfluoxetine, the main metabolite of fluoxetine, has characteristics that fulfill this role. Upon routine daily dosing of fluoxetine during the initial treatment of a major depressive episode, the blood concentration of norfluoxetine gradually rises and its half-life extends until it reaches 15 days. This half-life could enable less frequent dosing of fluoxetine, e.g., at weekly intervals. In addition to the blood level of norfluoxetine remaining stable over this dosing interval, the long half-life has another distinct compliance advantage. If the individual misses a dose by a day or 2, there is very little overall fluctuation in blood level. This flexibility in dosing could facilitate and encourage the individual to continue the course of therapy.

Intrigued by an early report of once-weekly dosing of fluoxetine, we decided to test the hypothesis that fluoxetine's pharmacokinetic properties could be utilized to develop the first "depot antidepressant." This report describes further analyses of a study of weekly fluoxetine for the continuation phase of treatment of major depression.

METHOD

Subjects and Procedure

Subjects were recruited from clinics of the University of Nebraska Department of Psychiatry and through newspaper advertisements for this institutional review board–approved study. Following an explanation of the study, written informed consent was obtained. Subjects (N = 114, 68 women and 46 men) diagnosed with unipolar major depressive disorder (MDD) who had not received antidepressants or other psychoactive medications for at least 2 weeks and who had Hamilton Rating Scale for Depression (HAM-D)[1] scores of 18 or above entered a 7-week open-label trial of fluoxetine. Upon completion of the open-label trial, 70 subjects (47 women, mean age = 42.6 years; 23 men, mean age = 42.4 years) with HAM-D scores of 12 or less were randomly assigned into the double-blind phase. The HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS),[2] and Hopkins Symptom Checklist (SCL-90)[3] were administered, a blood sample and vital signs were taken, and reports of side effects and other medical problems were recorded at clinic visits. Subjects also rated sexual health as a function of sexual interest, enjoyment, arousal, orgasmic ability, and erectile functioning (males) on a scale of 1 to 4 (data were scored for each subject as an average of the ratings). If a subject dropped out of the study, the reason for termination was recorded. Following the initial visit of the open-label trial, subjects were seen at 1, 3, and 7 weeks. At the end of the open-label phase, subjects meeting the response criterion were randomly assigned into the double-blind phase. Subsequently, subjects were seen at 1, 2, 3, and 7 weeks after randomization. At each double-blind visit, subjects were asked to guess which treatment they were receiving.

Treatments

During the open-label trial, subjects received 20 mg of fluoxetine daily. Those qualifying for double-blind treatment were randomly assigned to 1 of 3 groups: 20 mg of fluoxetine daily (N = 21), 60 mg of fluoxetine once weekly (N = 28), or placebo (N = 21). All medication was dispensed in identical-appearing capsules. For 6 days per week of double-blind treatment, capsules contained either lactose (in the placebo and the 60-mg fluoxetine weekly groups) or fluoxetine (in the 20-mg fluoxetine daily group). On the seventh day of each week, all subjects received 3 capsules, containing as follows: lactose in all capsules, placebo group; lactose in 2 capsules and 20 mg of fluoxetine in 1 capsule, 20-mg fluoxetine daily group; and 20 mg of fluoxetine in all capsules, 60-mg fluoxetine weekly group. At each clinic visit, subjects took the capsules after the clinical evaluations. Medications were dispensed in a cassette with slots for each day of the week. Subjects were asked to return the cassettes at each clinic visit as a check for adherence to the protocol.

Blood Samples and Assays

A 20-mL blood sample was obtained at each clinic visit. After the blood clotted at room temperature, serum was separated by centrifugation into 3-mL aliquots of serum that were frozen at –40°C (–40°F)for subsequent high performance liquid chromatography (HPLC) analysis. Serum concentrations of fluoxetine and norfluoxetine were assessed by a modified HPLC analysis based upon the work of Wong et al.,[4] as previously described.[5] The day-to-day precision, obtained from the quality control results over an 8-month period, found the coefficient of variation for fluoxetine to be 5.3% and for norfluoxetine, 9.9%.

Data Analysis

A repeated-measures analysis of variance (ANOVA) with time as the covariate was performed on the HAM-D, MADRS, SCL-90, sexual functioning, and serum fluoxetine and norfluoxetine levels. The Fisher exact test compared correct versus incorrect treatment guesses across groups. Dropout rate across the groups was compared by the Kaplan-Meier survival analysis. The Pearson product moment correlation was used to assess the relationships between MADRS scores and fluoxetine, norfluoxetine, and fluoxetine + norfluoxetine.

RESULTS

Approximately 80% of the subjects who entered the open-label phase met the criteria for randomization to the double-blind portion of the study. A total of 70 subjects

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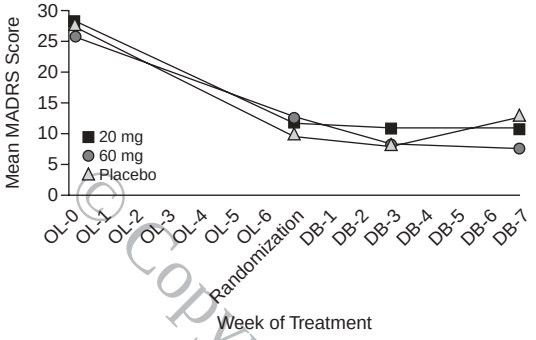
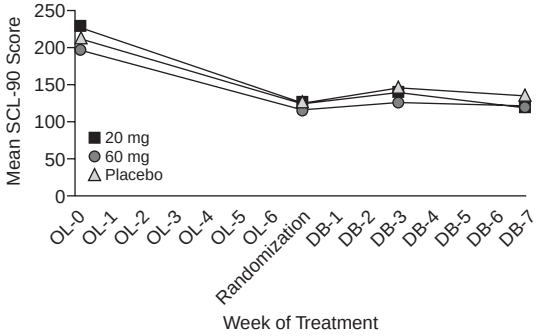
Figure 1. Mean Montgomery-Asberg Depression Rating Scale (MADRS) Scores From Beginning of Open-Label Treatment (OL) to Randomization and Through 7 Weeks of Double-Blind Treatment (DB)[a]



[a]Time is in weeks, with randomization at OL-7. Number of subjects per group by sex and mean age within groups were as follows: 20 mg of fluoxetine, N = 21 (14 women, 7 men), mean age = 42 years; 60 mg of fluoxetine, N = 28 (20 women, 8 men), mean age = 44 years; placebo, N = 21 (13 women, 8 men), mean age = 41 years.

Figure 2. Mean Hopkins Symptom Checklist (SCL-90) Scores From Beginning of Open-Label Treatment (OL) to Randomization and Through 7 Weeks of Double-Blind Treatment (DB)[a]



[a]Time is in weeks, with randomization at OL-7. Number of subjects per group by sex and mean age within groups were as follows: 20 mg of fluoxetine, N = 21 (14 women, 7 men), mean age = 42 years; 60 mg of fluoxetine, N = 28 (20 women, 8 men), mean age = 44 years; placebo, N = 21 (13 women, 8 men), mean age = 41 years.

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were followed to week 7 of randomization. The results of the HAM-D and blood fluoxetine and norfluoxetine levels have been reported elsewhere.[5,6]

The repeated-measures ANOVAs of the MADRS and SCL-90 during the open-label trial found no significant group effects. However, a significant visit effect (from baseline visit through randomization) was observed for both measures (MADRS, $F = 154.85$, $df = 2,67$; $p < .0001$; SCL-90, $F = 81.6$, $df = 2,67$; $p < .0001$; Figures 1 and 2). For the double-blind period (from randomization to week 7), the repeated-measures ANOVAs found no significant group effects for scores on the MADRS ($F = 0.36$, $df = 2,64$; $p = .7$) or the SCL-90 ($F = 0.59$, $df = 2,65$; $p = .56$). However, the visit effect from randomization to end of study was significant for MADRS score ($F = 5.1$, $df = 2,64$; $p < .001$) but not for SCL-90 score. Sexual health did not differ significantly among the treatment groups or across visits for the entire length of the study.

Kaplan-Meier survival analysis from randomization onward revealed no significant difference in dropout rates across groups ($\chi^2 = 2.34$, $p = .31$; –2 Log [LR]). Of the 19 subjects who terminated, 11 did so for lack of efficacy (placebo, N = 4; 20 mg/day, N = 4; 60 mg/week, N = 3). Fisher exact tests of patients' ability to correctly identify treatment assignment at study end revealed no significant difference across groups ($p = .47$). No significant correlations were observed at randomization or study end between MADRS scores and serum concentrations of fluoxetine ($r = 0.02$, $r = 0.07$), norfluoxetine ($r = 0.13$, $r = 0.3$), or fluoxetine + norfluoxetine ($r = 0.1$, $r = 0.23$), consistent with previous reports.[7–9]

Seventeen subjects were followed for 11 weeks after randomization (placebo, N = 4; 20 mg/day, N = 7; 60 mg/week, N = 6). The 2 fluoxetine groups at 11 weeks showed less depressive symptomatology than the placebo group, although statistically the groups did not differ.[6] In the subjects taking weekly fluoxetine, the blood levels of fluoxetine and norfluoxetine gradually declined. After a month, the fluoxetine levels were minimal while the norfluoxetine levels had fallen to approximately 50% of the original levels.[10]

DISCUSSION

In 1990, Montgomery et al.[11] provided the initial demonstration that weekly dosing of fluoxetine might be an effective strategy for major depression. 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 was not pursued until our initial report[6] demonstrated that weekly dosing showed promise as a treatment for the continuation phase of MDD.

While Montgomery's research involved the acute treatment phase, we think that weekly dosing of fluoxetine will most likely be used in the continuation and maintenance phases of MDD for several reasons. Foremost is the expectation of ill patients that they must take some form of medication each day. Even if further research confirms Montgomery's findings about acute treatment, we believe considerable effort and education would be necessary to overcome the bias for daily medication. As Sir William Osler stated, "the desire to take medication is perhaps the greatest feature which distinguishes man from animals."[12] Moreover, the use of weekly medication in the continuation and maintenance phases of major depression has a psychological advantage. Patients respond most favorably when informed that they have progressed enough to have treatment intensity lessened. This harkens back to the aban-

doned strategy with tricyclic antidepressant dosing wherein the patient with a stable treatment response would receive a reduced maintenance therapy. This strategy offered some reassurance to patients but unfortunately was linked to a higher relapse rate. Another advantage for weekly administration of fluoxetine is the fact that many of the side effects of the selective serotonin reuptake inhibitors (SSRIs) that lead to tolerability problems are dose related. With an initial lead-in period of daily dosing, tolerability problems are lessened. Only 1 patient in our study experienced difficulty in switching from daily to weekly fluoxetine. Additionally, our patients could not guess which group they were assigned to, furthering the notion that adverse events were minimal.[5]

In this current article, we present the outcomes of 3 measures that we did not previously report.[5] Our analyses of the MADRS data nicely echo the earlier findings with the HAM-D. Likewise, the SCL-90, a broader measure of psychological health, showed similar trends. There were also no significant differences in the average ratings of sexual health across the 3 treatment groups. Essentially, our findings suggest that the 2 formulations of fluoxetine were associated with comparable efficacy.

The lack of difference on the MADRS postrandomization is not surprising given the short duration of our study and the insufficient sample size. During the 7-week double-blind phase, norfluoxetine levels still were in flux[6] and, moreover, patients in the placebo group continued to exhibit some norfluoxetine during the early weeks postrandomization. In addition, previous studies reported slow relapse rates in placebo-treated patients during continuation treatment[13–15]; some reported that 50% of relapse did not occur until after almost a year of maintenance treatment.[15] Although our results suggest weekly dosing of fluoxetine can be tolerated, our data cannot definitively address the efficacy of weekly dosing of fluoxetine; that must be left to longer and larger trials. However, we do believe that this treatment design, an open-label lead-in followed by randomization of the responders, is particularly appropriate. First, it is closer to "real world" clinical practice in its initial stages. Second, it relegates the placebo period to a time in the trial when patients, by definition, have recovered and can more fully participate in deciding to accept the risk of receiving a placebo.

It is tempting to think of norfluoxetine as a "depot" antidepressant; however, there is no slow release of drug into the circulation. The sustained duration of action of norfluoxetine is based on its pharmacokinetic profile, which is unique among available antidepressants. No other drug, or drug metabolite, has a half-life and concentration that allows it to eventually be sustained for a week's duration at a stable concentration. It is important to note that, in this study, all subjects took "medication" daily (a single capsule for 6 days and 3 capsules on the seventh day of each week). Yet, fluoxetine's uniquely long half-life not only permits a weekly dosing strategy but also assures a several-day "safety zone" for taking the weekly dose. This characteristic of fluoxetine would be particularly desirable in those situations in which supervision of medication is necessary, for example, in various institutional and home settings. The intermittent dosing of fluoxetine could present an enormous opportunity to improve adherence and decrease the intensity of services required for routine medication administration. However, a weekly dosing does raise concerns about the individual patient's acceptance and adherence to such a strategy. Results from a recent study[16] indicated that patients assigned to take enteric-coated fluoxetine, 90 mg once weekly, were highly compliant with the weekly regimen during long-term treatment of their depression. That study suggests that patients will not be more likely to forget doses prescribed to be taken weekly than those to be taken daily.

A weekly dosing strategy does have the potential to minimize drug interactions. The SSRIs exact a number of effects on hepatic isoenzyme systems, including inhibition of the cytochrome P450 2D6 isoenzymes.[17] This enzyme system is responsible for metabolizing a number of drugs, most notably the tricyclic antidepressants. SSRIs inhibit this metabolism, leading to elevations in blood levels of tricyclic antidepressants and other drugs. This inhibition is dose related and, in the case of fluoxetine, with its long half-life, can cause drug interactions weeks after the drug is stopped. Presumably, the smaller dose of fluoxetine in a weekly dosing strategy would diminish the chance of such interactions.

In spite of our small sample size and the short duration of the study, we believe our findings support the viability of alternative dosing strategies for fluoxetine. We also acknowledge that a weekly dosing schedule is arbitrary. Given the relatively flat dose-response curve of fluoxetine and its long half-life, a longer or shorter dosing interval might be optimal. If other strategies are proved to be effective, the choice of dosing strategy may be merely a matter of preference for patients and their physicians. Likewise, the selection of 60 mg per week was also somewhat arbitrary, being based on tolerability concerns of a single large dose of fluoxetine and the lack of evidence for a fluoxetine dose-response curve. However, considering our initial work with the fluoxetine and norfluoxetine levels in this study,[6] it is likely that a higher weekly dose of fluoxetine is needed to keep the norfluoxetine level nearer the level achieved during daily dosing. The results of this work suggest the need for further exploration into treatment options for patients facing long-term medication maintenance.

Finally, by considering alternative treatment modalities for continuation and maintenance phases of MDD, we are putting to optimum use our understanding of the natural history of the disorder and the effectiveness of prophylactic treatment. Much knowledge has emerged over the last

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several decades concerning the typical length of depressive episodes and the need for long-term treatment of recurrent illness. The message sent by this information insists that we optimize treatment of MDD to enable our patients to comply with strategies that return and maintain their good health.

Drug name: fluoxetine (Prozac).

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