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# Safety of Abrupt Discontinuation of Fluoxetine: A Randomized, Placebo-Controlled Study

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**Selective serotonin reuptake inhibitors may be associated with new adverse events after abrupt discontinuation. Hypothesizing that the long half-life of fluoxetine would be protective, this study analyzed the effects of abrupt fluoxetine discontinuation during a randomized, double-blind, placebo-controlled study of depression maintenance treatment. After 12 weeks of fluoxetine treatment (20 mg/day), 395 responders were abruptly randomized to placebo (N = 96) or to continued fluoxetine (N = 299). Patients were seen at weeks 1, 2, 4, and 6 after randomization. Reports of new or worsened adverse events were similar for both groups at each visit after randomization. Patient discontinuations related to adverse events were also similar in both groups. Mild, self-limited lightheadedness or dizziness occurred in a small percentage of patients who discontinued fluoxetine treatment but was of little clinical significance. No cluster of symptoms suggestive of a discontinuation syndrome was observed. Abrupt discontinuation of fluoxetine treatment was well tolerated and did not seem to be associated with significant clinical risk. Fluoxetine may offer a potential safety advantage over shorter-acting agents with respect to treatment interruption and/or discontinuation and may be a better choice for those patients who are likely to miss doses because of travel or forgetfulness. (J Clin Psychopharmacol 1998;18:193–197)**

WHEN USED OVER EXTENDED periods of time, psychoactive pharmacologic agents can induce changes in neurotransmitter release, receptor numbers, and neuroendocrine secretion patterns that are associated with clinically observable phenomena. When drug administration is stopped abruptly, additional changes in brain homeostasis may produce further clinical consequences. Thus, benzodiazepines, tricyclic antidepressants, and other commonly used medications are associated with discontinuation syndromes of varying levels of severity.[1]

A number of recent reports have suggested that abrupt discontinuation of the newer antidepressants, including the selective serotonin reuptake inhibitors (SSRIs), may lead to the emergence of adverse signs and symptoms.[2,3] Among the SSRIs, most reports concern abrupt discontinuation of paroxetine treatment,[4–6] but abrupt discontinuation of sertraline[7] and fluoxetine treatment[8] has also been described. A recently reported prospective, double-blind, placebo-controlled study demonstrated that over periods of 5 to 9 days, abrupt discontinuation of paroxetine and sertraline, but not fluoxetine, was associated with increased numbers of both spontaneously reported and solicited adverse events as well as increased Hamilton Rating Scale for Depression (HAM-D) scores.[9] After discontinuation of paroxetine and sertraline treatment, the most common spontaneously reported symptoms that increased significantly were dizziness, nausea, insomnia, and nervousness. With respect to fluoxetine, the results of this study must be interpreted with care, because fluoxetine's longer half-life (and resulting slower clearance) could have delayed the appearance of discontinuation-related adverse events until several weeks after drug discontinuation and outside of the specified observation window. Alternatively, a drug such as fluoxetine with a longer half-life may be less prone to cause such syndromes, because plasma levels decrease very gradually even after abrupt discontinuation, potentially conferring a protective effect.

We hypothesized that abrupt discontinuation of fluoxetine, which has a longer half-life than either

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paroxetine or sertraline, would produce fewer clinical complications by allowing a more gradual readjustment to the medication-free state over both immediate and extended periods. In a recently completed double-blind, placebo-controlled trial of fluoxetine in the maintenance treatment of depression, fluoxetine responders were randomly assigned to either continued fluoxetine treatment or placebo. Adverse event data were systematically collected and recorded in a standardized manner at regular, frequent intervals throughout the trial for all patients and provided an opportunity to examine whether abrupt discontinuation of fluoxetine treatment is associated with a discontinuation syndrome both immediately and over a period of weeks. We report here an assessment of adverse events over a 6-week period after abrupt discontinuation of fluoxetine treatment.

## Methods

Subjects were men and women who initially met DSM-III-R criteria for major depression and had a 17-item HAM-D score ≥16 and whose depressive symptoms significantly improved during the acute phase of a multicenter examination of fluoxetine in the maintenance treatment of depression. Improvement was defined as a HAM-D-17 score ≤7 after 12 weeks of acute treatment with fluoxetine 20 mg daily. Upon completion of this acute phase of treatment, subjects were assigned by random allocation to double-blind placebo (N = 96) or to one of three arms of ongoing active treatment with fluoxetine 20 mg daily (N = 299) for various periods of time. (These three arms were pooled for analysis purposes in the current report.) Fluoxetine treatment was discontinued without a tapering-off period in patients assigned to placebo. The study was approved by the institutional review board of each participating site. Informed consent was obtained from all participants before their entering the study.

Investigators were required to record and report all adverse events at each patient visit regardless of perceived relationship to therapy. Reports were recorded in a uniform format using COSTART. Before the beginning of the study, all reporters received training on how to assess and report adverse events. Severity was rated on a scale from 1 (mild) to 3 (severe) based on discomfort, health risk, and interference with activity. Reports were collected by open-ended questioning about general well-being and problems with medication; questions about specific symptoms were posed only if the symptom was first reported by the patient in response to open-ended questioning.

### *Statistical analysis*

*Baseline assessment of adverse event frequency.* To assess the comparability of the placebo and actively treated groups, the numbers of patients in each group experiencing any new or worsened adverse event during the week before randomization were compared using Fisher's exact test. The frequencies of all specific individual events occurring in 2% or more of either group during the week before randomization were also compared using Fisher's exact test.

*Postrandomization assessment of adverse event frequency.* The numbers of patients reporting any new or worsened adverse events in the placebo- and fluoxetine-treated groups were compared using Fisher's exact test for each visit separately at weeks 1, 2, 4, and 6 after randomization. These comparisons were repeated for cumulative reports of adverse events for the entire 6-week period. The same analyses were then conducted at each visit (weeks 1, 2, 4, 6) and for the entire 6-week period for each specific new or worsened adverse event occurring in 2% or more of either treatment group. In addition, the distributions of patients reporting 0, 1, 2, or ≥3 new or worsened adverse events for each reporting interval (1, 2, 4, and 6 weeks and the entire 6-week period) were compared across placebo using the Kruskal-Wallis nonparametric ANOVA test. Reports from the patients who discontinued the study during the 6-week observation period were included in the overall 6-week analyses, as were individual visits during which they remained in the study.

*Assessment of discontinuations.* Proportions of patients who withdrew from the study during this 6-week period were compared in the fluoxetine- and placebo-treated groups using Fisher's exact test.

## Results

A total of 395 subjects (274 women, 121 men, mean age ± SD, 40 ± 10 years) were randomly assigned to continuation treatment with fluoxetine (N = 299) or placebo (N = 96). The mean HAM-D-17 score was 20.9 ± 3.6 at the outset of the trial, with no statistically significant difference existing between the placebo and fluoxetine treatment groups.

During the last week of fluoxetine treatment, before randomization to either placebo or continued fluoxetine treatment, reports of new or worsened adverse events were similar in both groups for the overall number of patients reporting one or more events (placebo 27%, fluoxetine 32%; $p = 0.38$; Table 1). Reports of individual events were generally similar with the exception of edema (fluoxetine 0, placebo 3 (3.1%); $p = 0.014$).

The incidence of new or worsened adverse events in both groups at baseline and at weeks 1, 2, 4, and 6 after randomization is shown in Table 1. There was no significant difference between groups in the number of patients reporting 0, 1, 2, or ≥3 new or worsened adverse

TABLE 1. Frequencies and new and worsened adverse events in patients randomized to placebo or to continued fluoxetine treatment[a]

| Week Post-randomization | Placebo Treatment Total Patient N | Placebo Treatment Patients Reporting Event | Placebo Treatment % | Fluoxetine Treatment Total Patient N | Fluoxetine Treatment Patients Reporting Event | Fluoxetine Treatment % | *p* Value |
|---|---|---|---|---|---|---|---|
| 0 Baseline | 96 | 26 | 27 | 299 | 96 | 32 | 0.38 |
| Week 1[b] | 95 | 32 | 34 | 299 | 106 | 36 | 0.81 |
| Week 2[b] | 91 | 29 | 32 | 294 | 83 | 28 | 0.51 |
| Week 4[c] | 75 | 26 | 35 | 279 | 116 | 42 | 0.29 |
| Week 6[c] | 58 | 23 | 40 | 250 | 76 | 30 | 0.21 |
| Whole 6-wk period surveyed | 95 | 64 | 67 | 299 | 223 | 75 | 0.19 |

[a]Patients reporting ≥1 new or worsened adverse event.
[b]One-week visit interval.
[c]Two-week visit interval.
[d]Note that 36 patients discontinued at week 6 but are included in the week 6 analysis.

events for any reporting interval. Also, there was no significant increase in the total number of new or worsened adverse events over the whole 6-week period surveyed. The profile of new adverse events reported (Tables 2 and 3) was also similar for both groups at each interval with the exception of dizziness and three other common events. At week 4, dizziness was reported in 5 (7%) of 75 patients who had discontinued medication and 4 (1%) of 279 patients on fluoxetine ($p = 0.023$). At week 6, dizziness was reported in 3 (5%) of 58 patients on placebo and 2 (1%) of 250 patients on fluoxetine ($p = 0.048$). Over the entire 6-week period after randomization to placebo or fluoxetine, this symptom was reported by 8 patients in the placebo-treated group and 13 patients in the fluoxetine-treated group (Table 4). In the placebo-treated group, the actual terms used by the patients were lightheadedness (four patients) and dizziness (four patients). Severity was rated as mild for six

TABLE 2. New or worsened adverse events occurring in ≥5% of patients in either treatment group at weeks 1, 2, 4, and 6 after randomization[a]

| Event/ Week Post-randomization | Placebo Treatment Total Patient N | Placebo Treatment Patients Reporting Event | Placebo Treatment % | Fluoxetine Treatment Total Patient N | Fluoxetine Treatment Patients Reporting Event | Fluoxetine Treatment % | *p* Value |
|---|---|---|---|---|---|---|---|
| Dizziness | | | | | | | |
| 4 | 75 | 5 | 6.7 | 279 | 4 | 1.4 | 0.023 |
| 6 | 58 | 3 | 5.2 | 250 | 2 | 0.8 | 0.048 |
| Headache | | | | | | | |
| 1 | 95 | 6 | 6.3 | 299 | 23 | 7.7 | 0.822 |
| 2 | 91 | 8 | 8.8 | 294 | 16 | 5.4 | 0.319 |
| 4 | 75 | 4 | 5.3 | 279 | 20 | 7.2 | 0.796 |
| 6 | 58 | 2 | 3.4 | 250 | 16 | 6.4 | 0.542 |
| Insomnia | | | | | | | |
| 1 | 95 | 5 | 5.3 | 299 | 7 | 2.3 | 0.171 |
| Pain | | | | | | | |
| 6 | 58 | 3 | 5.2 | 250 | 5 | 2.0 | 0.176 |
| Rhinitis | | | | | | | |
| 1 | 95 | 5 | 5.3 | 299 | 10 | 3.3 | 0.370 |
| 2 | 91 | 6 | 6.6 | 294 | 15 | 5.1 | 0.599 |
| 4 | 75 | 6 | 8.0 | 279 | 22 | 7.9 | 1.00 |
| 6 | 58 | 6 | 10.3 | 250 | 7 | 2.8 | 0.020 |

[a]Incidence of at least two reports in a treatment group.

TABLE 3. New or worsened adverse events occurring statistically significantly more frequently in one treatment group at weeks 1, 2, 4, and 6 after randomization[a]

| Event/ Week Post-randomization | Placebo Treatment Total Patient N | Placebo Treatment Patients Reporting Event | Placebo Treatment % | Fluoxetine Treatment Total Patient N | Fluoxetine Treatment Patients Reporting Event | Fluoxetine Treatment % | *p* Value |
|---|---|---|---|---|---|---|---|
| Dizziness | | | | | | | |
| 4 | 75 | 5 | 6.7 | 279 | 4 | 1.4 | 0.023 |
| 6 | 58 | 3 | 5.2 | 250 | 2 | 0.8 | 0.048 |
| Dysmenorrhea | | | | | | | |
| 6 | 58 | 2 | 3.4 | 250 | 0 | 0 | 0.035 |
| Rhinitis | | | | | | | |
| 6 | 58 | 6 | 10.3 | 250 | 7 | 2.8 | 0.020 |
| Somnolence | | | | | | | |
| 2 | 91 | 4 | 4.4 | 294 | 0 | 0 | 0.003 |

[a]Incidence of at least two reports in a treatment group.

TABLE 4. Patients reporting new or worsened dizziness following randomization to placebo or continued fluoxetine treatment at baseline and weeks 1, 2, 4, and 6 after randomization

| Week | Placebo Treatment Total Patient N | Placebo Treatment Patients Reporting Event | Placebo Treatment % | Fluoxetine Treatment Total Patient N | Fluoxetine Treatment Patients Reporting Event | Fluoxetine Treatment % | *p* Value |
|---|---|---|---|---|---|---|---|
| 0 (Baseline) | 96 | 1 | 1 | 299 | 0 | 0 | 0.243 |
| 1 | 95 | 0 | 0 | 299 | 5 | 2 | 0.343 |
| 2 | 91 | 1 | 1 | 294 | 2 | 1 | 0.556 |
| 4 | 75 | 5[a] | 7 | 279 | 4 | 1 | 0.023 |
| 6 | 58 | 3[a] | 5 | 250 | 2 | 1 | 0.048 |

[a]One patient reported dizziness at both week 4 and week 6.

TABLE 5. Postrandomization discontinuations

| Reason Discontinued | Placebo Treatment (N=96) n | Placebo Treatment (N=96) % | Fluoxetine Treatment (N=299) n | Fluoxetine Treatment (N=299) % | *p* Value |
|---|---|---|---|---|---|
| Lack of efficacy | 37 | 39 | 51 | 17 | <0.001 |
| Adverse event | 2 | 2 | 6 | 2 | 1.000 |
| Patient decision | 3 | 3 | 11 | 4 | 1.000 |
| Protocol requirement | 3 | 3 | 5 | 2 | 0.409 |
| Lost to follow-up | 3 | 3 | 2 | 1 | 0.095 |

patients and moderate for two, and three patients had complained of similar symptoms during 1 or more weeks of active treatment preceding randomization to placebo. The onset of dizziness in one patient in the placebo-treated group and one patient in the fluoxetine-treated group coincided with their becoming pregnant.

Other new or worsened adverse events that were more frequent in the placebo-treated group during the 6-week period included somnolence (placebo 4/91 [4%], fluoxetine 0/294 [0%]; $p < 0.01$) during week 2, and rhinitis (placebo 6/58 [10%], fluoxetine 7/250 [3%]; $p < 0.05$) and dysmenorrhea (placebo 2/58 [3%], fluoxetine 0/250 [0%]; $p < 0.05$) during week 6.

During the 6 weeks after randomization to placebo or fluoxetine, a total of 123 patients discontinued the study: 48 in the placebo group (50%) and 75 in the group that continued on fluoxetine (25%). Of the patients switched to placebo, 37 (39%) discontinued because of lack of efficacy and 2 (2%) because of adverse events. In the fluoxetine-treated group, 51 patients (17%) discontinued because of lack of efficacy and 6 (2%) because of adverse events. All reasons for study discontinuation are listed in Table 5.

## Discussion

When patients whose depression had responded to 12 weeks of daily fluoxetine 20-mg treatment were randomly assigned to placebo or continued fluoxetine treatment, the overall profile of new or worsening adverse events was similar for both groups for 6 weeks, suggesting that no pattern of discontinuation-related events emerges upon abrupt discontinuation of fluoxetine treatment.

Several previous reports have suggested that abruptly stopping fluoxetine administration is associated with a discontinuation syndrome[8, 10–11]; however, all were retrospective and were limited by small sample sizes and by poorly controlled or uncontrolled designs. Furthermore, none used systematic, uniform mechanisms for collecting adverse event data. In contrast, the current study had a large number of patients, the group whose fluoxetine treatment was discontinued had been randomly selected, and both patients and treaters were blind to treatment condition. Adverse event data were gathered and catalogued systematically and at regular, specified intervals, and patients were followed up for a sufficiently long period that any discontinuation-related events would be expected to be observed.

Several factors potentially limit the interpretation of these data. Patients were not treated with more than 20 mg of fluoxetine daily, and it is possible that higher doses could cause problems upon abrupt discontinuation. We note, however, that the longer half-life of fluoxetine would be expected to be protective at higher doses as well as at 20 mg. It is also possible that a 12-week treatment period is too short to predispose patients to problems upon abrupt discontinuation. However, because this period is two to three times the average required for depressive symptoms to respond to treatment, as well as considerably longer than the time required to reach steady-state plasma drug levels for fluoxetine and its active metabolite, it seems likely that physiologic changes that might lead to discontinuation effects would have occurred. The nature of discontinuation syndromes related to SSRI use is uncertain, and no specific instrument to measure discontinuation-related signs and symptoms was used. Thus, a very diverse syndrome in which each patient experienced different symptoms could potentially have gone unnoticed. We would expect, however, that had patients experienced significant discomfort, it would have been reported, and thus any undetected discontinuation-related symptoms are likely to have been mild and of little clinical consequence.

The finding of a small increase in reports of dizziness among patients who discontinued the drug (7% at week 4 vs. 1% among patients remaining on medication) is of uncertain clinical significance. Einbinder[8] reported on a patient with the onset of dizziness 9 days after the discontinuation of fluoxetine which resolved with reinstitution of treatment, and Blomgren and colleagues[9] found spontaneous reports of dizziness of 18% and 29%, respectively, among patients on sertraline and paroxetine 5 to 9 days after abrupt medication discontinuation. Review of the records of the patients who reported dizziness in the current study showed that the complaints were mild and of minimal clinical significance, and in half of these patients the dizziness had also occurred before fluoxetine discontinuation. Thus, it is uncertain whether these complaints were related to fluoxetine discontinuation, but whatever their etiology they seemed to have been of minimal clinical importance. That these events occurred 4 to 6 weeks after drug discontinuation supports the hypothesis that the longer half-life of fluoxetine protects against adverse events associated with brief treatment interruptions of several days to weeks. None of the other symptoms commonly reported after abrupt discontinuation of other SSRIs (e.g., nausea, insomnia, nervousness) were significantly increased among patients who abruptly discontinued fluoxetine in this study compared with those who did not discontinue medication. The other symptoms that were statistically significantly more frequent in the placebo group occurred only at one visit (rhinitis, somnolence, and dysmenorrhea) and were also mild. These symptoms, which occurred in extremely small numbers at a single visit, are not among

those described in previous reports as associated with SSRI discontinuation, may well have been chance variations (particularly as there was no correction for multiple comparisons), and seem unlikely to have been part of clinically significant discontinuation syndrome.

Although reports of new adverse events did not generally increase after discontinuation of fluoxetine, there was also not a significant decrease in reports over the 6 weeks surveyed. Several factors could account for this finding. Most importantly, the overall rate of new events reported was relatively low and included all adverse events, whether treatment-related or not. Thus, events such as colds, surgical procedures, etc., which would be expected to be similar in frequency before and after discontinuation, are included in the overall rate. Because fluoxetine is well tolerated, the rates of medication-related side effects such as headache and insomnia are relatively low, and thus the power to detect changes even in a study as large as the current one is quite small for most adverse events. In addition, the rate of return of depressive symptoms in the discontinuation group was extremely high (approximately 50%), and it is likely that recurrent anxiety and depression accounted for many of the increased reports of somatic symptoms. This reasoning is supported by the fact that more placebo- than fluoxetine-treated patients discontinued the study due to the recurrence of depressive symptoms. There was no increase in patient dropout due to adverse events in the placebo group, providing further evidence for the lack of a discontinuation syndrome.

In summary, the current prospective, controlled study provides evidence that abrupt discontinuation of fluoxetine is not associated with a clinically significant discontinuation syndrome. A small percentage of patients may experience mild, self-limited lightheadedness or dizziness from 4 to 6 weeks after drug discontinuation. Fluoxetine may be a better choice for patients who are likely to miss doses because of travel or forgetfulness. Patients who abruptly discontinue treatment do not seem to be at significant clinical risk for discontinuation-related symptoms.

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