Changes in Adverse Events Reported by Patients During 6 Months of Fluoxetine Therapy

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Background: Although a period of 6 to 12 months of antidepressant therapy is recommended for most patients with depression, systematic examinations of the course of adverse events over time, the resolution of early-onset events, and the possible emergence of later-onset events are limited. We examined the safety of fluoxetine, 20 mg/day, in a large, prospective, long-term treatment trial, and we report a comparison of early- and late-onset adverse events and the course of adverse events over 26 weeks of treatment.

Method: Adverse events were recorded at each visit in a uniform format by open-ended questioning, regardless of perceived causality. New or worsened events reported in either the first 4 weeks of treatment (early-reporting interval) or weeks 22 through 26 of treatment (late-reporting interval) were compared.

Results: Patients (N = 299) whose depression (DSM-III-R) remitted with 12 weeks of fluoxetine treatment entered continuation therapy, and 174 completed 26 weeks of therapy. All events that occurred in ≥ 5% of patients early in treatment decreased in frequency over time ($p < .05$), and no events occurred significantly more frequently during continuation therapy. No previously uncommon adverse events became common during long-term treatment.

Conclusion: Common adverse events associated with initiating fluoxetine treatment in depressed patients, including nausea, insomnia, nervousness, and somnolence, resolve in the majority of patients and become significantly less frequent with continued treatment over a 6-month period. No adverse events present initially become more frequent late in treatment. Therapy with fluoxetine, 20 mg/day, is well tolerated over 6 months, and most adverse events observed early in treatment resolve.

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Selective serotonin reuptake inhibitors (SSRIs) are safe and well tolerated and have become the most widely used antidepressant medications. Nonetheless, like all pharmacologic treatments, they are associated with undesirable effects in some patients. In general, the adverse event profiles of the SSRIs have been characterized in registration studies designed to determine acute efficacy and safety.[1–6] Much less systematic information has been reported about the course of adverse effects beyond 6 weeks, the resolution of early-onset events, and the possible emergence of later-onset events.

Patients often take antidepressant medications for a longer time than the period used to establish acute efficacy and safety in clinical trials. Four to 9 months of continuation therapy with antidepressants following recovery from acute illness is recommended to prevent relapse,[7] and available evidence suggests that for patients with recurrent illness, indefinite maintenance therapy with antidepressants protects against new episodes.[8,9] The absence of systematic data concerning the likely course of adverse events and the risk of late-onset events complicates clinical decisions regarding the benefit-to-risk ratio of extending therapy beyond acute symptom resolution, particularly for patients who experience adverse events early in treatment.

To characterize adverse events associated with long-term fluoxetine treatment, we analyzed adverse event data

from a large depression relapse prevention study. We report a comparison of early- and late-occurring adverse events, as well as the course of common adverse events over time during 26 weeks of treatment with fluoxetine, 20 mg/day.

METHOD

These data were obtained as part of a study examining the efficacy of fluoxetine treatment in depression relapse prevention. Details of the study design have been reported elsewhere.[10] Following a 1-week, drug-free, lead-in period, all patients began treatment with open-label fluoxetine at 20 mg/day for up to 12 weeks. Patients whose illness remitted after 12 weeks (modified 17-item Hamilton Rating Scale for Depression [HAM-D-17] score of ≤ 7 during weeks 10–12) were randomly assigned to treatment in a 4-arm, double-blind, progressively placebo-controlled, 1-year, fixed-dose (20 mg/day), relapse prevention trial. The active treatment arms differed only in the length of maintenance therapy. The only concomitant psychotropic medications allowed were lorazepam or chloral hydrate on an as-needed basis for insomnia. Details of the efficacy data for this trial, which show decreased relapse rates on fluoxetine treatment compared with placebo, have been reported elsewhere.[11] The data reported here are from patients in the active treatment arms assigned to at least 26 weeks of fluoxetine treatment (12 weeks open-label followed by 14 weeks under double-blind, randomized conditions).

Subjects

The study was approved by the institutional review board at each site. Patients were recruited by referral and advertisement and met *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R) criteria for depression at study entry.[12] Patients received a complete explanation of all procedures and provided written informed consent prior to study entry.

Assessment of Adverse Events

During the early-reporting interval (weeks 1–4 of treatment) patients were seen weekly, and during the late-reporting interval (weeks 22–26 of treatment) patients were seen every 2 weeks. All investigators were required to record and report all adverse events at each visit regardless of perceived relationship to therapy. 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 the open-ended questioning. The actual descriptive words used by the patients were standardized into uniform adverse event terminology using the U.S. Food and Drug Administration's *Coding Symbols for a Thesaurus of Adverse Reaction Terms* dictionary (COSTART)[13]; all reporters were trained on assessment and reporting of adverse events using this system prior to study initiation. Although generally unambiguous, several of the COSTART terms deserve clarification. The COSTART term *somnolence* refers to sleepiness or drowsiness without a sense of physical distress (feeling groggy); the COSTART term *asthenia* incorporates physical distress and refers to lack or loss of strength and energy (weakness). The COSTART term *anxiety* refers to an unpleasant emotional state involving a psychophysiologic response to real or imagined danger (fear, panic); the COSTART term *nervousness* refers to excessive excitability and irritability (agitation, tension).

Statistical Analysis

New or worsened adverse events reported by at least 2% of patients in either the early-reporting interval or the late-reporting interval were tabulated for all patients who were randomly assigned to fluoxetine treatment. This list of adverse events was then narrowed to those expected for fluoxetine treatment by selecting those events that occurred significantly more frequently in fluoxetine-treated patients compared with placebo-treated patients in the U.S. fluoxetine clinical trial databases. These databases contain adverse event data from over 2700 depressed patients who participated in randomized, placebo-controlled studies of fluoxetine.

Adverse events in the early-reporting interval were defined as events that first occurred or worsened during the initial 4 weeks of fluoxetine treatment. Adverse events in the late-reporting interval were defined 2 ways. First, late-reporting interval events were defined as events that began or worsened any time after the initiation of fluoxetine treatment and were still present between weeks 22 and 26 of treatment. Comparing these late events to the early events provided an estimate of the persistence of early events. Second, late-reporting interval events were defined as events that first occurred or worsened after at least 12 weeks of fluoxetine treatment and were still present during weeks 22 through 26 of treatment, with the events observed from study entry through the first 12 weeks of fluoxetine treatment as the baseline. Comparing these late events to the early events provided a summary of any new categories of events first occurring during chronic treatment. Both analyses were repeated including just those patients who completed 26 weeks of therapy; in addition, both analyses were repeated excluding all patients who took either chloral hydrate or lorazepam during the trial.

In order to control for patients discontinuing prior to reaching the late-reporting interval, the adverse event information from the last 2 visits after randomization was carried forward to the late-reporting interval. Thus, the numbers of patients in each reporting interval were identical. Statistical comparison of the early- versus late-reporting intervals was made using the McNemar test.[14]

Table 1. Analysis of Persistence of Adverse Events[a]

	Events Occurring in Early-Reporting Interval[b] (N = 299)		Events Occurring in Late-Reporting Interval[c] (N = 299)		
Event	N	%	N	%	p Value
Headache	97	32.4	51	17.1	< .001
Nausea	87	29.1	10	3.3	< .001
Insomnia	67	22.4	27	9.0	< .001
Somnolence	44	14.7	18	6.0	< .001
Diarrhea	39	13.0	9	3.0	< .001
Dizziness	39	13.0	6	2.0	< .001
Asthenia	36	12.0	21	7.0	.032
Nervousness	33	11.0	9	3.0	< .001
Dry mouth	30	10.0	10	3.3	< .001
Anorexia	27	9.0	3	1.0	< .001
Dyspepsia	27	9.0	12	4.0	.017
Anxiety	26	8.7	7	2.3	< .001
Flatulence	16	5.4	6	2.0	.021

[a]Events present in ≥ 5% of patients in the early-reporting period.
[b]Events first occurring or worsening in weeks 1–4 of fluoxetine treatment.
[c]Events first occurring or worsening any time after starting fluoxetine treatment and persisting to weeks 22–26 of treatment.

Table 2. Analysis of Late-Onset Adverse Events[a]

	Early-Onset Events[b] (N = 299)		Late-Onset Events[c] (N = 299)		
Event	N	%	N	%	p Value
Headache	97	32.4	17	5.7	< .001
Nausea	87	29.1	6	2.0	< .001
Insomnia	67	22.4	12	4.0	< .001
Somnolence	44	14.7	9	3.0	< .001
Diarrhea	39	13.0	3	1.0	< .001
Dizziness	39	13.0	2	0.7	< .001
Asthenia	36	12.0	14	4.7	.001
Nervousness	33	11.0	4	1.3	< .001
Dry mouth	30	10.0	0	0	< .001
Anorexia	27	9.0	2	0.7	< .001
Dyspepsia	27	9.0	8	2.7	.002
Anxiety	26	8.7	6	2.0	< .001
Flatulence	16	5.4	2	0.7	.001

[a]Events present in ≥ 5% of patients in the early-reporting period.
[b]Events first occurring or worsening in weeks 1–4 of fluoxetine treatment.
[c]Events first occurring or worsening after at least 12 weeks of fluoxetine treatment and persisting to weeks 22–26 of treatment.

Table 3. Early Treatment Discontinuation[a] (N = 299)

Reason for Discontinuation	N	%
Relapse	83	27.8
Patient decision	18	6.0
Protocol violation	10	3.3
Adverse event	9	3.0
Lost to follow-up	4	1.3
Other	1	0.3

[a]Patients who completed at least 13 weeks of fluoxetine but discontinued prior to week 26. Percentages given here are of total number of patients who continued fluoxetine treatment.

To examine the course of common adverse events over time, we calculated the percentage of occurrence of the 6 most common adverse events that were more frequent with fluoxetine than with placebo in the clinical trials database (nausea, insomnia, somnolence, diarrhea, dizziness, and asthenia) over 2-week intervals from the early-reporting interval to the late-reporting interval. In this analysis, last visit adverse event information was carried forward for patients who left the study prior to reaching the final reporting interval.

RESULTS

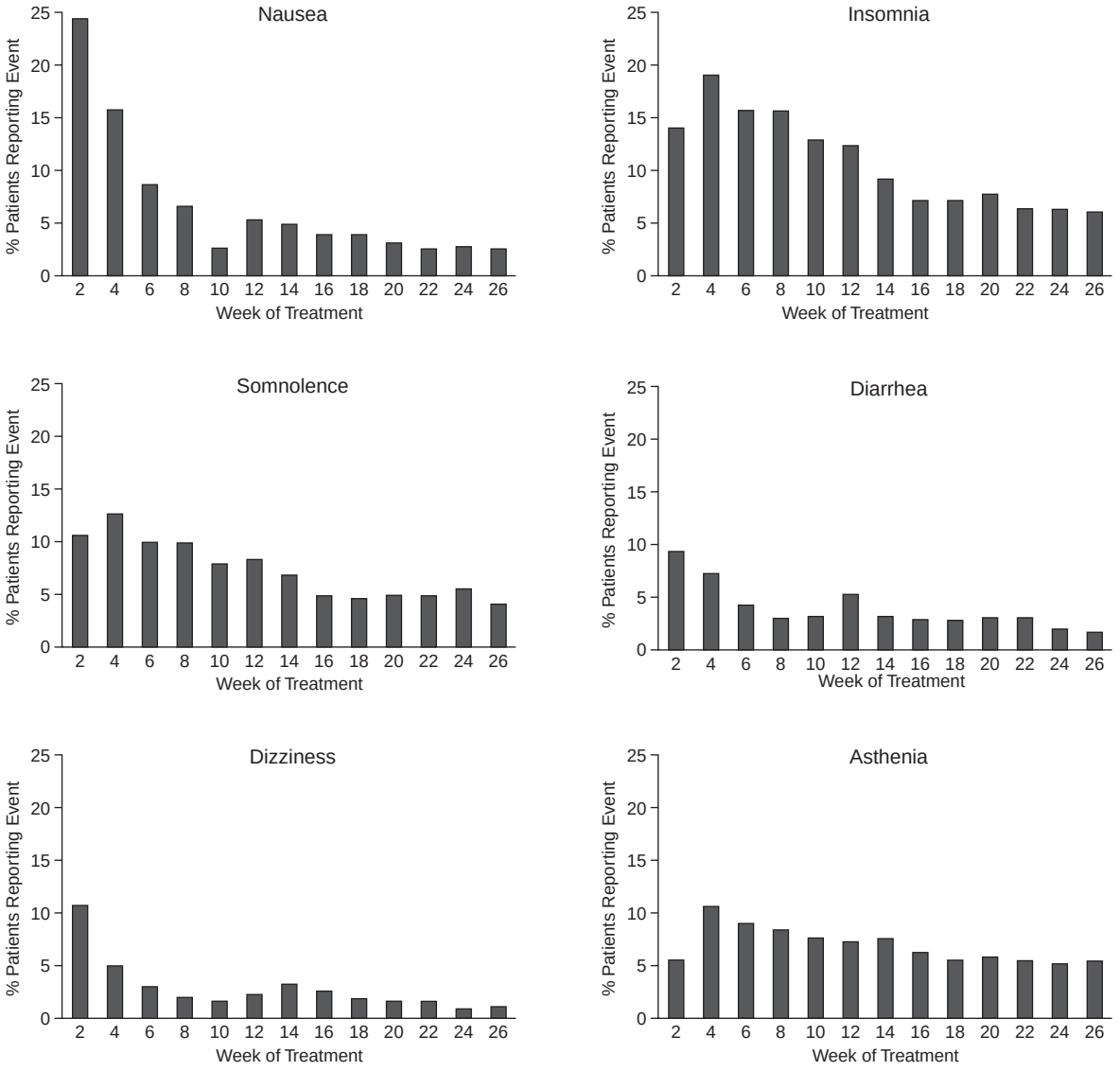
Of the 839 patients who entered the clinical trial, 395 met criteria for remission of depression and were randomized into the continuation phase. Of these, 299 received continued fluoxetine treatment, and 174 of these completed 26 full weeks of treatment. Eighteen adverse events were reported by at least 2% of these patients and were considered expected for fluoxetine treatment based on the cumulative clinical trials databases. Headache, although not significantly more frequent among fluoxetine-treated than placebo-treated patients in the cumulative databases, was also included in the present analysis because it was the most frequently reported event.

The frequency of all common adverse events (events present in ≥ 5% of patients) early in treatment decreased significantly over time (Table 1). No categories of adverse events were reported at 26 weeks of treatment that had not been reported in at least 2% of patients during the first 4 weeks of treatment, and no commonly reported adverse events were increased in frequency at 26 weeks (Table 2). Although some fluoxetine-treated patients did report common events for the first time during the late-treatment interval, the frequency of these events was similar to the frequency of events reported over the same interval by patients assigned to placebo at week 12. Analyses that included just those patients who completed 26 weeks of therapy produced comparable results.

After excluding 51 patients who had used either lorazepam or chloral hydrate at least once following study entry, results were similar. All of the early-onset events (except for dyspepsia) occurred significantly less frequently over the 26 weeks in this subset of patients. Likewise, this subset of patients did not report any new categories of adverse events at 26 weeks of treatment that had not been reported in at least 2% of patients during the first 4 weeks of treatment, nor did they experience an increase in the frequency of any commonly reported adverse events late in treatment.

Of the 299 patients completing at least 13 weeks of treatment, 125 dropped out of the study before 26 weeks. Among these, 9 reported adverse events as their primary reason for leaving (2 patients for somnolence and 1 patient each for agitation, nausea, nervousness, manic reaction, weight gain, pancreatitis, and depression). Other reasons for discontinuation included relapse, protocol violations, and patient decision (summarized in Table 3).

Figure 1. Percentage of Patients Who Experienced 1 of the Most Common Adverse Events Over 2-Week Intervals From the Early-Reporting Interval to the Late-Reporting Interval[a]



[a]The 6 most common adverse events that occurred more frequently with fluoxetine than with placebo in the clinical trial database.

The percentages of patients experiencing the 6 most common adverse events over consecutive 2-week intervals are shown in Figure 1.

DISCUSSION

We systematically assessed the occurrence of adverse events early and late in fluoxetine treatment. All events that occurred in ≥ 5% of patients early in treatment decreased in frequency over time, no new categories of adverse events emerged late in treatment, and there was no significant increase in frequency of any adverse event late in treatment. The frequencies of new events reported by fluoxetine-treated patients during the late-reporting interval were similar to the frequencies of those reported over the same interval by patients assigned to placebo at week 12, suggesting that these newly reported events were not specifically associated with extended fluoxetine treatment.

The adverse event profile of extended fluoxetine treatment is of interest from several perspectives. Information about the likely course of adverse events is important for patients who experience early-onset events and are undecided about continuing treatment. Information about late-onset events is important for patients and clinicians concerned with the risks of extending treatment beyond the resolution of acute illness. To our knowledge, there have

been no previous large-scale, long-term studies addressing the issue of the safety of fluoxetine and comparing its acute and chronic side effect profiles.

Several factors limit the interpretation of these results. Although this was a large study with considerable statistical power, there may be highly infrequent events associated with extended treatment that would only be detected in a much larger sample. Additionally, we cannot rule out the possibility that very late–onset events may occur beyond the 26-week treatment window of this study, although we are unaware of evidence suggesting that treatment with fluoxetine over longer periods is associated with marked changes in its side effect profile.[15]

These patients were responders to acute fluoxetine monotherapy at 20 mg/day. Since chronic therapy is not commonly instituted in nonresponders and since 20 mg is the most common therapeutic dose for depressed patients, these data are relevant to clinical practice; however, it is possible that patients treated with higher doses of fluoxetine might have different adverse event profiles with chronic therapy. Similarly, patients taking concomitant psychoactive medications could experience a different safety profile. The only concomitant psychotropic medications allowed during this study were lorazepam and choral hydrate for the treatment of insomnia. Reanalysis excluding patients who used these drugs yielded similar results, providing evidence that the decline in adverse events over time is not an artifact of such symptomatic treatment.

Visits were weekly during the early interval and were every 2 weeks during the late interval, which potentially decreased reported rates for the late interval. Any such decrease, however, is likely to be related to mild, relatively unimportant events that patients forgot, and hence would be of minimal clinical significance. The low rate of dropouts for adverse events, together with the fact that the analysis was performed carrying forward the last observations of patients who dropped out between weeks 13 and 26, provides evidence that the observed decline in adverse events is not an artifact of patients with intolerable adverse effects leaving the study.

It may be that solicited reports or use of a structured instrument would have resulted in higher overall rates of reported adverse events. However, open-ended questioning at regular intervals may be more relevant to actual clinical practice since patients presumably report what they feel to be of significance (as noted below, this may not be true for sexual dysfunction). The rates of adverse events described here are probably accurate reflections of medication tolerability and may be better predictors of patient discomfort and compliance than solicited reports.[16]

Adverse events that did not decrease over time occurred infrequently (< 5% of patients in the early-reporting interval), limiting the power of this study to detect any changes in rates of occurrence. Among these were abnormal ejaculation and anorgasmia (occurring in 2.0% and 1.7% of patients in the early-reporting interval, respectively), symptoms of sexual dysfunction that have been associated with SSRIs. Evaluating antidepressant-associated sexual dysfunction is difficult since the effects of depression, recovery, and quality of interpersonal relationships confound analysis and since many patients and clinicians are not at ease discussing sexual problems. As a result, spontaneous reports of problems related to sexual function may underestimate the actual occurrence of the problems.[17,18] In addition, sexual function includes distinct appetitive, arousal, and consummatory aspects that were not evaluated separately in the current study. Thus, further studies specifically focused on sexual function in patients treated with SSRIs are needed to clarify these issues.

There was no evidence of increased weight as a late-onset event based on spontaneous reports. However, weight is more appropriately evaluated by means of actual measurement, and we note that a recent completed evaluation of actual weights from this study was consistent with the spontaneous report data, suggesting that marked weight gain over extended periods of treatment is not a fluoxetine-specific adverse event.[19]

Neither fatigue nor asthenia-like symptoms became more common in the late-treatment portion of this study. The most common adverse event terms that capture symptoms of fatigue are *somnolence* and *asthenia*. Reports of both of these adverse events decreased significantly in frequency during chronic treatment, suggesting that, for periods up to 26 weeks, increased fatigue does not appear to be associated with fluoxetine treatment.

Several factors could potentially account for the decrease in reports of adverse events over time. Attempts to restore normal central nervous system homeostasis, such as receptor down- or up-regulation and compensatory changes in production and secretion of nonserotonin neurotransmitters and neurohormones, could account for some of the observed effect. It is also possible that patients accommodate to some adverse events, become less aware of them over time, and stop reporting them. Because patients were on fluoxetine monotherapy, the observed declines in adverse events cannot be attributed to adjuvant symptomatic treatment. Some of the decline may be due to resolution of depressive symptoms, since somatic complaints can themselves be a symptom of depressive illness. Most importantly, although adverse events resolve over time, fluoxetine's therapeutic effect was not diminished over time. Fluoxetine retained its protective antidepressant effects over the entire 26-week period and, as reported elsewhere, was superior to placebo in preventing depressive symptom relapse.[11]

This study suggests that for patients who derive therapeutic benefit from daily treatment with fluoxetine at 20 mg, adverse events reported early resolve for most of

them over continued therapy for up to 6 months. Adverse events that are common early in treatment decrease in frequency over time, and no events that are uncommon initially become more common late in treatment. Therapy with fluoxetine over 6 months is well tolerated and is not associated with the emergence of previously unobserved categories of late-onset adverse events.

Drug names: fluoxetine (Prozac), lorazepam (Ativan and others).

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