What Happens With Adverse Events During 6 Months of Treatment With Selective Serotonin Reuptake Inhibitors?

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Objective: Although adverse events are a key factor in compliance, their evolution during treatment with antidepressants is poorly documented. Therefore, the time course of adverse events during 6 months of antidepressant treatment was investigated.

Method: 85 psychiatric outpatients with a DSM-IV diagnosis of major depressive disorder (with the exclusion of other DSM-IV Axis I disorders) were enrolled between September 2002 and March 2003 in a multicenter, randomized, double-blind trial with selective serotonin reuptake inhibitors (fluoxetine [N = 42] and paroxetine [N = 43]). At each visit, the presence and severity of treatment-emergent adverse events were assessed systematically using the UKU Side Effect Rating Scale (UKU). General linear mixed modeling was used to investigate the predictors of the time course of adverse events.

Results: Overall, the number of at least moderately severe adverse events decreased with time. More severely depressed patients reported overall more (at least moderately severe) adverse events than less severely depressed patients ($p = .0002$), but the decrease in reported adverse events was comparable over time. Men (N = 30) and women (N = 55) reported initially the same number of at least moderately severe adverse events, but the habituation was more rapid in men ($p < .0001$). Completers (N = 58) and dropouts (N = 27) did not differ initially, but completers' habituation was more rapid ($p = .014$). The habituation of adverse events was also more rapid in recurrent than in first-episode patients but only in men ($p = .0025$).

Conclusion: The time course of adverse events varies with the severity of depression, sex, completer or dropout status, and recurrent versus first-episode depression.

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Rates of nonadherence are high among all classes of antidepressants.[1] In studies measuring clearly defined medication nonadherence, the median prevalence of nonadherence is 53%.[2] Up to 15% of patients never start taking the prescribed antidepressants,[3] between 28% and 44% of patients discontinue within 3 months of treatment,[4] and up to 25% of patients do not inform their physicians when stopping treatment.[5–7]

Only 1% to 2% of all publications on the treatment of affective disorders explore factors associated with medication nonadherence.[2] Tolerability of the antidepressant is of course an important reason for discontinuation, although patients' attitudes and beliefs seem to be at least as important.[2] Early discontinuation is more due to perceived lack of efficacy and reported adverse events, while late discontinuation is more due to patients' beliefs.[5]

The advent of selective serotonin reuptake inhibitors (SSRIs) has not changed overall patterns of nonadherence,[3,8] although a better tolerability profile has been associated with a small improvement in adherence: a meta-analysis of 95 randomized trials including 10,839 patients found that the difference in discontinuation rates due to adverse events between tricyclic antidepressants (TCAs) (with more adverse events) and SSRIs (with fewer adverse events) was statistically significant (17.3% vs. 12.4%, $p < .0001$), but the clinical significance was unclear.[9] Another meta-analysis of 11 randomized trials in primary care comparing the tolerability of SSRIs with TCAs con-

cluded that significantly fewer patients taking SSRIs withdrew from treatment specifically because of adverse events (relative risk = 0.73, 95% CI = 0.60 to 0.88).[10] Although dropout rates due to adverse events are a worthy measure of tolerability, it should be noted that dropout rates in randomized clinical trials can differ significantly from those that occur in clinical practice. While clinical trials suggest that the most common reason for discontinuation is "experiencing adverse events," more naturalistic studies suggest that it is "patient feeling better."[5,7]

It should also be noted that the methods used to obtain information from patients on the occurrence of adverse events partly explain the differences in reported rates. The difference in reported pooled rates of occurrence of nausea (compared with TCAs) was 10% higher with SSRIs when based on a checklist, 7% higher when based on spontaneous reports, 12% higher when based on indirect questioning, 9% higher when based on the Treatment Emergent Symptom Scale, and 15% higher when information was obtained by unspecified methods.[11] It is also well known that more adverse events are reported in clinical trials run in the United States than in Europe, which probably reflects a greater sensitivity to possible lawsuits. Just 1 example hereof is the incidence of nausea in trials looking at placebo versus 10 mg of escitalopram: in a study conducted in Europe and Canada, the incidence was 3.7% and 12%, respectively, and in a study conducted in the United States, the incidence was 6% and 21%, respectively.[12,13]

Systematic examination of the course of adverse events over time, including the resolution of early-onset events and the possible emergence of later-onset events, is quite limited. During a 6-month open-label study of treatment with fluoxetine, the adverse events reported in the first 4 weeks of treatment were compared with those reported in weeks 22 through 26 of treatment.[14] The frequency of all common adverse events (> 5%) early in treatment decreased significantly over time, while adverse events that were less frequent (< 5%) did not.

Another study investigating reasons for dropout in patients treated with SSRIs demonstrated that 43% of patients who discontinued treatment within 3 months of initiating therapy did so because of adverse events, and this proportion dropped to 27% in the following 3 months of treatment, suggesting again that patients who discontinue treatment because of adverse events are most likely to do so early in the course of therapy.[15] Interestingly, most adverse events (like drowsiness/fatigue, anxiety, headache, nausea, insomnia, and dizziness) became less frequent reasons for dropout in the late-treatment stage, while sexual dysfunction and emotional blunting became more frequent reasons for dropout.

Therefore, the aim of the current study is to further investigate the likely course of adverse events during 6 months of treatment with SSRIs.

METHOD

Inclusion Criteria

Eighty-five patients suffering from DSM-IV–diagnosed major depressive disorder (with the exclusion of other DSM-IV Axis I disorders) were enrolled by psychiatrists in an outpatient setting between September 2002 and March 2003. In this double-blind, randomized, multicenter study with competitive enrollment, patients were treated with either fluoxetine (N = 42) (20 mg/day) or paroxetine (N = 43) (20 mg/day) for 22 weeks after a 1-week washout placebo lead-in period at a regimen of 1 pill per day. It was the first treatment with antidepressants for the current depressive episode.

Patient visits were at baseline (visit 1) and at the end of the 1-week placebo run-in period (visit 2) and then subsequently 2 weeks (visit 3), 6 weeks (visit 4), 10 weeks (visit 5), 14 weeks (visit 6), 18 weeks (visit 7), and 22 weeks (visit 8) after the actual treatment was initiated. The study was performed according to the standards of Good Clinical Practice. The protocol was approved by the ethical committees of all the participating centers, and all patients gave their written consent.

Outcomes

The clinical evolution was assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D-17).[16] Treatment-emergent adverse events were assessed with the UKU Side Effect Rating Scale (UKU),[17] systematically investigating the presence/absence of 48 adverse events in several categories (psychic, neurologic, autonomic, and other, including dermatologic, gynecologic, and sexual adverse events as well as weight changes and headaches) and their severity (absent = 0, mild = 1, moderate = 2, severe = 3). The scoring of the severity was based upon the last 3 days prior to the visit. The investigator administered both the HAM-D-17 and the UKU at each visit.

Statistical Analysis

Results are reported as mean ± SD or as counts and percentages. Time-related data were analyzed by means of the generalized linear mixed-model approach to assess the time effect and baseline covariates, while accounting for repeated assessments in each patient. Results were considered to be significant at the 5% critical level ($p < .05$). Calculations were performed using SAS (version 8.2 for Windows) (SAS Institute, Cary, N.C.) and S-Plus (version 6.2) (Insightful Corporation, Seattle, Wash.) statistical software.

RESULTS

The characteristics of the patient population are given in Table 1. The mean age was 40.5 (SD = 10.5) years. Thirty male and 55 female patients were included, of

Table 1. Demographic and Clinical Characteristics of 85 Patients With Major Depressive Disorder (MDD) at Baseline

Variable	Patients
Age, mean ± SD (range), y	40.5 ± 10.5 (22–63)
Sex, N (%)	
Men	30 (35)
Women	55 (65)
Type of MDD, N (%)	
First episode	44 (52)
Recurrent	41 (48)
HAM-D-17 global score, mean ± SD (range)	26.3 ± 3.5 (21–36)

Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Table 2. Evolution of (at least moderately severe) Adverse Events in Patients With Major Depressive Disorder During Treatment With SSRIs

			UKU Side Effect Rating Scale	
Visit	Week	No. of Patients	No. of Patients With at Least 1 Moderately Severe Adverse Event (%)	No. of at Least Moderately Severe Adverse Events per Patient (mean ± SD)
1	0	85	NA	NA
2	1	83	48 (58)	3.51 ± 3.5
3	3	77	53 (69)	3.09 ± 3.2
4	7	74	43 (58)	1.97 ± 2.6
5	11	69	38 (55)	1.70 ± 2.2
6	15	64	32 (50)	1.58 ± 2.2
7	19	61	30 (49)	1.31 ± 1.9
8	23	58	24 (41)	1.19 ± 1.8

Abbreviations: NA = not applicable, SSRI = selective serotonin reuptake inhibitor.

whom 44 suffered from a first episode and 41 from a recurrent episode of depression (with at least 1 previous episode during which antidepressants were taken). Among the 85 patients, 58 reached 6 months of treatment. The mean ± SD HAM-D-17 global score was 26.3 ± 3.5 at baseline and decreased progressively to 8.6 ± 8.8 at endpoint. Completers were older than dropouts (mean ± SD = 43.1 ± 11.0 vs. 35.7 ± 8.1 years; p = .004) and more severely depressed (HAM-D-17 score: mean ± SD = 27.0 ± 3.5 vs. 25.2 ± 3.3; p = .02). Overall, adverse events decreased with time: the percentage of patients with at least 1 moderately severe adverse event decreased from 58% at week 2 to 41% at 6 months of treatment, and the mean number of at least moderately severe adverse events per patient decreased from 3.5 at week 2 to 1.2 at 6 months of treatment (Table 2).

More severely depressed patients reported overall more (at least moderately severe) adverse events than less severely depressed patients (p = .0002), but the decrease in reported adverse events was comparable over time. This was especially true for the psychic (p = .0001), neurologic (p = .03), and autonomic adverse events (p = .005) as well as for headaches (p = .0004). For dermatologic, gynecologic, and sexual adverse events as well as for weight changes, no significant correlation was found with the initial severity of depression.

The decrease in reported adverse events over time (between visit 2 and last observation) was moderately but significantly correlated with the decrease in severity of depression (r = 0.26, p = .03).

A generalized linear mixed model, including sex (men vs. women), dropout status (dropouts vs. completers), and episode (first vs. recurrent) as predictive variables, was fitted to the evolution in number of at least moderately severe adverse events as dependent variable (Figure 1). The number of reported adverse events decreased nonlinearly with time (linear and quadratic effects; p < .0001 and p < .0001, respectively). Men and women initially experienced the same number of at least moderately severe adverse events, but the decrease (habituation) was more rapid in men (p < .0001). Dropouts and completers initially experienced the same number of at least moderately severe adverse events, but the decrease (habituation) was more rapid in completers (p = .014). Male patients suffering from a recurrent episode had a more rapid decrease in adverse events than those suffering from a first episode (p = .0025); this effect was not found in female patients.

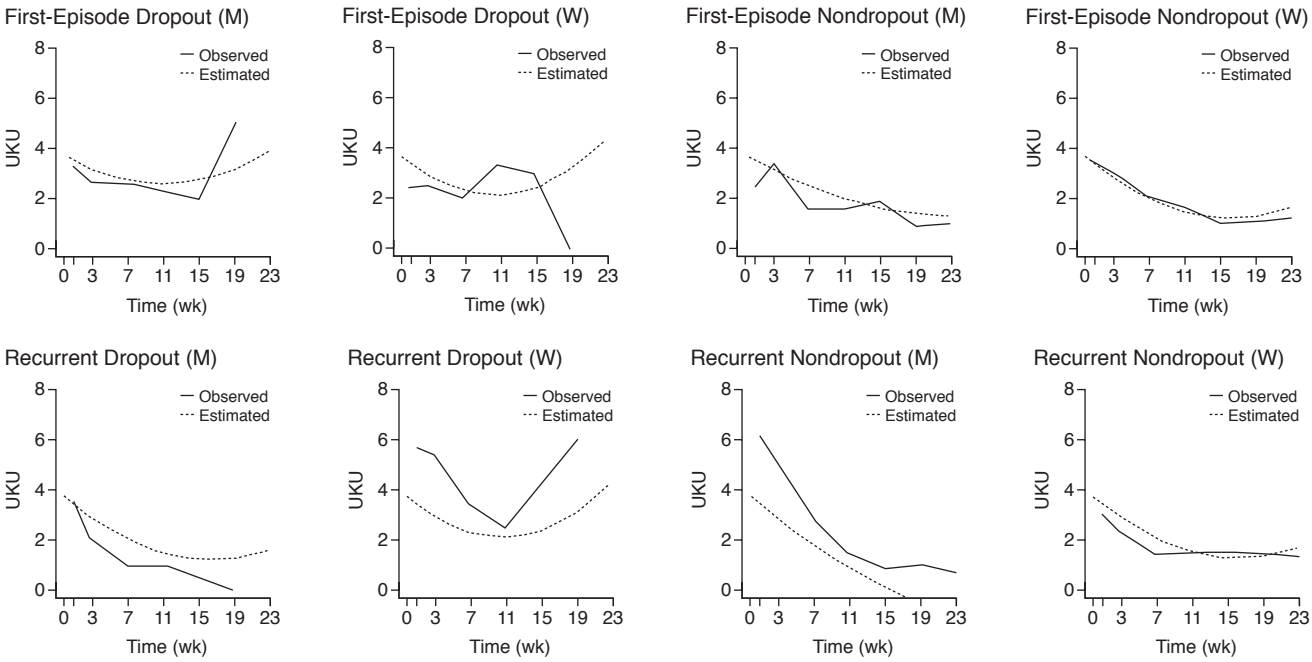
The initial number of reported adverse events and the evolution over time was not different for patients taking fluoxetine or patients taking paroxetine. At all visits, the proportion of patients reporting at least 1 moderately severe or severe adverse event was comparable for fluoxetine and paroxetine users.

DISCUSSION

The number of patients reporting at least 1 moderately severe or severe adverse event as well as the number of reported adverse events per patient decreased with time. This is consistent with the existing literature, in which it was indeed described that, overall, the resolution of early-onset events is more important than the possible emergence of later-onset events.[12] This decrease over time has been most frequently reported with nausea.[18] With paroxetine, it was shown that the onset of nausea occurred within the first week after treatment initiation (2.5 ± 1.3 days) and lasted 4.5 ± 3.5 days; with fluoxetine, it occurred somewhat later (13.5 ± 10.8 days), and the duration was roughly equivalent (5.3 ± 5.2 days).[19] With the latest SSRI, escitalopram, it was shown that for nausea being the most frequently reported adverse event, the difference to placebo disappeared within the first 2 weeks of double-blind treatment.[14] With the dual reuptake inhibitor duloxetine, patients reporting treatment-emergent nausea first did so within 2 days of initiating treatment, while the median duration of nausea was 5 days.[20]

More severely depressed patients report more adverse events than less severely depressed patients, but the decrease in reporting is similar regardless of initial de-

Figure 1. Evolution of the Number of Adverse Events (as assessed with the UKU Side Effect Rating Scale) Over Time in Patients With Major Depressive Disorder During Treatment With SSRIs[a,b]



[a]Men vs. women, dropouts vs. completers, and first- vs. recurrent-episode patients.
[b]Observed evolutions are represented by solid lines, and fitted evolutions, as obtained by a generalized linear mixed-model analysis, are represented by dotted lines.
Abbreviations: M = men, SSRI = selective serotonin reuptake inhibitor, W = women.

pression severity. This has been insufficiently investigated with antidepressants. A tendency for more adverse events as well as more severe adverse events in more severely depressed patients has been reported, at least during antipsychotic treatment. It was indeed shown that among patients who were no longer considered ill at the time of assessment, 50% were considered to have no side effects at all, whereas among the most severely ill patients, only 21% were considered free of side effects.[17] Further, among the least ill patients, only 16% were considered to have side effects that interfered with their daily performance, whereas among the most severely ill patients, 49% were affected by interfering adverse events.

Our finding of a more frequent reporting of adverse events in the more severely depressed patients has to be interpreted with caution. Indeed, the UKU has 10 items on psychic side effects (concentration difficulties, asthenia/lassitude, sleepiness/sedation, failing memory, depression, tension/inner unrest, increased duration of sleep, reduced duration of sleep, increased dream activity, emotional indifference). Therefore, the differentiation between symptoms of depression and treatment-emergent psychic adverse events is difficult. However, the finding that the decrease in adverse events is significantly—but only slightly—correlated with the decrease in HAM-D-17 scores ($r = 0.26$, so less than 7% of correlation) suggests that the investigators were most probably able to differentiate between psychic symptoms of the depressive disorder and treatment-emergent psychic symptoms.

The most interesting and new finding is the different course in adverse events in men and women, in completers and dropouts, and in first-episode and recurrent-episode patients. Men and women showed no significant sex differences in baseline reporting of at least moderately severe adverse events, but the decreasing course over time was more pronounced in men than in women, suggesting a slower habituation in women.

We did not find one study in the literature looking at sex differences in the 6-month course of reported adverse events with antidepressants. A recent study also using the UKU showed that all sex differences in reported adverse events (in patients treated with clomipramine, paroxetine, or moclobemide) were statistically nonsignificant.[21] However, the study was run only over 5 weeks. Moreover, the authors only looked at 2 timepoints and found no significant sex differences in prevalence of adverse events at baseline or after 4 weeks of treatment. Whether the slower habituation in women than in men is due to pharmacodynamic or pharmacokinetic differences or to psychological mechanisms (awareness, acceptance, attribution, or willingness to report) is speculative but supports the thesis that too little basic clinical research has been conducted on sex

differences in therapeutic effects and side effects of antidepressants.[22] A limitation of this study is that due to the small number of patients, we were not able to control for menstrual-phase–specific or for premenstrual versus postmenopausal differences.

Adverse events are generally believed to be the most important reason for early discontinuation of treatment, at least in clinical trials. However, the present data suggest that dropouts and completers (in a 6-month trial) initially report similar rates of adverse events but that dropouts habituate less to these adverse events. The existing literature never reported on the time course of adverse events until patient dropout.

Only in men, a history of treatment with antidepressants for a previous episode results in a more rapid habituation to the adverse events. Again, to the best of our knowledge, this has never been reported in the literature to date. The number of previous episodes treated with antidepressants was not assessed in the present study; however, the patient population was too small to analyze a possible relation with the number of previous episodes (with antidepressant treatment).

No significant difference in severity or time course of adverse events was found in patients treated with fluoxetine or patients treated with paroxetine. However, the number of investigated subjects was too small to detect possible differences. For example, initial weight loss (of at least 3–4 kg) was found in 17% of fluoxetine users and in 5% of paroxetine users, while at the end of the study, weight gain (of at least 3–4 kg) was found in 4% of fluoxetine users and in 10% of paroxetine users, but the number of included patients was too small to find statistically significant differences.

A few additional limitations of the present study need to be addressed. First, the reporting of adverse events may be influenced by the way this reporting is done. Our method (using the UKU to assess adverse events in a more systematic way) may result in an overestimation if the patient is made to feel that such symptoms are acceptable. However, other methods like spontaneous self-reporting may result in an underestimation if the patient feels that such symptoms are not acceptable. Second, we cannot conclude on a real association or attribution of causal inference between the antidepressant and the adverse event. The investigators were not invited to give their judgment on the likeliness of a causal link between the reported adverse event and the antidepressant treatment. However, the reliability of such judgments has never been adequately proven.

In conclusion, the study demonstrates that adverse events are more frequent in more severely depressed patients. The reporting of adverse events also decreases with time. Moreover, dropouts initially do not experience more adverse events than completers, but their habituation to the adverse events is slower. Men and women initially experience comparable rates of adverse events, but there is a more rapid habituation in men. Finally, when comparing recurrent with first-episode patients, the habituation to the adverse events is faster in recurrent-episode patients but only in men.

Drug names: clomipramine (Anafranil and others), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac and others), paroxetine (Paxil and others).

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