ORIGINAL ARTICLES

Selective Serotonin Reuptake Inhibitor Discontinuation Syndrome: A Randomized Clinical Trial

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Background: *Recent reports describe discontinuation-emergent adverse events upon cessation of selective serotonin reuptake inhibitors including dizziness, insomnia, nervousness, nausea, and agitation. We hypothesized that interruption of fluoxetine treatment would be associated with fewer discontinuation-emergent adverse events than interruption of sertraline or paroxetine treatment, based on fluoxetine's longer half-life.*

Methods: *In this 4-week study, 242 patients with remitted depression receiving maintenance therapy with open-label fluoxetine, sertraline, or paroxetine for 4–24 months had their maintenance therapy interrupted with double-blind placebo substitution for 5–8 days. The Symptom Questionnaire (SQ), the Discontinuation-Emergent Signs and Symptoms checklist, the 28-item Hamilton Depression Rating Scale, and the Montgomery–Asberg Depression Rating Scale were used to assess somatic distress and stability of antidepressant response.*

Results: *Two hundred twenty patients (91%) completed the study. Following interruption of therapy, fluoxetine-treated patients experienced fewer discontinuation-emergent events than either sertraline-treated or paroxetine-treated patients ($p < .001$). The mean SQ somatic symptom scale score in fluoxetine-treated patients was significantly lower than that in sertraline-treated and paroxetine-treated patients ($p < .001$). Fluoxetine-treated patients also experienced less reemergence of depressive symptoms than sertraline-treated or paroxetine-treated patients ($p < .001$).*

Conclusions: *Abrupt interruption of antidepressant therapy for 5–8 days was associated with the emergence of new somatic and psychological symptoms in patients treated with paroxetine and to a lesser degree sertraline, with few symptoms seen with fluoxetine.* Biol Psychiatry 1998;44:77–87 © *1998 Society of Biological Psychiatry*

Key Words: Discontinuation-emergent events, selective serotonin reuptake inhibitors, withdrawal events, treatment interruption, fluoxetine

Introduction

Major depressive disorder is a recurrent illness that often requires long-term antidepressant therapy to minimize the risks of relapse and recurrence. During any long-term pharmacologic treatment regimen, the potential for deviations from the prescribed dosing instructions is substantial. Patient noncompliance with treatment regimens has been reported to be as high as 82% (Buckalew and Sallis 1986), but generally it is estimated to be between 20% and 50% (Olivier-Martin 1986; Young et al 1986).

Since becoming available in the late 1980s, selective serotonin reuptake inhibitors (SSRIs) have emerged as first-line drugs for treating depressive disorders, perhaps in part because of the greater simplicity of dosing relative to the older tricyclic antidepressants (TCAs). In addition, while not proven to be more efficacious than the TCAs, the SSRIs present an improved safety and tolerability profile during treatment (Montgomery et al 1994).

The possibility of adverse effects upon discontinuation of a TCA is well documented (Ceccherini-Nelli et al 1993; Dilsaver et al 1983; Dilsaver and Greden 1984). Symptoms may include abdominal pain, anorexia, chills, diaphoresis, diarrhea, fatigue, headache, malaise, myalgia, nausea, vomiting, and weakness (Lejoyeux et al 1996). To minimize these effects, gradual tapering of the TCA dose at the end of the treatment course has become standard practice.

Less is known regarding the relative tolerability of abrupt discontinuation of the SSRIs at the end of treatment; however, recent reports have described apparent discontinuation-emergent signs and symptoms occurring upon cessation of SSRI treatment (Barr et al 1994; Einbinder 1995; Fava and Grandi 1995; Frost and Lal 1995; Kasantikul 1995; Koopowitz and Berk 1995; Leiter et al 1995; Louie et al 1994; Pyke 1995; Stoukides and Stoukides 1991). Dizziness, headache, nausea, vomiting, diarrhea, movement disorders, insomnia, irritability, visual disturbance, lethargy, anorexia, tremor, electric shock sensations, and lowered mood have all been reported in association with cessation of SSRI treatment (Coupland et al 1996; Lejoyeux et al 1996; Price et al 1996). During clinical trials designed to assess the efficacy of paroxetine

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Table 1. Demographic and Symptom Measurements at Visit 1

Characteristic	Fluoxetine (n = 81)	Sertraline (n = 79)	Paroxetine (n = 82)
Age (years) (mean ± SD)	42.0 ± 10.6	44.3 ± 12.4	46.1 ± 12.8
Sex (M/F) [No. (%)]	24 (29.6)/57 (70.4)	15 (19.0)/64 (81.0)	16 (19.5)/66 (80.5)
SSRI maintenance therapy (mg/day) (mean ± SD)	24.7 ± 26.7	74.7 ± 80.9	21.7 ± 22.6
Duration of current SSRI therapy (months) (mean ± SD)	11.3 ± 5.2	11.4 ± 5.5	11.6 ± 5.9
$HDRS_{28}$ total score (mean ± SD)	7.7 ± 5.2	8.4 ± 6.6	7.8 ± 6.0
MADRS total score (mean ± SD)	6.7 ± 5.1	7.2 ± 5.9	6.3 ± 4.9

$HDRS_{28}$, 28-item Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor.

in obsessive–compulsive disorder and panic disorder, between 35% and 50% of patients experienced discontinuation-emergent events following cessation of therapy (Barr et al 1994; Keuthen et al 1994; Oehrberg et al 1995), and a medication taper did not always prevent their occurrence (Barr et al 1994; Keuthen et al 1994). Discontinuation-emergent symptoms are usually mild and transient, but debilitating symptoms causing severe discomfort and absenteeism have been reported (Barr et al 1994; Koopowitz and Berk 1995).

Previous studies have suggested that the risk for these events is related to drug half-life, but these studies have been retrospective, lacking placebo control, and without a consistent and systematic method for collection of adverse events (Bhaumik and Wildgust 1996; Coupland et al 1996; Gillespie et al 1996; Keuthen et al 1994; Lazowick and Levin 1995; Oehrberg et al 1995; Price et al 1996).

The purpose of the current study was to examine in a prospective, controlled manner the effects of abrupt interruption of long-term antidepressant treatment that mimics intermittent noncompliance. We hypothesized that because fluoxetine has a longer half-life than sertraline or paroxetine (van Harten 1993), interruption of fluoxetine treatment would be associated with fewer discontinuation-emergent adverse events than interruption of sertraline or paroxetine treatment.

Methods and Materials

Study Design

This was a multicenter open-label, 4-week study, which included a 1-week (5–8 days) randomized double-blind, placebo-substitution period. The primary objective of the study was to compare the mean number of discontinuation-emergent events following a treatment interruption (placebo-substitution) period in patients with remitted depression on maintenance therapy with fluoxetine, sertraline, or paroxetine. Secondary objectives were to compare specific reported adverse events and to assess stability of antidepressant response following a brief interruption of SSRI therapy.

The study consisted of three study periods: baseline (Study Period I), treatment interruption (Study Period II), and restabilization (Study Period III). Patients were seen weekly from the baseline visit through the final visit. The actual interval allowed for weekly visits was 5–8 days; thus, the actual number of days of placebo substitution (if subject was randomized to placebo) was determined by the scheduling of the next visit. Eighty-three percent of the patients were randomized to receive placebo substitution for 1 week (5–8 days) at either Visit 2 or Visit 3; the remaining 17% of the patients were randomized to continuous SSRI therapy. Prior to and immediately following placebo substitution, patients received active SSRI therapy. Clinicians and patients were blinded to the occurrence and timing of the treatment interruptions. The alternative scheduling of the placebo substitution and the small number of patients randomized to continuous SSRI therapy were intended to create and preserve the blinding of the study. The number of patients randomized to continuous SSRI therapy was too small to serve as a control group.

Participants

The eligibility criteria for participation in the trial were 1) age ≥18 years; 2) historical diagnosis of unipolar depressive disorders for which the current effective maintenance therapy with fluoxetine, sertraline, or paroxetine was prescribed; 3) Montgomery–Asberg Depression Rating Scale (MADRS) score of ≤25; and 4) current continuous maintenance treatment (fluoxetine 20, 40, or 60 mg/day; sertraline 50, 100, or 150 mg/day; or paroxetine 20, 40, or 60 mg/day) of depression for >4 months and <24 months. Mean doses are presented in Table 1.

Exclusionary conditions were 1) pregnant or lactating women or women of child-bearing potential not using a medically accepted means of contraception; 2) risk for suicide; 3) comorbid serious medical illness that was not stabilized and possibly requiring hospitalization within the next 3 months; 4) presence of a seizure disorder with a seizure occurring within the last year; 5) presence of one or more of the following DSM-IV diagnoses: organic mental disorder, substance-use disorder, schizophrenia, delusional disorder, psychotic disorders not elsewhere classified, bipolar disorder, and antisocial personality disorder; 6) mood-congruent or mood-incongruent psychotic features; 7) concomitant use of any antidepressant (other than study drugs), anxiolytic, or other psychotropic medication within 7 days prior to

study entry, with the exception of chloral hydrate and zolpidem; and 8) hyper- or hypothyroidism (thyroid replacement was allowed, and patients were allowed to enter if they were clinically and biochemically euthyroid).

The study was approved by the Western Institutional Review Board, and all participants gave written informed consent to be in the study.

Measurements and Procedures

Data were collected at baseline and at the end of each visit interval by clinicians blinded to treatment group assignment (timing of placebo-substitution or continuous SSRI therapy).

DISCONTINUATION-EMERGENT SIGNS AND SYMPTOMS (DESS) CHECKLIST. Assessment of possible discontinuation-emergent events was made using the DESS checklist (see Appendix). The DESS checklist is a clinician-rated instrument that queries for signs and symptoms associated with discontinuation or interruption of SSRI treatment. The 43-item list was developed by the investigators based on an evaluation of signs and symptoms reported in the available literature.

SYMPTOM QUESTIONNAIRE (SQ). All patients were administered the SQ (Kellner 1987). The SQ is a self-rating scale consisting of 92 items, of which 68 describe symptoms (symptom scales) and 24 describe antonyms of some of the symptoms to collectively indicate well-being (well-being scales). The 92 items form the basis for four scales: depression, anxiety, anger–hostility, and somatic symptoms. Validity of this instrument has been well established in clinical research settings, and these self-rating scales have been shown to be more sensitive than observer-rated scales (Kellner 1987, 1992).

The somatic symptom scale was used to assess somatic distress. The depression, anxiety, and anger–hostility scales were used to assess stability of antidepressant response.

COLLECTION OF SPONTANEOUSLY REPORTED EVENTS. Spontaneously reported adverse events were elicited by general inquiry prior to administration of the SQ and the DESS checklist.

MADRS AND 28-ITEM HAMILTON DEPRESSION RATING SCALE ($HDRS_{28}$). A maximum score on the MADRS (Montgomery and Asberg 1979) was used to assess eligibility for enrollment and, in conjunction with the $HDRS_{28}$ (Hamilton 1960), to monitor the stability of antidepressant response under conditions of missed doses. Both the $HDRS_{28}$ and MADRS are valid, widely accepted clinician-rated instruments, which measure depressive symptomatology.

Statistical Analyses

Two sets of statistical analyses were conducted. The majority of the analyses were comparisons among the drug treatment groups and included only the patients whose treatment was interrupted. To confirm the results of the drug-to-drug comparisons, additional analyses were conducted to compare these three groups: patients whose treatment was interrupted at Visit 2, patients whose treatment was interrupted at Visit 3, and patients whose treatment was not interrupted. These analyses were conducted separately within each drug treatment group.

For the drug-to-drug comparisons among the patients whose treatment was interrupted, the number of discontinuation-emergent events, the SQ scales, the MADRS, and the $HDRS_{28}$ were treated as continuous measurements. In these analyses, patients whose treatment was interrupted at Visit 2 were combined with patients whose treatment was interrupted at Visit 3, and comparisons among the drugs were made before treatment interruption, after treatment interruption, and after restabilization on active therapy. The change from the beginning to the end of the treatment interruption period and from the beginning to the end of the restabilization period was also computed for each patient.

For each continuous variable, the mean and standard deviation of the change from the beginning to the end of the treatment interruption period and from the beginning to the end of the drug restabilization period were calculated. A least-squares estimate of the mean change, adjusted for investigator effects, was used to test the hypothesis that these changes were equal to 0. Continuous measurements and changes in continuous measurements were compared among groups using analysis of variance (ANOVA) with terms for drug treatment group and investigator. Terms for drug treatment group by investigator interaction were added to the models if the associated p values were .1 or lower.

For each continuous variable analyzed, pairwise differences of the means of the three drug treatments were computed. These were treated as planned comparisons. Statistical significance was assessed using Fisher's method of protected least-significant differences, with a preset $\alpha = .05$ significance level.

To simplify interpretation of the results, several sets of categorical variables were defined from the continuous variables. Patients were classified as experiencing a "discontinuation syndrome" if the number of DESS checklist events reported increased by four or more from the beginning to the end of the treatment interruption period. The presence or absence of the syndrome was treated as a categorical measurement. To examine breakthrough of depressive symptoms, indicator variables were defined for each patient marking increases of 8, 10, and 12 points in the $HDRS_{28}$ score after placebo substitution and decreases of 8, 10, and 12 points in the $HDRS_{28}$ score after active drug restabilization. To provide additional clinical context, a depressive relapse was defined as an increase of 8 points or more in the $HDRS_{28}$ score and a total score of 16 or higher.

Categorical variables were compared among the drug treatments using likelihood ratio χ^2 statistics with 2 df. The likelihood ratio χ^2 statistics were decomposed into a component due to the difference between the fluoxetine group and the combined sertraline and paroxetine groups and a second component due to the difference between the sertraline and paroxetine groups. To assess potential confounding due to investigators, these comparisons were repeated with the analysis stratified by investigative site using a Cochran–Mantel–Haenszel (CMH) statistic with 2 df.

The number of discontinuation-emergent events and the $HDRS_{28}$ were compared among the three interruption groups within each drug. The Visit 1 measurement was subtracted from

the Visit 2, 3, 4, and 5 measurements to adjust for baseline variation among the interruption groups. ANOVA models were then fit for these changes from baseline using the same procedure as for the comparison between the drug treatments. In addition to pairwise comparisons of the means of the interruption groups, linear contrasts were used to compare patients whose treatment was interrupted at Visit 2 with a group of patients whose treatment was interrupted at Visit 3 combined with the patients whose treatment was not interrupted. As a check against possible departures of the data from a normal distribution, the treatment interruption group comparisons were repeated using the Brown–Mood median test, and the nonparametric results were compared with the ANOVA results.

To assess the effects of length of placebo interruption on severity of patient symptoms at interruption, analysis of covariance (ANCOVA) models with terms for Drug, Investigator, and Drug × Investigator interaction were fit to the total number of DESS, the SQ Somatic Symptoms scale, the $HDRS_{28}$ total score, and the MADRS total score. The models contained continuous variables that assumed separate slopes for interruption length. If the interaction terms were not significant at the level of $\alpha = .1$, the models were refit without the Drug × Investigator interaction terms. Comparisons among the drug treatments were made by computing least squares means of the symptoms at interruption and testing for differences between them. Additionally, the mean severity of symptoms after 7 days of interruption was estimated through the model. As a check on the ANCOVA results, a subgroup model was fit including only those patients whose interruptions lasted precisely 7 days.

The effects of duration of prior therapy on severity of patient symptoms were assessed by similar ANCOVA models, although here the models fit a single overall slope and two terms for Duration of Therapy × Drug interaction. As a check on the subgroup analysis for duration of therapy, mean severity of symptoms was estimated after 11 months of SSRI treatment, and a subgroup model was fit including only patients whose duration of prior therapy fell in the midrange of durations, computed over all treatment groups combined.

Results

Baseline Patient Comparisons

The treatment groups were demographically comparable at baseline. Mean duration of therapy, mean $HDRS_{28}$ scores, and mean MADRS scores also were comparable, as shown in Table 1.

Of the 242 patients randomized to the experimental conditions, 231 remained eligible for Study Period II; 192 patients were assigned to interrupted therapy (placebo substitution) for 1 week and 39 patients were assigned to continue on active therapy.

Two hundred twenty patients (91%) completed the study. Four patients discontinued during the placebo-substitution period due to adverse events: 1 fluoxetine-treated patient discontinued to seek medical intervention for an ovarian cyst, and 3 paroxetine-treated patients discontinued due to vertigo, abnormal dreams, and vomiting, respectively. Other discontinuations were due to protocol violations, patient decision, protocol continuation criteria not being met at Visit 2, physician or sponsor decision, or loss to follow-up.

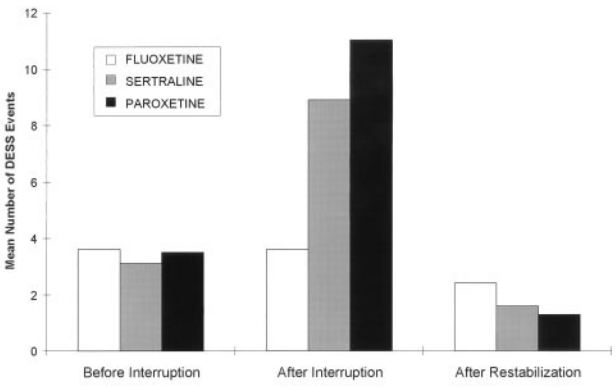

Figure 1. Mean numbers of events on the Discontinuation-Emergent Signs and Symptoms (DESS) checklist. The two interrupted groups were pooled and compared before interruption, after 1 week of interruption, and after 1 week of restabilization. The three treatments showed no difference in the mean numbers of DESS before interruption. Following interruption, the mean number of DESS in the fluoxetine-treated patients was significantly lower than that in either the sertraline-treated or paroxetine-treated patients (both, $p < .001$); the mean number of events in the sertraline-treated patients was significantly lower than that in the paroxetine-treated patients ($p = .020$). After restabilization, the mean number of events in the paroxetine-treated patients was significantly lower than that in the fluoxetine-treated patients ($p = .010$).

Somatic Distress

DESS CHECKLIST. Following treatment interruption, mean increases in the number of DESS were significant in the sertraline-treated (5.7 ± 6.96; $p < .001$) and paroxetine-treated (7.8 ± 8.55; $p < .001$) patients but not in the fluoxetine-treated (0.2 ± 5.22; $p = .578$) patients.

When comparing across treatment groups, the mean numbers of DESS were statistically significantly different after treatment interruption and after restabilization but not before treatment interruption (Figure 1). Following treatment interruption, the mean number of DESS was significantly lower in the fluoxetine-treated patients than in either the sertraline-treated or paroxetine-treated patients (both, $p < .001$). The mean number of DESS was also significantly lower in the sertraline-treated than in the paroxetine-treated patients ($p = .020$). At the end of restabilization, the mean number of DESS was significantly higher in the fluoxetine-treated than in the paroxetine-treated patients ($p = .010$).

Table 2. Percentage of DESS Reported by ≥10% of Patients (in Descending Order by Pooled Treatments)

Symptom	Fluoxetine (n = 63)	Sertraline (n = 63)	Paroxetine (n = 59)
Worsened mood	22	28	45
Irritability	17	38	35
Agitation	16	37	31
Dizziness	3	29	50
Confusion	14	23	42
Headache	14	31	34
Nervousness	9	31	34
Crying	6	26	40
Fatigue	16	23	32
Emotional lability	13	31	26
Trouble sleeping	9	22	39
Dreaming	6	25	37
Anger	5	28	29
Nausea	6	14	40
Amnesia	8	17	24
Sweating	8	17	24
Depersonalization	8	17	21
Muscle aches	6	14	23
Unsteady gait	5	15	23
Panic	2	15	21
Sore eyes	6	14	15
Diarrhea	5	6	24
Shaking	2	11	21
Muscle tension	8	14	11
Chills	2	11	18

DESS, discontinuation-emergent signs and symptoms.

At the end of the placebo-substitution period, the incidence of an SSRI "discontinuation syndrome" observed in fluoxetine-treated patients was significantly lower than the pooled incidence for sertraline-treated and paroxetine-treated patients (14%, 60%, 66%, respectively; $p < .001$). The incidence did not differ significantly between sertraline-treated and paroxetine-treated patients ($p = .508$). The most frequently reported events comprising the discontinuation syndrome varied by drug treatment. Table 2 shows the percentages of DESS reported by ≥10% of patients. In the fluoxetine-treated group, seven events were reported by ≥10% of patients; however, the relative incidence of these events in the sertraline-treated and paroxetine-treated groups was greater. In the sertraline-treated group, 27 events were reported by ≥10% of the patients, and in the paroxetine-treated group, 35 events were reported by ≥10% of the patients.

SQ SOMATIC SYMPTOM SCALE. Following treatment interruption, mean score changes were significant in the sertraline-treated (2.3 ± 3.93; $p < .001$) and paroxetine-treated (3.9 ± 5.61; $p < .001$) patients but not in the fluoxetine-treated (-0.2 ± 3.56; $p = .614$) patients.

When comparing across treatment groups, the mean scores were statistically significantly different after treatment interruption but not before treatment interruption or after restabilization (Figure 2). Following treatment interruption, the mean score was significantly lower in the fluoxetine-treated patients than in either the sertraline-treated or paroxetine-treated patients (both, $p < .001$). The difference between the mean scores in the sertraline-treated and paroxetine-treated patients was not significant ($p = .318$).

SPONTANEOUS ADVERSE EVENTS (TREATMENT INTERRUPTION). For patients undergoing placebo substitution, there was no statistically significant difference across treatment groups in the number of spontaneously reported adverse events at the beginning of treatment. Following treatment interruption, fluoxetine-treated patients reported significantly fewer events than sertraline-treated ($p = .001$) or paroxetine-treated ($p < .001$) patients. At the end of restabilization, there were no statistically significant differences across treatment groups.

When comparing across treatment groups following placebo substitution, the only event spontaneously reported by ≥10% of fluoxetine-treated patients (16%) was headache. Four events (dizziness, 18%; headache, 18%; nervousness, 18%; and nausea, 11%) were reported spontaneously by ≥10% of sertraline-treated patients, and eight events (dizziness, 29%; nausea, 29%; insomnia, 19%; headache, 17%; abnormal dreams, 16%; nervousness, 16%; asthenia, 11%; and diarrhea, 11%) were reported by ≥10% of paroxetine-treated patients.

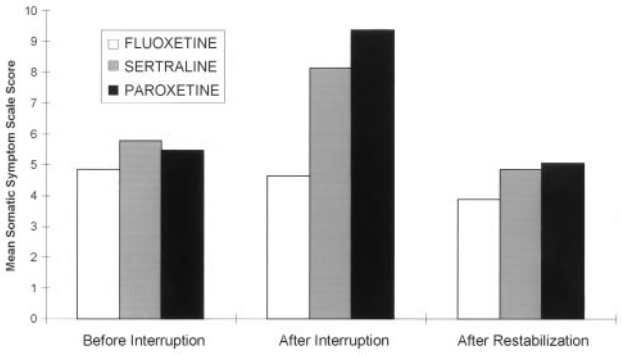

Figure 2. Mean scores on the Symptom Questionnaire (SQ) somatic symptoms scale. The two interrupted groups were pooled and compared before interruption, after 1 week of interruption, and after 1 week of restabilization. The three treatments showed no difference in mean scores before interruption. Following interruption, the mean score in the fluoxetine-treated patients was significantly lower than that in either the sertraline-treated or paroxetine-treated patients (both, $p < .001$). The three treatments showed no difference in mean scores after restabilization.

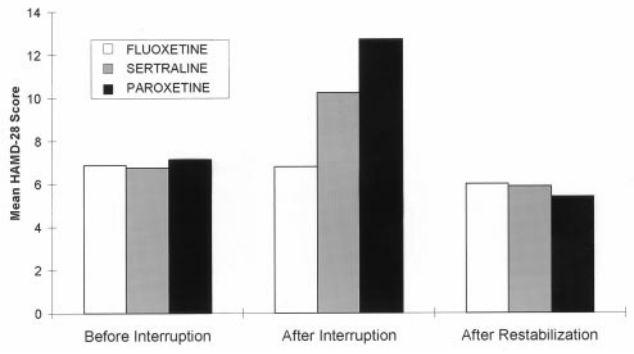

Figure 3. Mean scores for the 28-item Hamilton Depression Rating Scale ($HAMD_{28}$). The two interrupted groups were pooled and compared before interruption, after 1 week of interruption, and after 1 week of restabilization. The three treatments showed no difference in mean scores before interruption. Following interruption, the mean score in the fluoxetine-treated patients was significantly lower than that in either the sertraline-treated ($p = .004$) or paroxetine-treated ($p < .001$) patients. The three treatments showed no difference in means after restabilization.

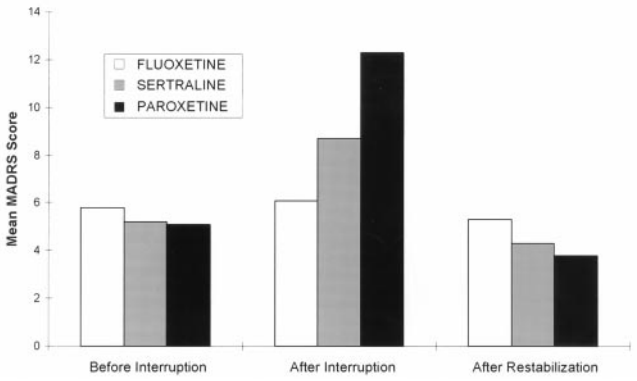

Figure 4. Mean scores for Montgomery–Asberg Depression Rating Scale (MADRS). The two interrupted groups were pooled and compared before interruption, after 1 week of interruption, and after 1 week of restabilization. The three treatments showed no difference in mean scores before interruption. Following interruption, the mean score in the fluoxetine-treated patients was significantly lower than that in either the sertraline-treated ($p = .019$) or paroxetine-treated ($p < .001$) patients. The three drug treatments showed no difference in means after restabilization.

Stability of Antidepressant Response

$HDRS_{28}$ SCORES. Following treatment interruption, mean changes in $HDRS_{28}$ scores were significant in the sertraline-treated (3.5 ± 6.68; $p < .001$) and paroxetine-treated (5.6 ± 9.20; $p < .001$) patients but not in the fluoxetine-treated (-0.1 ± 5.26; $p = .943$) patients.

When comparing across treatment groups, the mean $HDRS_{28}$ scores were statistically significantly different after treatment interruption but not before treatment interruption or after restabilization (Figure 3). Following treatment interruption, the mean score was significantly lower in the fluoxetine-treated patients than in either the sertraline-treated ($p = .004$) or paroxetine-treated patients ($p < .001$). The difference between the mean scores in the sertraline-treated and paroxetine-treated patients was not significant ($p = .062$) but showed a trend toward significance.

The numbers and proportions of patients experiencing large increases in $HDRS_{28}$ scores after placebo substitution are given in Table 3. Fewer fluoxetine-treated patients showed substantial increases in depressive symptoms from the beginning to the end of the treatment interruption period. Substantial increases in $HDRS_{28}$ scores (≥ 8 points) during the treatment interruption week occurred in 30% of sertraline-treated and 36% of paroxetine-treated patients. Examination of the likelihood ratio χ^2 statistics showed highly significant differences between fluoxetine-treated patients and those treated with the two comparator drugs combined ($p < .001$), but did not show significant differences between sertraline-treated and paroxetine-treated patients ($p = .523$). Repeating the comparisons after adjusting for investigator effects using the CMH statistic gave similar results.

Table 3. Changes in $HDRS_{28}$ Scores after Treatment Interruption

Increase during 5–8 days of placebo substitution	Fluoxetine ($n = 63$)	Sertraline ($n = 63$)	Paroxetine ($n = 59$)
≥ 8	4 (6%)	19 (30%)	21 (36%)
≥ 10	2 (3%)	12 (19%)	16 (27%)
≥ 12	1 (2%)	9 (14%)	12 (20%)

$HDRS_{28}$, 28-item Hamilton Depression Rating Scale.

The numbers and proportions of patients experiencing a relapse in depression were significantly smaller in fluoxetine-treated patients (2%) than in the pooled group of patients treated with sertraline (14%) or paroxetine (27%) ($p < .001$ for paroxetine and sertraline pooled). The fraction of sertraline-treated patients experiencing a relapse was not significantly less than that in the paroxetine-treated patients ($p = .079$), although the difference showed a trend toward significance.

MADRS SCORES. Following treatment interruption, mean increases in MADRS scores were significant in the sertraline-treated (3.6 ± 7.00; $p < .001$) and paroxetine-treated (7.3 ± 10.33; $p < .001$) patients but not in the fluoxetine-treated (0.3 ± 6.12; $p = .616$) patients.

When comparing across treatment groups, the mean MADRS scores were statistically significantly different after treatment interruption but not before treatment interruption or after restabilization (Figure 4). Following treatment interruption, the mean score was significantly lower in the fluoxetine-treated than in either the sertraline-

treated ($p = .019$) or paroxetine-treated ($p < .001$) patients. The difference between the mean scores in the sertraline-treated and paroxetine-treated patients was not significant ($p = .058$), although a trend toward significance was shown.

SQ ANXIETY SCALE. Following treatment interruption, mean changes in the anxiety scale scores were significant in the sertraline-treated (2.9 ± 6.54; $p < .001$) and paroxetine-treated (4.0 ± 7.96; $p < .001$) patients but not in the fluoxetine-treated (0.5 ± 4.50; $p = .515$) patients.

When comparing across treatment groups, the mean scores were statistically significantly different after treatment interruption but not before treatment interruption or after restabilization. Following treatment interruption, the mean score was significantly lower in the fluoxetine-treated than in either the sertraline-treated ($p = .017$) or paroxetine-treated ($p = .001$) patients. The difference between the mean scores in the sertraline-treated and paroxetine-treated patients was not significant ($p = .372$).

SQ DEPRESSION SCALE. Following treatment interruption, mean changes in the depression scores were significant in the sertraline-treated (3.0 ± 5.97; $p < .001$) and paroxetine-treated (4.4 ± 6.44; $p < .001$) patients but not in the fluoxetine-treated (0.0 ± 4.56; $p = .998$) patients.

When comparing across treatment groups, the mean scores were statistically significantly different after treatment interruption but not before treatment interruption or after restabilization. Following treatment interruption, the mean score was significantly lower in the fluoxetine-treated patients than in either the sertraline-treated $p = .049$) or paroxetine-treated ($p = .009$) patients. The difference between the mean scores in the sertraline-treated and paroxetine-treated patients was not significant ($p = .497$).

SQ ANGER/HOSTILITY SCALE. Following treatment interruption, mean increases in the anger/hostility scores were significant in the sertraline-treated (4.8 ± 7.39; $p < .001$) and paroxetine-treated (4.8 ± 7.68; $p < .001$) patients but not in the fluoxetine-treated (1.4 ± 5.55; $p = .143$) patients.

When comparing across treatment groups, the mean scores were statistically significantly different after treatment interruption but not before treatment interruption or after restabilization. Following treatment interruption, the mean score was significantly lower in the fluoxetine-treated patients than in either the sertraline-treated ($p = .010$) or paroxetine-treated ($p = .006$) patients. The difference between the mean scores in the sertraline-treated and paroxetine-treated patients was not significant ($p = .828$).

INTERRUPTED VS. UNINTERRUPTED. The means and standard deviations for the change in number of DESS checklist events and $HDRS_{28}$ scores from Visit 1 to Visits 3, 4, and 5 were compared by drug treatment and treatment interruption group (Table 4).

LENGTH OF INTERRUPTION AND DURATION OF PRIOR TREATMENT. None of the models incorporating terms for length of interruption detected any significant contribution of interruption length to severity of symptoms. Similarly, results for estimating the effects of duration of prior therapy in this sample were also not significant. Introduction of terms for duration of prior therapy had neglible effects on the estimated means for drug treatment groups, and no effect on the significance of drug-to-drug comparisons.

Discussion

In the present study, patients with interrupted fluoxetine treatment experienced statistically significantly fewer adverse events than patients with interrupted sertraline or paroxetine treatment, as assessed by the DESS checklist, SQ somatic symptom scale, and spontaneously reported adverse events. Furthermore, sertraline-treated and paroxetine-treated patients but not fluoxetine-treated patients experienced a reemergence of depressive symptoms, as assessed by the $HDRS_{28}$ and MADRS.

A number of previous studies have assessed the relative reporting of discontinuation-emergent adverse events associated with individual SSRIs and have suggested that the risk for these events is related to drug half-life (Bhaumik and Wildgust 1996; Coupland et al 1996; Gillespie et al 1996; Keuthen et al 1994; Lazowick and Levin 1995; Oehrberg et al 1995; Price et al 1996); however, these studies were retrospective, lacked placebo control, and were without a consistent and systematic method for collection of adverse events. This study was prospective, with a randomized, double-blind interruption period, and included a systematic method for adverse event collection. Furthermore, both somatic and psychological distress were evaluated. The results observed in patients whose fluoxetine or paroxetine treatment was interrupted were consistent with previous reports; however, interruption of sertraline treatment was associated with more psychological and somatic symptoms than had been reported previously. Following treatment interruption, no statistically significant differences were observed in somatic distress and stability of antidepressant response between sertraline and paroxetine treatment except in the mean number of DESS events reported. While the objective of this study was to evaluate changes in several dimensions following treatment interruption, an interesting pattern of apparently

Table 4. DESS Checklist Events and $HDRS_{28}$ Total Score—Change from Baseline

	Patients interrupted at Visit 2		Patients interrupted at Visit 3		Patients never interrupted	
DESS measurement	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
Fluoxetine						
To Visit 3	28	2.7 ± 4.4	35	2.3 ± 5.0	14	2.3 ± 5.7
To Visit 4	29	2.1 ± 5.0	33	1.7 ± 4.9	14	5.7 ± 8.0
To Visit 5	29	1.6 ± 4.5	33	0.0 ± 3.4	13	−0.1 ± 4.0
Sertraline						
To Visit 3	33	5.9 ± 6.1[b]	31	2.8 ± 4.4[a]	11	5.1 ± 6.3
To Visit 4	30	0.5 ± 4.5[b]	30	7.5 ± 6.9[a,f]	11	2.6 ± 3.7[e]
To Visit 5	30	−0.1 ± 4.1	30	−0.8 ± 3.1	10	3.5 ± 7.9
Paroxetine						
To Visit 3	29	8.4 ± 7.1[e,f]	30	2.0 ± 4.8[d]	13	0.8 ± 3.7[d]
To Visit 4	28	−0.4 ± 3.3[e]	31	9.7 ± 7.4[d,f]	12	0.8 ± 4.0[e]
To Visit 5	28	−0.4 ± 3.5	31	−1.4 ± 2.9	11	0.0 ± 1.9
$HDRS_{28}$ Total						
Fluoxetine						
Visit 3	29	0.5 ± 4.2	35	−0.7 ± 5.7	14	−0.1 ± 5.1
Visit 4	29	−0.1 ± 5.4	34	−1.4 ± 4.7	14	2.5 ± 4.5
Visit 5	29	0.3 ± 6.0	34	−2.5 ± 4.3	14	−3.0 ± 4.5
Sertraline						
Visit 3	32	2.5 ± 6.3	31	−0.7 ± 5.9	11	1.2 ± 7.5
Visit 4	31	−1.4 ± 6.6	31	1.9 ± 8.0[c]	12	−2.2 ± 6.7[b]
Visit 5	30	−2.9 ± 4.9	32	−2.9 ± 5.0	11	0.3 ± 9.0
Paroxetine						
Visit 3	30	4.9 ± 6.6[b,c]	32	−1.0 ± 6.6[a]	13	−1.6 ± 4.1[a]
Visit 4	28	−0.9 ± 5.3[e]	32	5.3 ± 8.3[d,f]	13	−0.8 ± 4.9[e]
Visit 5	28	−1.6 ± 5.8	31	−3.4 ± 5.7	11	−3.6 ± 2.3

p values are computed between interruption groups within drug treatment, using SAS PROC GLM least squares means with Fisher's method of protected least significant differences.

[a] $p < .05$ versus patients interrupted at week 2.
[b] $p < .05$ versus patients interrupted at week 3.
[c] $p < .05$ versus patients never interrupted.
[d] $p < .01$ versus patients interrupted at week 2.
[e] $p < .01$ versus patients interrupted at week 3.
[f] $p < .01$ versus patients never interrupted.

enhanced benefit after restarting active treatment was noted. This pattern was unanticipated and merits further exploration. Our speculation as to possible explanations for these observations includes a rating artifact due to relief from discontinuation discomforts after resuming treatment or potentially to a postsynaptic sensitization on discontinuation and consequent enhanced neurotransmission when drug is restarted. Again, to explore this hypothesis systematically, a follow-up period would ideally be longer, and would include neurophysiologic measures.

In the present study, the specific adverse events associated with the interruption of fluoxetine, sertraline, and paroxetine treatment were similar to those reported previously. In paroxetine-treated patients the most common spontaneously reported events were nausea, dizziness, insomnia, headache, and nervousness; when patients were queried, the most common events were dizziness, worsened mood, confusion, crying, and nausea. In sertraline-treated patients the most common spontaneously reported events were headache, dizziness, nervousness, nausea, and insomnia; when patients were queried, the most common events were agitation, irritability, headache, nervousness, and emotional lability. In fluoxetine-treated patients the most common spontaneously reported events were headache, insomnia, abnormal dreams, asthenia, and anxiety; when patients were queried, the most common events were worsened mood, irritability, fatigue, headache, and agitation.

When assessing stability of antidepressant response or general somatic distress, fluoxetine-treated patients repeatedly experienced a different and less disrupted course following treatment interruption. Fewer fluoxetine-treated patients reported discontinuation-emergent symptoms, and those reporting events reported statistically significantly fewer events than either sertraline-treated or paroxetine-treated patients.

Changes in measures of depressive severity also were statistically significantly different across treatment groups. Approximately one third of paroxetine-treated and sertraline-treated patients experienced depressive symptoms

sufficient to increase $HDRS_{28}$ scores to a level generally associated with a major depressive episode. Increases in somatic distress as a consequence of the physiological perturbations from SSRI discontinuation may be captured by depression rating scales such as the HDRS and MADRS without reflecting relapse of depression itself; indeed, the rapid response with reintroduction of treatment is not typical of the usual latency to antidepressant response in major depression; however, the SQ Depression scale includes only items that pertain to depressed mood, lack of interest and motivation, reduced ability to enjoy life, thoughts of death, and feelings of worthlessness and hopelessness. Thus, the SQ Depression scale differences between drugs suggests that depressive symptoms emerge in addition to physical symptoms triggered by treatment interruption. Our study, which involves the enrollment of patients who had already responded to antidepressant treatment, cannot address the question whether within each patient the constellation of symptoms experienced during the treatment interruption reproduces the patient's original depressive symptoms.

It is likely that pharmacokinetic differences among the SSRIs may provide an explanation for these findings. There appears to be a meaningful relationship between the plasma half-lives of these drugs (fluoxetine, 2–6 days; norfluoxetine, 7–15 days; paroxetine, 10–21 hours; sertraline, 26 hours; and demethylsertraline, 62–104 hours) (van Harten 1993), the likely rate of decrease of serum concentration in the absence of continuous dosing, and the development of discontinuation-emergent events when the drugs are abruptly discontinued or treatment is interrupted. A previous prospective study demonstrated that abrupt discontinuation of fluoxetine treatment was not associated with clinically significant effects over periods as long as 6 weeks (Zajecka et al 1998).

The pathophysiology of the adverse events induced by discontinuation of antidepressant drugs remains to be understood. Syndromes of adverse events following withdrawal from TCAs are largely attributed to cholinergic hyperexcitability as an aftermath of the prolonged blockade of cholinergic receptors by these compounds (Dilsaver et al 1983; Dilsaver and Greden 1984; Petersen and Richelson 1982; Tollefson et al 1982). Some investigators have suggested cholinergic rebound as a mechanism for adverse symptoms and signs related to withdrawal of paroxetine (Barr et al 1994; Pyke 1995). Increases in dopaminergic (Dilsaver et al 1987) and noradrenergic activity (Charney et al 1982) have also been suggested as the basis for some discontinuation-emergent events linked to TCAs. Serotonin-mediated inhibition of dopamine transmission has been proposed as the cause of extrapyramidal symptoms seen with discontinuation of fluoxetine (Stoukides and Stoukides 1991). Indeed, most SSRI-induced discontinuation-emergent events have been ascribed to serotonergically mediated mechanisms (Barr et al 1994; Fava and Grandi 1995; Leiter et al 1995; Louie et al 1994; Mallya et al 1993). If differences across SSRIs in risk of interruption-related events are found, they may also be hypothesized to be related to variations in specificity and potency of serotonin reuptake blockade.

The findings of this study have several clinical implications. Given the relatively high rates of treatment noncompliance that have been reported (Buckalew and Sallis 1986; Olivier-Martin 1986; Young et al 1986), clinicians should be concerned that patients experiencing uncomfortable adverse events or worsening of depressive symptoms may have missed doses of drug. A recent study of prescription refill data indicates that 30% of patients on SSRIs may miss 4–15 days of therapy between prescription refills (Data on file, PCS Health Systems, Inc., Phoenix, AZ, 1997. Data analyzed independently by ZS Associates). Furthermore, 58% of patients with a once daily antidepressant regimen had an adherence of less than 50% of correct intake within a 9-week period in a study by Demyttenaere et al (1998). Compliance to current treatment regimens should be confirmed before dosage adjustments are made based on psychological or somatic symptom emergence.

The management of somatic and depressive symptoms due to missed doses may lead to unnecessary utilization of health care resources. Thompson et al (1996), in a pattern of antidepressant use study, have shown partial compliance and early discontinuation to be associated with an increase in direct medical costs. Further studies would be necessary to explicate such a relationship.

In a recent small study, Rothschild (1995) suggested that drug holidays may allow improved sexual functioning in some patients taking sertraline and paroxetine but not fluoxetine. While differences in Hamilton depression scores did not differ statistically significantly after a 48-hour interruption of treatment, 1 paroxetine-treated and 1 sertraline-treated patient experienced increases in HDRS score after interruptions of active drug treatment. The replication of this finding within 2 individuals suggests some possible correlation with interrupted treatment and warrants further inquiry.

Readers assessing the significance of these results should bear in mind the limitations of this study, which was designed only to assess effects of intermittent missed doses, rather than to compare consequences of treatment cessation. Further, participants had been receiving continuous maintenance SSRI treatment for at least 4 months, as prescribed by psychiatric or general practice physicians. Hence, patients were not diagnosed in a uniformly systematic way and not randomly assigned to drug treatment. While these conditions would allow different patient types

to be preferentially treated with one drug or another or prescribed different doses, the large magnitude of the postinterruption treatment differences and the lack of significant treatment differences at baseline suggest that differences observed between drugs are not an artifact of the patient selection process. The purpose of the study was to conduct a comparison of symptoms and events reported by patients treated naturalistically and experiencing dose interruptions that might mimic intermittent noncompliance.

Neither clinicians nor patients were blinded to patients' drug treatments. This combined with the short duration of the study raises the possibility that investigator and patient expectation might have affected the results. This was partially offset by the double-blind assignment of patients to treatment interruption groups and the presence of a small group of patients whose therapy was not interrupted. That this small group of patients did not demonstrate the same pattern of symptom reporting suggests some success in this blinding technique (Table 4). It is also possible that clinicians' biases might have amplified the recording of events or symptoms occurring among patients treated with sertraline or paroxetine; however, the results from the patient-rated SQ were consistent with those obtained with clinician-rated instruments.

Finally, the highly unbalanced randomization design was intended to function as an additional blind to the study design and provided insufficient power to support comparisons between patients whose treatment was interrupted vs. those who continued on active therapy.

The repeated robust statistically significant differences demonstrate that adverse events and recrudescence of depressive symptoms are differentially more likely risks of abrupt interruptions of chronic treatment with sertraline or paroxetine. In contrast, abrupt interruption of treatment with fluoxetine is much less likely to produce discontinuation-emergent somatic distress or provoke worsening of depressive symptoms. Because the syndrome is not well characterized and because missed doses may occur accidentally, intentionally, or be prescribed, further studies using a prospective, randomized design are needed to address this important safety issue, potentially a clinically meaningful differentiating feature of the SSRIs.

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Appendix. Discontinuation-Emergent Signs and Symptoms

Symptom
1. Nervousness or anxiety
2. Elevated mood, feeling high
3. Irritability
4. Sudden worsening of mood
5. Sudden outbursts of anger (“anger attacks”)
6. Sudden panic or anxiety attacks
7. Bouts of crying or tearfulness
8. Agitation
9. Feeling unreal or detached
10. Confusion or trouble concentrating
11. Forgetfulness or problems with memory
12. Mood swings
13. Trouble sleeping, insomnia
14. Increased dreaming or nightmares
15. Sweating more than usual
16. Shaking, trembling
17. Muscle tension or stiffness
18. Muscle aches or pains
19. Restless feeling in legs
20. Muscle cramps, spasms, or twitching
21. Fatigue, tiredness
22. Unsteady gait or incoordination
23. Blurred vision
24. Sore eyes
25. Uncontrollable mouth/tongue movements
26. Problems with speech or speaking clearly
27. Headache
28. Increased saliva in mouth
29. Dizziness, lightheadedness, or sensation of spinning (vertigo)
30. Nose running
31. Shortness of breath, gasping for air
32. Chills
33. Fever
34. Vomiting
35. Nausea
36. Diarrhea
37. Stomach cramps
38. Stomach bloating
39. Unusual visual sensations (lights, colors, geometric shapes, etc.)
40. Burning, numbness, tingling sensations
41. Unusual sensitivity to sound
42. Ringing or noises in the ears
43. Unusual tastes or smells

Patient was asked, “During the past 7 days, have you experienced any changes in the following symptoms.” Patient chose one of four responses (new symptom; old symptom, but worse; old symptom, but improved; old symptom, but unchanged or symptom not present).