Fluoxetine Versus Sertraline and Paroxetine in Major Depressive Disorder: Changes in Weight With Long-Term Treatment

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Background: The effects of extended selective serotonin reuptake inhibitor (SSRI) treatment on weight are not well characterized. Also unknown is whether different agents have differential effects. To examine these questions, we assessed weight changes in patients randomly assigned to long-term treatment with fluoxetine, sertraline, or paroxetine.

Method: Patients (N = 284) with major depressive disorder (DSM-IV) were randomly assigned to double-blind treatment with fluoxetine (N = 92), sertraline, (N = 96), or paroxetine (N = 96) for a total of 26 to 32 weeks. The mean percent change in weight was compared for each group, as was the number of patients who had ≥ 7% weight increase from baseline.

Results: Patients (fluoxetine, N = 44; sertraline, N = 48; paroxetine, N = 47) who completed the trial were included in these analyses. Paroxetine-treated patients experienced a significant weight increase, fluoxetine-treated patients had a modest but nonsignificant weight decrease, and patients treated with sertraline had a modest but nonsignificant weight increase. The number of patients whose weight increased ≥ 7% from baseline was significantly greater for paroxetine-treated compared with either fluoxetine-treated or sertraline-treated patients.

Conclusion: Risk of weight gain during extended SSRI treatment differs depending on which SSRI is used.

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Weight gain is a common, undesirable effect of many antidepressant medications. Weight gain is also a major cause of antidepressant noncompliance.[1] Although there is little doubt that tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have a pharmacologic action related to weight gain,[1–3] data on the effects of selective serotonin reuptake inhibitors (SSRIs) on weight are somewhat limited. SSRIs are typically viewed as weight-neutral or, in some cases, as weight-loss agents during short-term treatment. In a 6-week double-blind study of fluoxetine and maprotiline in the treatment of major depression, De Jonghe et al.[4] reported weight loss with fluoxetine and weight gain with maprotiline. Michelson et al.,[5] in a large study of depressed outpatients (N = 832), reported a small but statistically significant weight loss (mean = –0.35 kg) following a 12-week acute therapy period with fluoxetine. An 8-week study by Croft et al.[6] comparing bupropion and sertraline in depressed patients (N = 360) showed similar decreases in mean body weight for both treatment groups (–0.79 kg for sertraline-treated patients and –1.06 kg for bupropion-treated patients). Finally, in studies reviewed by Mackle and Kocsis[7] with duration < 8 weeks, a ≥ 7% increase in body weight was reported in 0.5% of citalopram-treated patients and in 0.9% of placebo-treated patients.

The data on the long-term effects of SSRIs on weight are much more limited. In the study by Michelson et al.,[5] the percentage of fluoxetine-treated patients who experienced a 7% or greater weight increase after 26 weeks of continuation treatment was 4.8%, a rate comparable with that of placebo-treated patients (6.3%). Mackle and Kocsis[7] presented similar data concerning citalopram. In 6-month studies comparing the percentages of patients who had a ≥ 7% increase in body weight, the rates for citalopram and placebo were not significantly different (3.9% vs. 2.8%, respectively). Consistent with these findings, a 12-month study of citalopram in depressed patients showed that 4.7% of 541 patients reported weight gain > 5 kg.[8] On the other hand, there have been recent reports suggesting that the occurrence of excessive weight gain during long-term SSRI treatment is much more common, with incidence rates as high as 50%, and that weight

gain may be a class effect of the SSRIs.[9,10] These reports, however, are based primarily on either retrospective observations or uncontrolled studies and case reports and must be treated with caution. It is possible, as suggested by both Benazzi[9] and Sussman and Ginsberg,[10] that the observed weight gain during treatment was at least partially associated with recovery from depression rather than with SSRI treatment or was attributable to concurrent use of other medications.

To systematically assess the effects of extended SSRI treatment on weight, and to examine whether different agents have differential effects, we analyzed weight changes in depressed patients randomly assigned to treatment with fluoxetine, sertraline, or paroxetine who completed 26 to 32 weeks of double-blind treatment.

METHOD

Patient Population

The study was conducted at 15 academic centers in the United States by psychiatrists or physicians specialized in psychiatry. All patients gave written informed consent prior to enrollment. The study population included male and female outpatients, at least 18 years old, who met the criteria for major depressive disorder (MDD), including MDD with atypical features, using the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria. Duration of the current episode must have been at least 1 month. Patients were required to exhibit a baseline score ≥ 16 on the first 17 items of the 28-item Hamilton Rating Scale for Depression (HAM-D-17).[11] The DSM-IV diagnosis of MDD or MDD with atypical features was made by administering the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition[12] (SCID-I/P) during the screening visit or within the 6 months prior to the screening visit. Patients were excluded from the study for any of the following reasons: pregnancy, lactation, failure to use a medically accepted means of contraception by women of childbearing potential; serious suicidal risk; serious comorbid illness that was not stabilized; presence of a seizure disorder with a seizure occurring within the last year; presence of any of the following DSM-IV diagnoses: organic mental disorder, substance use disorder, schizophrenia, delusional disorder, psychotic disorders not otherwise specified, bipolar disorder, or antisocial personality disorder; mood-congruent or mood-incongruent psychotic features; history of allergy to the study drugs or history of multiple adverse drug reactions; concomitant use of any antidepressant (other than study drugs), anxiolytic, or other psychotropic medication within 7 days prior to study entry (and throughout the study), with the exception of chloral hydrate; use of MAOIs within 2 weeks of active therapy or anticipated need to use an MAOI within 5 weeks of discontinuing the study; hyper- or hypothyroidism (thyroid replacement was allowed, and patients were allowed to enter if they were clinically and biochemically euthyroid); and lack of response to treatment of current major depression episode by any SSRI, defined as 6 weeks or more of treatment with either fluoxetine, ≥ 40 mg/day; sertraline, ≥ 150 mg/day; or paroxetine, ≥ 40 mg/day.

Study Design

Patients were entered into a 1-week (5–9 days) single-blind, placebo lead-in phase to eliminate placebo responders (visits 1 and 2). Responders to placebo treatment (patients who achieved a score of 1 or 2 on the Clinical Global Impressions-Improvement [CGI-I][13] scale during the placebo lead-in period) were discontinued prior to randomization. After the placebo lead-in period, 284 patients were randomly assigned to 4 weeks of double-blind treatment with fluoxetine, 20 mg/day (92 patients); sertraline, 50 mg/day (96 patients); or paroxetine, 20 mg/day (96 patients). Patients who achieved a CGI-Severity of Illness (CGI-S) score of 1 or 2 at weeks 3 and 4 of active treatment continued therapy at their original dose for an additional 6 weeks (visits 12 and 13). Patients not achieving the required CGI-S scores entered an optional 1- to 6-week dose titration phase. During this phase, dose titration was permitted within the range of fluoxetine, 20 to 60 mg/day; sertraline, 50 to 200 mg/day; or paroxetine, 20 to 60 mg/day. The dose at which a patient was deemed stable and responding (a CGI-S score of 1 or 2 for 2 consecutive weeks) was continued for an additional 6 weeks. Thus, patients received 10 to 16 weeks of acute, active drug treatment.

After the acute treatment phase (with a duration depending on the length of the optional titration period), patients whose symptoms responded (CGI-S score of 1 or 2 for 2 consecutive weeks) continued treatment for an additional 16 weeks, for a total of 26 to 32 weeks. Nonresponders to the initial acute treatment phase were dropped from the study. To assess the effects of SSRI treatment interruption, the study included 2 blinded 4- to 6-day treatment interruptions that occurred between weeks 14 and 28.

Statistical Analysis

To systematically assess the effects of extended SSRI treatment on weight, we compared the mean percent change in weight for all patients who completed the trial. We also examined the number of patients who experienced a ≥ 7% increase in weight, considered the standard of "extreme" weight gain in clinical trials. We further examined the patients with extreme weight gain to determine the number with normal (20–25 kg/m^2) or greater than normal (> 25 kg/m^2) body mass index (BMI) according to the World Health Organization.[14] In addition, to rule out the possibility that weight changes may have occurred because of the protocol-specified treatment inter-

Table 1. Patient Characteristics at Baseline[a]

Characteristic	Fluoxetine (N = 44)	Sertraline (N = 48)	Paroxetine (N = 47)
Sex, female/male	24/20	30/18	23/24
Age (y), mean ± SD	42.1 ± 13.0	46.0 ± 15.8	44.5 ± 13.7
Weight (kg), mean ± SD	73.2 ± 17.8	77.1 ± 20.3	77.3 ± 17.8
Body mass index (kg/m^2), mean ± SD	25.1 ± 5.2	27.9 ± 7.7	26.2 ± 6.1
17-Item HAM-D score, mean ± SD	19.4 ± 3.9	20.6 ± 4.6	20.0 ± 5.0

[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

ruption, we repeated these analyses prior to the interruption periods (from week 10 to week 16).

Baseline characteristics were compared using analysis of variance with treatment in the model for continuous variables and the Pearson chi-square test for discrete variables. Changes in weight were compared using analysis of variance with treatment in the model. Within-treatment changes were tested using a paired t test. The proportions of patients with ≥ 7% weight increase were compared using the Pearson chi-square test. Differences in effect caused by gender (female vs. male) and age (patients < 50 years vs. patients ≥ 50 years) were assessed using the Breslow-Day test for homogeneity of the odds ratio. The analytic plan was reviewed and approved by all study authors, and the actual statistical analyses were performed by the study biostatistician (M.E.N.) and were also reviewed and approved by all study authors.

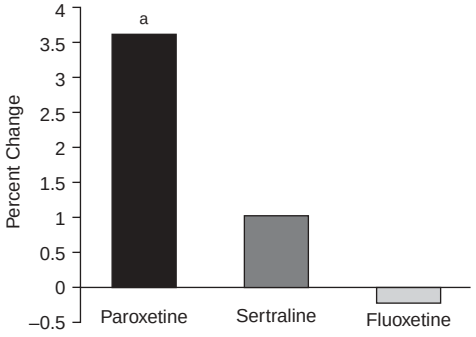
RESULTS

Among the patients who completed 26 to 32 weeks of therapy (fluoxetine, N = 44; sertraline, N = 48; paroxetine, N = 47), baseline variables were similar for all groups. There were no significant differences among the fluoxetine, sertraline, and paroxetine groups in age, gender, weight, BMI, or HAM-D-17 score (Table 1). The final mean daily dose was 42 mg for fluoxetine, 94 mg for sertraline, and 37 mg for paroxetine.

Striking differences emerged when comparing mean percent change in weight from baseline to endpoint for the 3 SSRIs (Figure 1). Fluoxetine patients showed a small mean decrease in weight (–0.2%), and sertraline patients showed a small mean increase in weight (1.0%); neither of these changes was statistically significant compared with baseline nor compared with each other. In the paroxetine-treatment group, there was a significant increase in weight compared with baseline (3.6%), which was also significant when compared with the fluoxetine and sertraline groups.

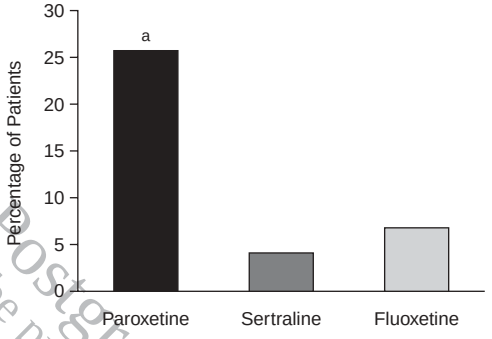
In addition, a significantly higher proportion of paroxetine patients (25.5%) gained ≥ 7% in weight compared with the other treatment groups (fluoxetine, 6.8%; sertraline, 4.2%) (Figure 2). Extreme weight gain among

Figure 1. Mean Percent Change in Weight From Baseline to Endpoint After 26 to 32 Weeks of Therapy



[a]Significant difference within paroxetine group compared with baseline (t = 3.92, df = 46, p < .001), and for paroxetine vs. sertraline (t = 2.46, df = 136, p = .015) and paroxetine vs. fluoxetine (t = –3.55, df = 136, p < .001) at endpoint.

Figure 2. Percentage of Patients With ≥ 7% Weight Gain at Endpoint After 26 to 32 Weeks of Therapy



[a]Significant difference for paroxetine vs. sertraline ($\chi^2 = 8.63$, df = 1, p = .003) and paroxetine vs. fluoxetine ($\chi^2 = 5.78$, df = 1, p = .016) at endpoint.

paroxetine-treated patients was more prevalent in women (39.1%) than in men (12.5%), with a Breslow-Day test for homogeneity of .077 for the fluoxetine versus paroxetine comparison and .190 for the sertraline versus paroxetine comparison. When patients were categorized by age (patients < 50 years vs. patients ≥ 50 years), there were no differences in effects between the 2 age categories. A further examination of the patients with extreme weight gain showed that the majority (11 of 12 paroxetine-treated patients, 2 of 2 sertraline-treated patients, and 2 of 3 fluoxetine-treated patients) had a normal or high baseline BMI (> 20 kg/m^2).

To rule out the possibility that weight changes may have occurred because of treatment interruption, the analyses were repeated prior to the interruption periods (from week 10 to week 16). There were no significant differences in baseline variables among the treatment groups (fluoxetine, N = 63; sertraline, N = 70; paroxetine,

N = 67). When comparing mean percent change in weight from baseline to endpoint, fluoxetine patients showed a significant decrease in weight (–1.3%; $p < .008$), sertraline patients showed a nonsignificant increase in weight (0.1%; $p = .858$), and paroxetine patients showed a significant increase in weight (1.7%; $p < .001$). In addition, a higher proportion of paroxetine patients (9.0%) gained ≥ 7% in weight compared with the other treatment groups (fluoxetine, 1.6%; sertraline, 2.9%), although the differences were not statistically significant. Less than 3% of the patients (2.8% of paroxetine-treated patients, 2.7% of sertraline-treated patients, and 0% of fluoxetine-treated patients) had reported extreme weight gain (i.e., ≥ 7% of body weight) during the first 6 to 12 weeks of the acute phase treatment.

Only 1 patient discontinued treatment because of weight gain. The patient was a paroxetine-treated woman who withdrew after approximately 15 weeks of treatment with a weight gain of 7.7 kg. After 26 to 32 weeks of therapy, the maximum weight gain for any patient was 7.7 kg for fluoxetine, 8.6 kg for sertraline, and 14.1 kg for paroxetine.

DISCUSSION

Weight gain as a complication of antidepressant therapy can be of considerable clinical importance. While weight gain may be acceptable for patients treated over a limited time, especially in the treatment of depression accompanied by anorexia, excessive weight gain can result in loss of self-esteem, jeopardize patient compliance, and pose serious health hazards.[1–3] Because a minimum of 4 to 6 months of continuation treatment is recommended following successful SSRI therapy,[15,16] potential weight gain has become a very important consideration in the long-term management of depression.

Although TCAs, MAOIs, and lithium have been found to stimulate appetite and carbohydrate craving,[1] it is less certain whether SSRIs also exert a pharmacologic action related to weight gain, especially during extended therapy. The current study differs from previous reports in the larger number of patients studied, the systematic collection of weight data, and the double-blind comparison of 3 treatment arms. Patients treated with fluoxetine or sertraline experienced no significant changes in weight, while patients treated with paroxetine experienced significant increases in weight. Furthermore, a significantly higher proportion of paroxetine patients (25.5%) gained ≥ 7% in weight compared with patients in the other treatment groups (fluoxetine, 6.8%; sertraline, 4.2%). A post hoc analysis of the paroxetine-related extreme weight gain (≥ 7% increase in body weight) showed that such weight gain among paroxetine-treated patients was more prevalent in those with a maintenance daily dose of 40 mg (54.6%; 6/11) than in patients with a maintenance daily dose of either 20 mg (18.2%; 4/22) or 60 mg (14.3%; 2/14). Finally, it appears that at least 10 to 16 weeks of exposure to paroxetine is needed before extreme weight changes are detected in more than 3% of the patient population.

Because the study design did not include a placebo arm, it is not possible to determine whether the rates of weight gain observed with these 3 SSRIs represent a true increased risk for such an event. Considering the 6.3% rate of significant weight gain with placebo from the Michelson et al. study,[5] as well as the 2.8% rate of significant weight gain with placebo from the study by Mackle and Kocsis,[7] it would seem unlikely that the 25.5% rate of significant weight gain observed in conjunction with paroxetine during 6 months of treatment in this trial could be due to the spontaneous rate of weight gain in this population. On the other hand, the rates of weight gain reported with fluoxetine (6.8%) and sertraline (4.2%) fall in the range of placebo in previous studies. In addition, it is not possible to establish whether patients who gained weight in the long term did so because of a return of depressive symptoms, including overeating, or because of a pharmacodynamic effect of the antidepressant treatment itself (e.g., true side effect).

The higher risk for significant weight gain with paroxetine, compared with other SSRIs, has been confirmed by Agren et al.[17] in a 24-week, double-blind study of sertraline versus paroxetine and by Joubert et al.[18] in a comparative study of 4 antidepressants and their effect on weight. In addition, in a 1-year, double-blind study comparing paroxetine and imipramine,[19] 10 of 46 paroxetine-treated patients had increased weight (range, 1–7 kg) at the end of treatment, although the weight gain was significantly less than that with imipramine. Because paroxetine is a highly potent inhibitor of serotonin uptake, these findings are paradoxical and indicate that an interaction with other mechanisms is clearly involved.[20]

While the mechanisms associated with the differences in weight change among SSRIs are uncertain, the relatively greater anticholinergic effects of paroxetine may be an important factor. In this study, the majority of patients with extreme weight gain had a normal or high baseline BMI, indicating that the weight gain was most likely not a beneficial effect and did not simply reflect a return to normal weight following the weight loss characteristic of depression.

In summary, these data provide evidence that different SSRIs are associated with different risks for weight gain during extended treatment. The clinical relevance of this finding is heightened in the context of treatment of depressed patients in whom added weight could pose serious health risks or for whom noncompliance with a treatment regimen could be hazardous.

Drug names: bupropion (Wellbutrin), citalopram (Celexa), fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft).

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