Serum Prolactin Levels Among Outpatients With Major Depressive Disorder During the Acute Phase of Treatment With Fluoxetine

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Objective: To determine changes in serum prolactin levels in outpatients with DSM-IV–diagnosed major depressive disorder (MDD) following a 12-week open-label trial of fluoxetine.

Method: 87 outpatients enrolled in the trial had serum prolactin levels determined at baseline and during their final visit (week 12 or discontinuation visit). In addition, serum testosterone levels were measured in 44 of the 46 men during these 2 visits. Hyperprolactinemia was defined as a serum prolactin level greater than 16.5 ng/mL or 18.9 ng/mL for men and women, respectively. The study was conducted from September 1997 to March 2002.

Results: Of 80 patients with normal prolactin levels at baseline, 10 (12.5%) developed hyperprolactinemia following fluoxetine treatment. Specifically, 2 (4.5%) of 44 men and 8 (22.2%) of 36 women with normal prolactin levels at baseline developed hyperprolactinemia following treatment with fluoxetine (p = .0174 for between-gender difference). In addition, there was a significant increase in mean ± SD serum prolactin levels following treatment with fluoxetine in all patients with normal baseline prolactin levels (6.4 ± 3.4 to 10.0 ± 7.0 ng/mL, p = .002). There were no significant changes from baseline in testosterone levels in men following fluoxetine treatment (448.4 ± 139.6 to 439.5 ± 142.1 ng/dL, p > .05; normal above 245 ng/dL), while none of the 44 men developed low testosterone levels following fluoxetine treatment.

Conclusion: 4.5% of men and 22.2% of women with MDD developed new onset hyperprolactinemia following fluoxetine treatment.

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A growing number of case reports suggest that treatment of major depressive disorder (MDD) with the selective serotonin reuptake inhibitors (SSRIs) may be associated with hyperprolactinemia,[1,2] galactorrhea,[1,3–10] and breast enlargement,[11,12] thought to occur secondary to stimulation of inhibitory serotonergic (5-hydroxytryptamine$_2$ [5-HT$_2$]) receptors located on tuberoinfundibular dopaminergic neurons involved in the inhibition of prolactin release from the pituitary.[13] However, studies that attempt to systematically evaluate the risk of hyperprolactinemia during short-term (1–12 weeks) daily SSRI administration present conflicting findings, with some studies suggesting an increase in serum prolactin levels in depressed women[12] or healthy volunteer men[14,15] and women,[16] while other studies suggest no increase in serum prolactin levels in depressed men,[17] depressed women,[17–19] or healthy volunteer men and women.[20] However, two major limitations of these studies have been their relatively small sample size (N = 36 being the largest study[18]) and often short duration of drug therapy. In addition, the

potential impact of acute treatment of MDD with the SSRIs on serum testosterone levels in men has yet to be studied.

Hyperprolactinemia interferes with the normal pulsatile secretion of gonadotropin-releasing hormone and causes subsequent disturbances in the normal pulsatile secretion of luteinizing hormone and follicle-stimulating hormone, resulting in hypogonadism.[21,22] Therefore, if treatment with serotonergic antidepressants such as the SSRIs were, in fact, to result in increased prolactin levels in men and women, this increase in prolactin secretion could potentially also lead to a suppression of normal gonadal function. Studying the effects of SSRI treatment on serum prolactin levels is important since hyperprolactinemia and hypogonadism have been linked to oligospermia/infertility and decreased libido in men[22]; amenorrhea, oligomenorrhea, infertility, and galactorrhea in women[23]; and osteopenia in both men and women.[24–26] Decreased bone-mineral density has also been reported in MDD patients,[27–29] and particularly in men with MDD,[28] although to what degree the decreased bone mineral density seen in patients with MDD is due to the illness or its treatment remains unknown.[30] The purpose of the following study is to measure changes in serum prolactin levels in men and women with MDD following a 12-week, open-label trial of fluoxetine. In addition, serum testosterone levels were measured in men enrolled in the study.

METHOD

Overview and Study Population

Six hundred twenty-seven patients, aged 18 to 65 years, with MDD diagnosed with the use of the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P),[31] were enrolled in a 1-week, medication-free, washout period followed by a 12-week, flexible-dose, open-label trial of up to 60 mg/day of fluoxetine. Patients were enrolled at either of 2 hospital-based, academic sites: the Depression Evaluation Service Center of the New York State Psychiatric Institute (N = 373), an affiliate of Columbia University, or the Depression Clinical and Research Program (DCRP) at Massachusetts General Hospital (MGH) (N = 254), an affiliate of Harvard Medical School. Patients who experienced sufficient symptom improvement following the 12-week treatment period were then randomly assigned in a double-blind fashion to either continue their treatment with fluoxetine or switch to placebo for a 52-week follow-up period. The present report focuses on the acute phase of the study in only a subset of patients (N = 87) enrolled at the DCRP at MGH. The study was conducted from September 1997 to March 2002.

Exclusion Criteria

The following patients were excluded from the study: pregnant women; women of childbearing potential who were not using a medically accepted means of contraception; women who were breast-feeding; patients with serious suicidal risk, history of seizure disorder, serious and unstable medical disorders, clinical or laboratory evidence of hypothyroidism without adequate stable replacement, or a history of an allergy to fluoxetine; and patients who were concurrently using any of a list of exclusionary drugs. Exclusionary drugs included terfenadine and astemizole, oral steroids (corticosteroids and androgens), anticoagulants (with the exception of aspirin), antiarrhythmics, and psychotropic medications (including antidepressants, hypnotics, anxiolytics, sedatives, antipsychotics, and mood stabilizers).

Patients meeting criteria for the following DSM-IV diagnoses were also excluded: organic mental disorders, alcohol or substance use disorders that were active within the past 6 months, schizophrenia, delusional disorder, psychotic disorders, bipolar disorder, or the presence of psychotic features. Finally, patients with a history of nonresponse to an adequate trial of fluoxetine, defined as a 4-week trial of a minimum of 40 mg/day of fluoxetine, patients treated with fluoxetine within the last 4 weeks prior to the screen visit or any other antidepressant or benzodiazepine within the last week prior to the screen visit, and patients treated with psychotherapy for less than 1 month prior to screen visit were also excluded.

Study Procedures

Once patients had agreed to participate in the study by signing an institutional review board–approved informed consent document, the SCID-I/P was administered, a full medical and psychiatric history was taken, and a physical examination was performed. All patients were also administered the following instruments: the 28-item Hamilton Rating Scale for Depression (HAM-D-28)[32] and the Clinical Global Impressions-Severity of Illness scale (CGI-S) and -Improvement scale (CGI-I).[33]

Following a 1-week drug washout period, patients returned for their baseline visit. The HAM-D-28 and CGI scales were also administered during the baseline visit. Patients with a CGI-I score > 2 (thereby the improvement was minimal or absent) during the baseline visit were enrolled in the acute phase of the study and were started on fluoxetine 10 mg daily.

All subsequent study visits were conducted according to the method described by Fawcett et al.,[34] modified to reflect the use of an SSRI for the baseline and subsequent study visits. Patients were seen weekly during the first 6 weeks, every other week during the next 4 weeks, and weekly for the last 2 weeks of the open-label phase of the study. The HAM-D-28, CGI-I, and CGI-S were administered during all study visits.

At the beginning of week 2, the fluoxetine dosage was increased to 20 mg/day for the next 3 weeks. At week 5, the dose was increased to 40 mg/day, and this dose was

continued for the next 4 weeks. Patients who responded to 40 mg/day were continued on this dose for the next 4 weeks. For the purposes of dose titration, response was defined as a CGI-I score ≤ 2 during that visit. For patients who did not respond to 40 mg/day, clinicians had the option of having their dose increased to 60 mg/day at weeks 9, 10, or 11.

For patients experiencing intolerable adverse events, the first attempt was to lower the dose. For intolerable adverse events even at the lowest dose, patients were discontinued from the study. Patients who were discontinued from the study for any reason were eligible for 3 months of free care at either site. Patients who were administered exclusionary drugs during the acute phase were discontinued from the study. The only exceptions were lorazepam (0.5–1.0 mg), alprazolam (0.5 mg), zolpidem (5–10 mg), clonazepam (0.25 mg), or diphenhydramine (25–100 mg) for patients suffering from severe insomnia as a side effect of the fluoxetine.

Plasma Prolactin and Testosterone Measurements

Forty-six men and 41 women enrolled at the DCRP of the MGH had serum prolactin levels measured during their baseline and final (week 12 or discontinuation) visits. Hormone levels were drawn during patient visits. Forty-four of 46 men also had serum testosterone levels measured during their baseline and final (week 12 or discontinuation) visits. Given that the present study was an add-on to a much larger trial, we did not systematically collect information regarding premenopausal, postmenopausal, or menstrual status; menstrual function; or the presence of galactorrhea.

Prolactin was measured by a solid-phase immunoradiometric assay (Diagnostic Products Corp., Los Angeles, Calif.). Intraassay precision is reported as 7 levels between 3.7 and 131.0 ng/mL, with the coefficient of variation (CV) ranging from 2.7% to 1.1% (as per the manufacturer). Interassay precision is reported as 7 levels between 3.8 and 130.0 ng/mL, with CV ranging from 6.3% to 1.6% (as per the manufacturer of the assay kit). Hyperprolactinemia in men was defined as a serum prolactin level greater than normal for this assay (normal: ≤ 16.5 ng/mL, as per the manufacturer of the assay kit). Hyperprolactinemia in women was defined as a serum prolactin level greater than normal for this assay (normal: ≤ 18.9 ng/mL, as per the manufacturer of the assay kit).

Testosterone was measured by radioimmunoassay (Diagnostic Products Corp., Los Angeles, Calif.). Interassay precision is reported as 7 levels with means from 76 to 1300 ng/dL and CV from 11.0% to 5.9%. (For reporting intraassay precision, the manufacturer presents a graph.) A low serum testosterone level in men was defined as a level less than normal for this assay (normal: ≥ 245 ng/dL, as per the manufacturer of the assay kit).

Statistical Tests

Clinical response was defined as a 50% or greater decrease in 17-item HAM-D (HAM-D-17)[32] scores from baseline to endpoint, and remission was defined as a HAM-D-17 score of 7 or less at endpoint. An intent-to-treat analysis with the last observation carried forward was used to define the severity of depression at endpoint, in which the last recorded HAM-D-17 score substituted the week 12 score for patients who prematurely discontinued the study. Appropriate parametric tests were used to compare differences in dichotomous and continuous variables between patients with and without measured serum prolactin/testosterone levels, as well as in patients with measured serum prolactin/testosterone levels before and after treatment with fluoxetine (χ^2, paired and unpaired t tests). Statistical significance was defined at the $\alpha = .05$ level, 2-tailed. A Pearson's correlation test was used to test for any correlation between 2 continuous variables.

RESULTS

The mean ± SD age of the patient sample (N = 87) was 39.0 ± 10.8 years, and the mean body mass index (BMI) was 26.3 ± 6.1 kg/m^2 (for men: 26.8 ± 5.2 kg/m^2, for women: 25.8 ± 7.0 kg/m^2). Overall, 20.7% of all patients (18/87) prematurely discontinued treatment following a mean of 6.7 ± 2.8 weeks of treatment. The mean maximum fluoxetine dose was 49.3 ± 11.7 mg/day. For 4 patients, the maximum fluoxetine dose was 20 mg/day; for 39 patients, the maximum fluoxetine dose was 40 mg/day; and for 44 patients, the maximum fluoxetine dose was 60 mg/day. 64.3% (56/87) of all patients responded to the trial, and 46.0% (40/87) of all patients remitted. 39.0% (16/41) of women were on hormone-replacement therapy or oral contraceptives during their baseline visit. None of the 41 women in the study initiated or discontinued hormone-replacement therapy or oral contraceptives during the 12-week trial.

There were no statistically significant differences in mean age (39.0 ± 10.8 vs. 37.4 ± 11.6 years), BMI (26.3 ± 6.1 vs. 28.1 ± 7.3 kg/m^2), age at onset of MDD (25.7 ± 13.3 vs. 26.1 ± 15.2 years), baseline HAM-D-17 scores (19.5 ± 5.7 vs. 18.6 ± 5.3), baseline CGI-S scores (4.1 ± 0.7 vs. 4.1 ± 0.7), maximum fluoxetine dose (49.3 ± 11.7 vs. 41.4 ± 14.8 mg/day), or endpoint (intent-to-treat) HAM-D-17 scores (10.0 ± 7.5 vs. 10.3 ± 6.7) in patients with MDD enrolled at the DCRP who did (N = 87) versus did not (N = 167) have serum prolactin/testosterone levels collected before and after treatment ($p > .05$ all comparisons).

Two men (prolactin levels 17.3 and 26.0 ng/mL) and 5 women (mean prolactin level 31.8 ± 9.2 ng/mL) had elevated prolactin levels at baseline. Both hyperprolactinemic men had normal testosterone levels at baseline. Two of the hyperprolactinemic women were on hormone-

Table 1. Change (increase) in Prolactin Levels Among Patients Who Developed Hyperprolactinemia During Treatment With Fluoxetine (N = 10)

Gender	Prolactin Increase (ng/mL)
Male	14.4
Male	9.7
Female	26.2
Female	23.0
Female	21.4
Female	18.9
Female	17.3
Female	14.1
Female	13.0
Female	11.4

replacement therapy or oral contraceptives. One of the 2 men continued to be hyperprolactinemic following treatment with fluoxetine (26.0 ng/mL), and the other had a normal prolactin level following treatment (13.0 ng/mL). All 5 women continued to be hyperprolactinemic following treatment with fluoxetine. There was no statistically significant increase in prolactin levels at endpoint among women who were hyperprolactinemic at baseline (N = 5, 31.8 ± 9.2 ng/mL vs. 33.1 ± 11.5 ng/mL; $p > .05$). Finally, 2 men had low testosterone levels at baseline (testosterone levels 147.0 and 70.7 ng/dL; normal at ≥ 245 ng/dL); both had low testosterone levels following treatment with fluoxetine (215.0 and 22.3 ng/dL)—neither was hyperprolactinemic at baseline or endpoint.

Of 80 patients with normal prolactin levels at baseline, 10 (12.5%) developed hyperprolactinemia following fluoxetine treatment, representing a significant increase in the proportion of patients with hyperprolactinemia ($p < .0001$). Specifically, 2 (4.5%) of 44 men (posttreatment prolactin levels 18.8 and 29.6 ng/mL) and 8 (22.2%) of 36 women (mean posttreatment prolactin levels 29.1 ± 8.8 ng/mL) developed elevated prolactin levels following treatment with fluoxetine. Both of these men had normal testosterone levels following treatment, and 1 of these women was on hormone-replacement therapy or oral contraceptives. The degree of increase in prolactin levels among these 10 patients is listed in Table 1. Significantly more women than men developed hyperprolactinemia following treatment with fluoxetine ($p = .0174$).

In addition, there was a statistically significant increase in mean serum prolactin levels following treatment with fluoxetine in all patients with normal baseline prolactin levels (N = 80, 6.4 ± 3.4 to 10.0 ± 7.0 ng/mL; $p = .002$) as well as in the subset of men (N = 44, 5.4 ± 2.9 to 8.0 ± 4.9 ng/mL; $p < .0001$) and women (N = 36, 7.7 ± 3.6 to 12.2 ± 8.8 ng/mL; $p = .0029$) with normal baseline prolactin levels. However, there was no significant change from baseline in serum testosterone levels following treatment with fluoxetine (448.4 ± 139.6 to 439.5 ±142.1 ng/dL, $p > .05$) and no correlation between the changes in testosterone and prolactin levels from baseline to endpoint ($p > .05$) in men. None of the 44 men developed low testosterone levels following fluoxetine treatment.

There also was no statistically significant difference in baseline prolactin levels between women who were or were not on hormone-replacement therapy or oral contraceptives ($p > .05$). Finally, there was no statistically significant correlation between baseline prolactin levels or the degree of change in prolactin levels from baseline to endpoint and age, BMI, maximum fluoxetine dose, or the change in HAM-D-17 scores in the overall sample ($p > .05$ all analyses).

DISCUSSION

To our knowledge, the present study is the largest to examine changes in serum prolactin levels in men and women with MDD during SSRI administration and the only study to examine changes in serum testosterone levels in men with MDD during SSRI administration. The results of the present study suggest that the treatment of MDD with the SSRI fluoxetine is associated with alterations in serum prolactin levels in both men and women. Overall, 1 in 8 outpatients (12.5%), or 4.5% of men and 22.2% of women, developed new-onset hyperprolactinemia following treatment with fluoxetine. In addition, there was a significant increase in serum prolactin levels following treatment with fluoxetine, which appeared consistent and comparable regardless of the SSRI dose used.

That a significantly larger proportion of women than men developed hyperprolactinemia following treatment with fluoxetine is consistent with many other conditions associated with hyperprolactinemia, including surgical stress, primary hypothyroidism, and treatment with antipsychotic agents where women appear to be more likely to develop hyperprolactinemia than men.[35–38] However, it is important to point out that, while there does appear to be a significant increase in prolactin levels in outpatients treated with fluoxetine, the clinical significance of this finding remains to be clarified, particularly given that changes in testosterone levels in men were not observed, and any potential adverse impact of treatment with the SSRIs on bone density and fertility in men and women has yet to be demonstrated. Similarly, the number of women who developed oligomenorrhea or galactorrhea or who are at risk for loss of bone density as a result of hyperprolactinemia is also unknown. Future studies examining factors (i.e., serotonin transporter polymorphisms) that could potentially predispose MDD patients to develop hyperprolactinemia during treatment with the SSRIs, studies focusing on the impact of nonserotonergic antidepressants on serum prolactin levels in MDD, and studies exploring any potential adverse impact of treatment with the SSRIs on gonadal function, fertility, and

bone density in men and women with MDD are needed to help shed further light on the potential clinical relevance of our findings.

The main limitation of our study is the relatively short duration of treatment (up to 12 weeks). We cannot rule out the possibility that the changes in prolactin levels observed in the present study may subside over time. Due to the relatively short duration of the trial, it is also unknown whether the hyperprolactinemia, if persistent, would lead to decreased testosterone levels in men. A second limitation of the present study is the absence of placebo, the presence of which would help further clarify to what extent the effects of SSRI treatment on serum prolactin levels are mediated through the pharmacologic effects of fluoxetine versus nonspecific (nocebo) effects of treatment. An additional limitation is that information on menopausal and menstrual status was not systematically collected. We also did not record changes in stressful life events during the study, even though these events have been shown to have effects on androgen levels.[39]

Further limitations include the relatively small sample size, although ours is the largest such study to date, and the possibility of sampling bias. Clinical trials have a number of inclusion and exclusion criteria, and, as a result, patients in clinical trials do not directly reflect the typical outpatient population of MDD patients. This may be particularly true of the present study since patients who were receiving adjunctive treatment with other psychotropic medications were excluded. Therefore, it is quite possible that adjunctive treatment with other proserotonergic agents, a common practice among clinicians when treating MDD,[40] may have potentiated the effects of fluoxetine on serum prolactin levels, while treatment with adjunctive prodopaminergic agents may have attenuated such effects. Future studies addressing these limitations are necessary to shed light on the relationship between long-term changes in serum prolactin, gonadal function, fertility, bone density, and SSRI administration in men and women with MDD.

CONCLUSION

A total of 4.5% of men and 22.2% of women with MDD developed new-onset hyperprolactinemia following treatment with the SSRI fluoxetine. In addition, a mild elevation in prolactin levels among fluoxetine-treated patients was also noted. Treatment with fluoxetine, however, was not accompanied by significant changes in testosterone levels among men. Future studies are necessary in order to examine factors that could potentially predispose MDD patients to develop hyperprolactinemia during treatment with the SSRIs as well as shed light on any potential adverse impact of treatment with the SSRIs on serum prolactin, gonadal function, fertility, and bone density in men and women with MDD.

Drug names: alprazolam (Xanax, Niravam, and others), clonazepam (Klonopin and others), diphenhydramine (Benadryl and others), fluoxetine (Prozac and others), lorazepam (Ativan and others), zolpidem (Ambien).

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