Incidence of Sexual Dysfunction in Healthy Volunteers on Fluvoxamine Therapy

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Background: Current literature suggests that the incidence of sexual dysfunction secondary to fluvoxamine therapy is 1% to 8%, while other selective serotonin reuptake inhibitors may have rates as high as 75%. The objective of this study was to determine the incidence of sexual dysfunction secondary to fluvoxamine in healthy volunteers.

Method: 20 healthy volunteers (10 men, 10 premenopausal women) had adverse effects assessed at 6 visits while not receiving fluvoxamine, then twice while taking 150 mg fluvoxamine daily. Assessments occurred at 2-week intervals. Incidence rates for sexual dysfunction were calculated.

Results: No sexual dysfunction was reported prior to fluvoxamine therapy. After 2 weeks and 4 weeks of therapy respectively, sexual dysfunction occurred in 20% (N = 4) and 35% (N = 7) of the healthy volunteers.

Conclusion: The incidence of sexual dysfunction during fluvoxamine therapy in healthy volunteers is 35%. This incidence is higher than previously reported and similar to that of other selective serotonin reuptake inhibitors.

(J Clin Psychiatry 1999;60:187–190)

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Presented in part at the 150th annual meeting of the American Psychiatric Association, May 20, 1997, San Diego, Calif.

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Selective serotonin reuptake inhibitors (SSRIs) are frequently chosen over older agents as first-line therapy for depression and obsessive-compulsive disorder because of their efficacy and perceived low adverse event rate.[1–3] In spite of the perception of fewer adverse events and high rates of acceptability to patients, SSRIs are known to cause high rates of sexual dysfunction.[4–6] Sexual dysfunction among patients taking antidepressants may influence compliance with medication regimens, and the study of sexual dysfunction among medication-treated patients is complicated by a relationship of sexual dysfunction to the concurrent mood disorder as well as an underreporting of sexual side effects.[3] In order to avoid the confounding influence of concurrent psychiatric disorders, we evaluated the frequency of self-reported sexual dysfunction in healthy volunteers who received fluvoxamine as part of a metabolic phenotyping study.

METHOD

The Institutional Review Board of The Mary Imogene Bassett Hospital, Cooperstown, N.Y., approved this protocol. All subjects gave written informed consent prior to study participation. Twenty healthy volunteers (10 males and 10 premenopausal females) were enrolled in a phenotyping study using fluvoxamine as a metabolic enzyme inhibitor. In order to be included, subjects had to be nonsmokers, and women had to use acceptable barrier birth control or be surgically sterile. Exclusion criteria included renal or hepatic disease, use of any chronic medications including oral contraceptives, and regular alcohol consumption of greater than one 12-ounce beer per day. Subjects were healthy as determined by complete history and physical examination, review of medical records, and normal results of serum chemistries, complete blood count, urinalysis, and 12-lead electrocardiogram.

Subjects had 8 visits at 2-week intervals over a 16-week period. For the first 6 visits, subjects took no regular medications. The day after visit 6, subjects began fluvoxamine therapy in a titration schedule that began with 50 mg daily and increased over 7 days to 150 mg daily.

A 1-page, standardized, self-report questionnaire modified from Corso et al.[7] (see appendix) was used to assess adverse events at visits 1–6, before subjects began taking fluvoxamine, and visits 7–8, while subjects were receiving fluvoxamine. One of 15 questions pertained to sexual function. It reads, "Do you have any complaints or symptoms related to your sexual function or ability?" Subjects answered either "yes" or "no." If a subject reported an adverse event, an investigator administered a

Table 1. Self-Reported Adverse Events in 20 Healthy Volunteers[a]

	Baseline[b]		Fluvoxamine[c]		
Organ System	N	%	N	%	p Value
Skin	3	15	2	10	NS
Musculoskeletal	6	30	3	15	NS
Face	0	0	2	10	NS
Eyes	3	15	2	10	NS
Ears	0	0	0	0	NS
Oropharynx	3	15	5	25	NS
Throat	0	0	0	0	NS
Breasts	0	0	0	0	NS
Pulmonary/ cardiovascular	0	0	0	0	NS
Gastrointestinal	3	15	14	70	.001
Genitourinary	1	5	0	0	NS
Sexual function	0	0	7	35	.01
Neurologic	1	5	9	45	.01
Psychiatric	0	0	9	45	.001
Phlebotomy-related	1	5	0	0	NS

[a]Abbreviation: NS = not significant.
[b]Total number of subjects who reported an adverse event at least once during 6 baseline visits.
[c]Total number of subjects who reported an adverse event at least once during 2 visits while taking 150 mg/day of fluvoxamine.

Table 2. Reported Sexual Dysfunction During 4 Weeks of Fluvoxamine Therapy

Subject No.	Sex	Week 2	Week 4
1	M	None	None
2	M	None	None
3	M	None	Decreased sexual desire
4	M	None	None
5	M	None	None
6	M	None	None
7	M	None	None
8	M	None	None
9	M	Decreased abililty to keep an erection; decreased ability to achieve orgasm	Decreased ability to keep an erection; decreased ability to achieve orgasm
10	M	Decreased sexual desire	Decreased sexual desire
11	F	None	Decreased sexual ability
12	F	None	Decreased sexual ability
13	F	Decreased ability to achieve orgasm	Decreased ability to achieve orgasm
14	F	None	None
15	F	None	Decreased sexual desire
16	F	None	None
17	F	None	None
18	F	None	None
19	F	None	None
20	F	None	None

complete adverse event questionnaire.[7] The comprehensive adverse event form evaluated the presence or absence of "changes in sexual desire; decrease in sexual desire; decreased sexual ability; difficulty in ejaculating; impotence; difficulty in keeping an erection; inappropriate, frequent, or continuing erection; increase in sexual desire; painful erection; premature ejaculation; and other sexual function complaints."[7(p896)]

Statistical analyses used a Student t test for continuous variables and chi-square test for discrete variables. A p value of ≤ .05 was considered statistically significant. Data for continuous variables are presented as the mean ± standard deviation.

RESULTS

Twenty subjects were enrolled in the study: 10 men and 10 premenopausal women. The mean age was 36.4 ± 8.7 years and the mean total body weight was 78.0 ± 16.7 kg (no statistical difference by sex). No subject reported sexual dysfunction at any visit before beginning fluvoxamine. Table 1 shows the number of subjects reporting adverse events by organ system during the 6 baseline visits and the 2 visits while taking fluvoxamine. There was a significant increase in complaints related to the gastrointestinal, sexual, neurologic, and psychiatric systems in the subjects while they were taking fluvoxamine. Gastrointestinal complaints resolved within 2 weeks of initiation of therapy, but the sexual, neurologic, and psychiatric side effects persisted for the duration of fluvoxamine therapy.

Twenty percent of subjects (2 men and 2 women) reported sexual dysfunction 2 weeks after beginning fluvoxamine therapy. Thirty-five percent of subjects (3 men and 4 women) reported sexual dysfunction after 4 weeks of fluvoxamine therapy. All 4 subjects who reported sexual dysfunction at 2 weeks continued to report the sexual dysfunction of the same type at 4 weeks. Types of sexual dysfunction included decreased sexual ability (2 women, 1 man), decreased ability to achieve orgasm (1 woman), decrease in sexual desire (1 woman, 2 men), and impaired erection (1 man; Table 2). There were no reports of increased libido.

DISCUSSION

Sexual function is a complicated biologic response that involves serotonin activity and receptors, as well as cholinergic, adrenergic, and dopaminergic activity and neurohormonal-mediated effects.[8–11] Animal research has shown that serotonin inhibits sexual activity.[12] Serotonin is also purported to have a central role in sexual dysfunction in humans. It is postulated that serotonin works directly on central, spinal, or peripheral receptors to inhibit orgasm and ejaculation.[13] Serotonin may have direct peripheral effects to relax smooth muscle and thereby interfere with orgasm that way as well.[14] It has also been suggested that serotonin may play an inhibitory role on the noradrenergic nervous system or interact with other neurotransmitter systems.[15] In addition, increased serotonergic activity at the level of the serotonin receptors (5-HT_2) may impede sexual function both directly and indirectly via negative feedback on adrenergic activity.[11] These data support the

complexity of sexual functioning and the multifactoral etiology of sexual dysfunction.

Approximately one third of medication-free patients with depression have been found to report sexual dysfunction.[16] However, treatment with antidepressive medication has been demonstrated to cause additional impairment in 35% and improvement of sexual function in 10% of such patients.[17] Reported sexual adverse effects include decreased libido, ejaculation, and orgasm and dysfunction of erections.[15–19] It is therefore not surprising that we found fluvoxamine to cause a variety of types of sexual dysfunction.

Sexual dysfunction is a recognized side effect of fluoxetine, fluvoxamine, sertraline, and paroxetine, the 4 SSRIs currently approved for use in the United States. Data from package insert materials suggest sexual dysfunction is relatively infrequent, occurring in 2% to 13% of patients taking an SSRI.[20–23] The package insert data contrast with the higher sexual dysfunction rates published in the literature, where most authors have found incidence rates of 20% to 45% for fluoxetine, sertraline, and paroxetine,[5,6,10,24,25] although rates as low as 7.8%[15] and as high as 75%[4] are reported. Among the SSRIs, fluvoxamine has been thought to have the lowest rates of sexual dysfunction, with an incidence of less than 1%.[26] The FDA-approved package insert and advertising literature for fluvoxamine suggest that sexual dysfunction may be relatively infrequent, occurring in fewer than 8% of treated patients with depression.[21] Given the mechanism of action of SSRIs, it is unclear why fluvoxamine should have a lower rate of sexual dysfunction than other agents in this class. A trial of fluvoxamine[27] in 320 patients with obsessive-compulsive disorder found that 18% of males and 3.1% of females developed sexual dysfunction versus 0.0% among subjects taking placebo. Another trial of a daily dose of fluvoxamine in the 50–100 mg range for premenstrual dysphoric disorder found that 2 of 10 patients developed loss of libido.[28] Other published data on fluvoxamine-associated sexual dysfunction are in the form of case reports,[26,29,30] and incidence rates cannot be determined from such reports.

The 35% sexual dysfunction rate found for fluvoxamine in the present study is consistent with the previously reported sexual dysfunction rates for other SSRIs. It is interesting that the current study used self-reported sexual dysfunction, a method similar to that used in clinical trials, but found a much higher rate than the trials included in package insert data. One explanation for our higher self-reported rate may be our use of a structured questionnaire. In most phase 2 and 3 investigational trials (collected data from which the package insert data are drawn), adverse events are assessed via spontaneous self-report. It is possible that sexual dysfunction would be underreported by spontaneous self-report.

The questionnaires used in this study were not specifically designed to identify and document sexual dysfunction, but were part of an overall process of identifying adverse events. Some investigators have suggested that most existing sexual dysfunction questionnaires are best at eliciting male sexual dysfunction.[31] No specific attempts were made to modify the questionnaire in order to identify specifically female or male sexual dysfunction. Nevertheless, approximately half the reports of sexual adverse effects came from female subjects.

SSRIs have become first-line therapy for depression and obsessive-compulsive disorder because of their high levels of efficacy and perceived low adverse event rates.[1–3] However, the frequency of sexual dysfunction among patients treated with SSRIs is similar to that seen with tricyclic and heterocyclic antidepressants[17,32] and monoamine oxidase inhibitors.[19] Sexual dysfunction, sleep disturbance, and gastrointestinal side effects are frequent with the SSRIs. Sexual dysfunction has been recognized to affect both males and females and appears to be a class effect.[9,33] Since the SSRIs differ in structure but are similar in mechanism of action, it is reasonable to anticipate similar rates of sexual dysfunction with each of these agents if this adverse effect is mediated through 5-HT_2 receptors.[9] It is no surprise, then, that the finding in this study of a 35% incidence of sexual dysfunction is consistent with literature rates seen with fluoxetine, sertraline, and paroxetine.

The current trial offers important information about SSRI-induced sexual dysfunction. Since all of our subjects were healthy, we did not have to compensate for the confounding caused by concurrent mood or anxiety disorders. In addition, we had 6 baseline visits and were therefore able to establish the absence of sexual dysfunction prior to beginning fluvoxamine therapy. Also, subjects were asked to self-report sexual dysfunction as part of a panel of possible adverse events; we did not specifically elicit reports of sexual dysfunction. All adverse event reports were made while the subjects were on fluvoxamine therapy, avoiding the problem of recall bias that occurs with retrospective interviews. The study would have been strengthened by use of a placebo during the 6-visit baseline phase during which no medications were taken. However, there were no reports of sexual dysfunction during the baseline visits, but spontaneous reports of sexual dysfunction began during fluvoxamine therapy. This suggests that sexual dysfunction was of new onset and that, if anything, the incidence we report is a conservative estimate of the frequency of sexual dysfunction on this medication. Although our sample size was small, our incidence rate is similar to that found for SSRI-induced sexual dysfunction by other investigators and thereby strengthens the association of the dysfunction with the fluvoxamine therapy. Healthy adults have a 35% self-reported incidence of sexual dysfunction on moderate doses of fluvoxamine.

Drug names: fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft).

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Appendix 1. Adverse Drug Reaction Questionnaire

Please check (√) "yes" to any symptoms or complaints that you are experiencing.
Please make note of everything, even if you consider it insignificant, as it may be important for us to know.

	Yes	No
1. Do you have any complaints or symptoms related to your skin, scalp, hair, or nails?	☐	☐
2. Do you have any complaints or symptoms related to your muscles, bones, or joints?	☐	☐
3. Do you have any complaints or symptoms related to your head or face?	☐	☐
4. Do you have any complaints or symptoms related to your vision or eyes?	☐	☐
5. Do you have any complaints or symptoms related to your hearing/ears or nose?	☐	☐
6. Do you have any complaints or symptoms related to your mouth, lips, gums, teeth, tongue, or sense of taste?	☐	☐
7. Do you have any complaints or symptoms related to your throat, voice, or neck?	☐	☐
8. Do you have any complaints or symptoms related to your breasts?	☐	☐
9. Do you have any complaints or symptoms related to your breathing/lungs or heart/circulation?	☐	☐
10. Do you have any complaints or symptoms related to your stomach, digestive system, rectum, or bowel movements?	☐	☐
11. Do you have any complaints or symptoms related to your kidney, bladder, or urinary system?	☐	☐
12. Do you have any complaints or symptoms related to your sexual function/ability?	☐	☐
13. Do you have any complaints or symptoms related to your nervous system?	☐	☐
14. Do you have any complaints or symptoms related to your mental health?	☐	☐
15. Do you have any complaints or symptoms related to the place/site of your injection?	☐	☐