

Letters to the Editor

Sildenafil Treatment of Antidepressant-Induced Sexual Dysfunction

Sir: The case report by Drs. Ashton and Bennett¹ (January 1999 issue) is a welcome addition to the body of literature regarding the treatment of antidepressant-induced sexual dysfunction. One point needs clarification: the authors state that their cases possibly represent the first patients treated with sildenafil for antidepressant-induced sexual dysfunction. To date, an open trial² and 3 case reports³⁻⁵ have described the successful use of sildenafil to treat a most unwanted side effect. As the number of reports of the successful use of sildenafil to treat antidepressant-induced sexual dysfunction increases, clinicians will have more options for their patients. I agree with the authors that although further studies are needed, the use of sildenafil appears promising in treating antidepressant-induced sexual dysfunction.

Conclusions and opinions expressed are those of the author and do not necessarily reflect the position or policy of the U.S. Government, Department of Defense, Department of the Army, or the U.S. Army Medical Command.

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Dr. Ashton Replies

Sir: I very much appreciate the opportunity to reply to the thoughtful and accurate comments of Dr. Berigan. He commented that my letter with Dr. Bennett¹ reported "possibly . . . the first patients treated with sildenafil for antidepressant-induced sexual dysfunction." This may in fact be true since there is a lag time from patient trial to preparing a manuscript and subsequently achieving publication. The psychiatric literature is now reporting increasing numbers of patients receiving sildenafil to treat antidepressant-induced sexual dysfunction. To reinforce this issue, my report of paroxetine-induced anorgasmia in a woman was written in July 1998 but was not published until May 1999.²

As psychiatrists become more familiar with sexual side effects to psychotropic agents, clinical experience will continue to grow. A larger scale study addressing efficacy of sildenafil and other antidote strategies will help delineate whether a standard protocol can be developed and ultimately recommended to our patients.

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Improved Outcome in Fluvoxamine-Treated Patients With SSRI-Induced Sexual Dysfunction

Sir: I read with interest the recent article by Nafziger and colleagues¹ (March 1999 issue) describing the incidence of sexual dysfunction in 20 healthy volunteers who were administered fluvoxamine, 150 mg/day, for 2 to 4 weeks as part of a clinical pharmacology trial. The authors conclude that healthy normal adults (presumably free of underlying psychopathology) had a 35% rate of reporting symptoms of sexual impairment during fluvoxamine therapy as based on data from a structured adverse event questionnaire. The implication is that this result would also be true in patients who are taking fluvoxamine for obsessive-compulsive disorder or depression, and that the rate for fluvoxamine would then be comparable to the rate reported for other agents in the selective serotonin reuptake inhibitor (SSRI) class. However, these results must be viewed cautiously since data from normal volunteer studies do not often reflect real clinical, longitudinal experience in patients with psychiatric disorders. Additionally, this study was not specifically designed to assess sexual function, nor did it contain a control group.

My experience with 8 (5 men, 3 women) consecutive patients treated in a private psychiatric clinic who had developed sexual impairment due to previous SSRI therapy actually indicates improvement in sexual dysfunction symptoms after patients were switched to fluvoxamine treatment (Table 1). All patients had responded to previous SSRIs in terms of their psychiatric symptoms, but developed various forms of sexual impairment while taking those agents. Prior agents included paroxetine, fluoxetine, venlafaxine, nefazodone, sertraline, and mirtazapine. The sexual dysfunction symptoms reported included diminished libido, difficulty achieving orgasm, anxiety over sexual performance, and reduced ability to maintain an erection. Switching these patients to fluvoxamine, 100 to 300 mg/day, resulted in resolution or decrease in sexual dysfunction.

Table 1. Improved Outcome in 8 Fluvoxamine-Treated Patients With SSRI-Induced Sexual Dysfunction

| Patient | Age (y) | Gender | Psychiatric Symptoms ^a | Previous Therapy | Sexual Impairment Symptoms | Fluvoxamine Treatment | Outcome |
|---------|---------|--------|--|--|---|---|--|
| 1 | 44 | Male | Moderate depression, mild attention deficit disorder | Venlafaxine, bupropion, sertraline (+ methylphenidate) | Decreased libido, difficulty achieving orgasm | 100 mg/d | Resolution of sexual dysfunction and depression at 1-year follow-up |
| 2 | 35 | Female | Mixed anxiety and depression, bulimia nervosa, alcohol abuse in remission | Paroxetine, fluoxetine, nefazodone, bupropion | Decreased libido, anxiety over sexual performance, lack of orgasm | 100 mg/d | Able to achieve orgasm, further decrease in libido, efficacy in depression |
| 3 | 42 | Male | Dysthymia, recurrent depression | Fluoxetine, venlafaxine + bupropion | Decreased libido, reduced ability to maintain erection | 150 mg/d (+ bupropion, 150 mg/d) | Full improvement in sexual dysfunction and depression |
| 4 | 37 | Female | Depression, mild attention deficit disorder, obsessive-compulsive personality symptoms | Paroxetine, fluoxetine, venlafaxine, nefazodone (+ methylphenidate) | Decreased libido, decreased interest in sex | Up to 300 mg/d (+ methylphenidate, 30 mg/d) | Improvement in libido and depression |
| 5 | 47 | Male | Severe recurrent depression, mild obsessive-compulsive personality symptoms | Paroxetine, sertraline, fluoxetine, tricyclics; augmentation with lithium, nefazodone, mirtazapine | Decline in sexual function | 300 mg/d | Almost complete restoration of sexual function and acceptable efficacy in depression |
| 6 | 34 | Male | Depression, somatoform disorder | Sertraline, fluoxetine, nefazodone, bupropion (+ nortriptyline) | Decreased libido, decreased ability to achieve erection | 100 mg/d (+ nortriptyline) | Resolution of sexual dysfunction and acceptable efficacy in depression |
| 7 | 22 | Female | Recurrent depression | Sertraline, fluoxetine, bupropion, nefazodone | Decreased libido, unable to achieve orgasm | 200 mg/d | Improved libido, improved ease of orgasm |
| 8 | 28 | Male | Moderate depression, generalized anxiety | Sertraline, imipramine, fluoxetine, mirtazapine | Decreased libido, delayed orgasm | 300 mg/d | Resolution of libido and orgasm |

^aDSM-IV criteria used for diagnoses.

tion in all patients. Control of the underlying psychiatric symptoms was maintained or improved by fluvoxamine compared with the prior therapy.

My experience suggests that fluvoxamine may indeed have a lower incidence of sexual dysfunction in psychiatric patients compared with other SSRIs. This is supported by other studies and review articles²⁻⁴ on this subject. The article by Nafziger et al.¹ may be misleading to clinicians who seek alternative psychopharmacologic agents when patients develop sexual dysfunction. Many patients respond preferentially to SSRIs and cannot be successfully treated outside that class of medicines. Thus, fluvoxamine may be a viable alternative if patients develop sexual impairment during treatment with other SSRIs. Overlooking this promising feature of fluvoxamine would be unfortunate if one considered it just as likely as the other SSRIs to produce sexual adverse events.

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Dr. Nafziger and Colleagues Reply

Sir: We thank Dr. Banov for his thoughtful comments about our article.¹ We agree that longitudinal information from healthy volunteers is not the same as longitudinal information from patients with psychiatric disorders. Extrapolation of data from one population to another should always be undertaken with caution. Nonetheless, we consider the use of healthy volunteers to be a study strength rather than a study flaw because it allows assessment of drug side effects as separate from the sexual dysfunction that frequently coexists with psychiatric disorders (particularly depression).

We read with interest Dr. Banov's anecdotal experience in 8 patients. Limitations of case reports and clinical observations include generation of "wild goose chases" when incorrect conclusions are drawn from an inadequate number of cases,² the cases are nonrepresentative,² observation and reporting are dependent upon the reporter,² or the observed groups differ in some characteristics in addition to the specific factor under study (due to self-selection or physician-selection).³ All of these conditions lead to confounding and unmeasurable factors, making the role of the specific factor under investigation more difficult to demonstrate.³ For these reasons, experimental studies are superior to observational studies and case reports. It would be instructive to know how Dr. Banov measured sexual dysfunction before and after fluvoxamine therapy, and whether the absence of sexual dysfunction was durable or noted only on 1 visit. It does not appear that he used any standardized questionnaire to assess sexual dysfunction in his patients.

Dr. Banov reports on 8 patients who received a variety of antidepressant medications, all of who "developed various forms of sexual impairment while taking these agents." It is trouble-

some that Dr. Banov would conclude, based on a case series of 8 patients, that there is a lower incidence of sexual dysfunction with fluvoxamine than with other SSRIs. He presents no scientifically derived comparative data from his patient population to support this supposition.

The data provided on Dr. Banov's patients suggest that individual patients were taking various medications for unknown periods of time. Some patients appear to have been treated with 7 different medications over time. The reader cannot tell which medications caused which types of sexual dysfunction. We are not assured that these patients had adequate trials on any of these medications or that they experienced sexual dysfunction with each medication until fluvoxamine was instituted. In addition, there is no information about patients treated with agents other than fluvoxamine who did not develop sexual dysfunction or whose sexual dysfunction improved with antidepressant therapy. While readers often find anecdotes compelling, they are considerably less useful than clinical trial data for making rational, evidence-based decisions.

While we hope that readers will be aware of the high incidence of sexual dysfunction with fluvoxamine and incorporate our data into their clinical practice, readers should not abandon the use of fluvoxamine as an alternative when other agents have unacceptable adverse effects.

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Choreiform Dyskinesia With Acute Onset and Protracted Course Following Fluoxetine Treatment

Sir: Extrapyramidal symptoms are frequent adverse effects during treatment with antipsychotics, but are rarely seen with tricyclic antidepressants or specific serotonin reuptake inhibitors (SSRIs). We describe a case of choreiform dyskinesia with acute onset and a protracted course following treatment with fluoxetine.

Case report. Ms. A, a previously mentally and physically healthy 57-year-old woman, developed depressive symptoms in December 1994. From February 1995, she was treated with oxazepam, 15 mg p.r.n., clonazepam, 1 mg t.i.d., and zopiclone, 7.5 mg/day, for symptoms of anxiety and insomnia in the context of depression. In May, fluoxetine, 40 mg daily, was added. After 2 weeks, Ms. A noticed difficulties in controlling tongue movements. The dyskinesias increased in severity until the end of 1995. Fluoxetine treatment was not stopped until November 1995.

From the beginning of 1996, her dyskinesias were treated with numerous drugs for 6 weeks or less (pimozide, flupen-

thixol, biperiden, bromocriptine, tetrabenazine, vigabatrin) that were associated with aggravation, no or transitory effect, or unacceptable adverse effects (e.g., nausea, dizziness, tiredness, depression). In June 1996, Ms. A still had dyskinesias of moderate-to-severe degree with constant grimacing, lip smacking, periodical protrusion of the tongue, and marked dysarthria. Neurologic examination and laboratory test results were normal. On reexamination in April 1998, the dyskinesias were still evident.

Experiments on monkeys have demonstrated that SSRIs can induce dyskinesias similar to the tardive dyskinesias in humans.¹ In addition, we have found reports in the literature on 17 patients who developed choreiform dyskinesias during treatment with SSRIs.²⁻¹⁴ Thirteen individuals were women (mean age = 58 years), and 4 were men (mean age = 42 years). The patients had been treated with SSRIs for a maximum of 4 years before the dyskinesias appeared; however, in 10 of the women, the period was only 8 weeks or less, whereas it was 1 year or more in 3 of the men. Four of the patients had concomitantly received antipsychotic medication, and in 5 cases, an organic brain disorder possibly contributed to the etiology (parkinsonism, cerebral atrophy/dementia, central nervous system lupus, and lacunar infarction). In 10 cases, the dyskinesias remitted, and for the other 7 patients, the course was not adequately described. Gender, treatment with antipsychotic medication, and organic brain disorder did not seem to influence the tendency for remission.

Our patient developed a bucco-linguo-masticatoric syndrome after 2 weeks of fluoxetine treatment. Theoretically, the drugs oxazepam, clonazepam, and zopiclone may have had a causative role, but we find this unlikely and the literature does not support such a causality. Like most published cases, the dyskinesias following SSRI treatment appeared early during treatment, thereby supporting a causal relationship between fluoxetine and the dyskinesias. In contrast to the other cases, our patient suffered from a very protracted course with disabling symptoms 2½ years after the discontinuation of fluoxetine treatment. This protraction may be due to the continued treatment in spite of dyskinesias. The subsequent use of pimozide or flupenthixol may also have aggravated the course.

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Deliberate Self-Poisoning Following Fluoxetine-Neuroleptics Combination

Sir: Akathisia with suicidal ideation has been reported to be associated with 2 selective serotonin reuptake inhibitors, fluoxetine¹ and sertraline.² We report a case of deliberate self-poisoning following the development of akathisia after the introduction of fluvoxamine treatment.

Case report. Mr. A, a 68-year-old Chinese man, had a 30-year history of schizoaffective disorder. He had past episodes of aggressive behavior with auditory hallucinations, delusions, and either irritable or depressed mood. Eight years ago, he had cut his wrist during a depressive episode. Despite numerous hospitalizations following relapses of his illness, he had no further suicidality from then until 1997, during which time he was treated with chlorpromazine, thioridazine, haloperidol, amitriptyline, mianserin, and lithium. In 1997, Mr. A was admitted after another relapse. He responded well to treatment, and, as an outpatient, he was maintained on a monthly injection of flupenthixol decanoate, 20 mg, and daily oral medications of haloperidol, 5 mg/day, lithium, 400 mg b.i.d., and trihexyphenidyl (2 mg b.i.d., added as a prophylaxis for any extrapyramidal side effects).

In October 1998, because Mr. A complained of low mood, fluvoxamine, 50 mg/day, was added. Within a week, he became increasingly restless, with difficulty in sitting and standing still. While he was lying on his bed, his wife noticed incessant shaking of his legs. He complained of a distressing sense of agitation, restlessness, and "not knowing what to do with himself." This sense of agitation and restlessness escalated over the next few days and culminated in deliberate self-poisoning by swallowing detergent. He denied wishing to kill himself, stating that he could not tolerate the agitated feeling any longer and had acted to stop it. Upon admission, he was observed to be very restless and was unable to sit still. He would get up from his seat and march in place. Fluvoxamine was discontinued, and he was prescribed diazepam, 9 mg/day (in divided doses). Within a day, he began to feel less restless and agitated. His suicidal ideation also resolved. After 3 days, he was able to remain seated, although he still had some residual feeling of inner restlessness. His previous neuroleptic drugs were replaced by risperidone, 0.5 mg/day, together with lithium, 400 mg/day, and diazepam, 10 mg/day. After 8 days, he was discharged, and his subjective restlessness had resolved completely, although he would still rub his feet against each other. Two weeks later, his akathisia had resolved completely, with no recurrence at follow-up 2 months later.

Although this patient's last attempt at self-harm was not his first, he described motivating factors qualitatively different from those of the previous episode, with complaints typical of akathisia. Akathisia has been associated with the various seroto-

nin reuptake inhibitors,³ but this is the first report of suicidal behavior associated with fluvoxamine-induced akathisia. His concomitant medications make it difficult, however, to attribute the akathisia and suicide attempt solely to fluvoxamine. Lithium has been reported to have the potential to cause akathisia,⁴ and he was also receiving 2 different neuroleptics. However, he had been taking these medications for a considerable period of time without any complaints. The emergence of akathisia following initiation of fluvoxamine could have resulted from an additive pharmacodynamic effect through serotonin-dopamine interaction⁵ or through a pharmacokinetic effect from elevated haloperidol levels in the blood.⁶ Fluvoxamine has been reported to be a potentially efficacious adjunct to neuroleptics,⁷ but clinicians should be alert to the emergence of akathisia and suicidality in such circumstances.

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Penile Anesthesia Associated With Sertraline Use

Sir: Changes in sexual functioning are well-known side effects of antidepressant treatment with selective serotonin reuptake inhibitors (SSRIs). These include decreased libido and arousal¹ and orgasmic dysfunction.² As an infrequent adverse effect of treatment with fluoxetine, genital anesthesia has been reported for men^{3,4} as well as for women^{5,6} with the suggestion of relief by *Ginkgo biloba*.⁷ We report a case of penile anesthesia after treatment with sertraline.

Case report. Mr. A, a 36-year-old man, developed an adjustment disorder with depressed mood (DSM-IV criteria). He experienced loss of energy, sleep disturbances, and anhedonia. He had no history of prior psychiatric disorder or sexual dysfunction and was taking no other medications. Mr. A was prescribed sertraline, 50 mg/day, and after 3 days he noticed decreased sensation of his penis upon any form of stimulation. Erectile function remained unaffected. Because his mood began to improve rapidly, he continued receiving the medication for about 3 weeks. After discontinuation of sertraline, Mr. A experienced no deterioration of his mood state; penile sensation, however, returned to normal function after 2 days. One year later, while not suffering from any mood disturbances or sexual difficulties, Mr.

A, after having given informed consent to a reexposure test, started to take sertraline, 50 mg/day, again. After 2 days, he again noticed reduction of penile sensation, to a lesser extent than the first time, but of the same quality.

This is, to our knowledge, the first report on penile anesthesia most probably induced by an SSRI other than fluoxetine and the first one with a symptom reproduction after reexposure. Genital anesthesia does not seem to be a specific adverse effect of fluoxetine, but may be generally related to central nervous system serotonin increase. Hence, it may be associated with all antidepressants that enhance serotonergic neurotransmission.

The pathogenesis of this adverse effect remains unclear. In rats, modulation of the nociceptive sensation by serotonin and a possible interaction with opioid analgesia have been suggested.⁸ All reported patients with genital anesthesia, however, described a reduction of all sensation qualities, not specifically pain. Furthermore, there have been no reports on extragenital anesthesia associated with SSRI treatment. However, anesthesia of the genitals may be perceived more readily than decreased sensation elsewhere. Controlled studies are needed to evaluate the incidence of this particular side effect and the influence of increased serotonin neurotransmission on genital sensation and sensation in general.

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Tardive Dyskinesia Associated With Olanzapine Monotherapy

Sir: Olanzapine is an atypical antipsychotic agent with lower potential than the older agents to cause extrapyramidal symptoms,¹ including tardive dyskinesia.² Some reports indicate that tardive dyskinesia can improve with olanzapine therapy.³⁻⁵ The present case report of the occurrence of tardive dyskinesia in a young male patient after about 5 years of olanzapine monother-

apy may alert physicians to be vigilant to detect tardive dyskinesia in patients taking atypical antipsychotic drugs.

Case report. Mr. A, a 25-year-old black man diagnosed with paranoid schizophrenia, sought outpatient treatment in August 1993 for auditory hallucinations, persecutory delusions, loose associations, blunted affect, severe anxiety, and suicidal ideations. He had had 4 psychiatric admissions with episodic exposure to various neuroleptics beginning in 1983 and continuous exposure since 1992. On the basis of a neurologic examination, the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS) were completed in August 1993 and revealed no evidence of parkinsonism, akathisia, or tardive dyskinesia. Mr. A had no history of tardive dyskinesia.

Olanzapine, 20 mg daily, was started in August 1993 and was the sole medication continued thereafter. On this regimen, Mr. A improved remarkably. In May 1998, he complained of abnormal movements of his upper extremities and neck. A brain single photon emission computed tomography examination conducted in September 1993 during the course of the olanzapine treatment did not reveal any structural abnormality. Upon neurologic examination, choreoathetotic and dystonic movements of the upper extremities and neck, without parkinsonism or akathisia, were noted. Mr. A obtained a rating of 12 on the AIMS scale in May 1998. A diagnosis of drug-induced tardive dyskinesia and dystonia was made after other causes of tardive dyskinesia were eliminated. Mr. A continues to receive olanzapine, 20 mg daily, as his psychopathology has improved; his tardive dyskinesia, however, has continued unabated.

In conclusion, tardive dyskinesia and dystonia in this patient are most likely a result of olanzapine administration, as this is the only antipsychotic he received since his admission to outpatient care. The question of whether the previous intermittent or continuous exposure to neuroleptics for about 10 years played any role in the development of tardive dyskinesia cannot be answered. Even with atypical antipsychotic agents, tardive dyskinesia can occur occasionally, and physicians must be vigilant to detect it and take appropriate measures.

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