

# Letters to the Editor

## Sildenafil Treatment of Serotonin Reuptake Inhibitor-Induced Sexual Dysfunction

**Sir:** Serotonin reuptake inhibiting antidepressants (SRIs) are reported to cause decreases in sexual desire, arousal, and orgasm. Augmentation strategies proposed to reduce SRI-induced sexual dysfunction include cyproheptadine,<sup>1-3</sup> yohimbine,<sup>1,4,5</sup> amantadine,<sup>1,6,7</sup> stimulants,<sup>8</sup> buspirone,<sup>9</sup> bupropion,<sup>10,11</sup> and *Ginkgo biloba*.<sup>12</sup> Drug holiday also has been forwarded as a treatment option.<sup>13</sup> Spontaneous remission of SRI-induced sexual dysfunction is uncommon: reports suggest that this occurs in from 5.8% of patients within 6 months<sup>14</sup> to 9.8% of patients followed up to 38 months on continuing treatment.<sup>15</sup>

Sildenafil, a phosphodiesterase type 5 inhibitor, has recently been released to treat male erectile disorder of organic, psychogenic, or mixed origin that may have included a variety of medications including antidepressants.<sup>16</sup> To date, there have been no reports on its use specifically in SRI-induced sexual dysfunction. We report here the first cases of sildenafil used to treat this disorder.

**Case 1.** Mr. A, a 20-year-old white man, had a psychiatric history significant for major depression, recurrent obsessive-compulsive disorder, and panic disorder with agoraphobia. Brief trials of venlafaxine, bupropion, paroxetine, mirtazapine, and fluvoxamine were unsuccessful in controlling his psychiatric symptoms. Mr. A then obtained a remission of symptoms with fluoxetine, 20 mg q.d., and clonazepam, 0.5 mg b.i.d. There was no report of sexual dysfunction prior to initiation of fluoxetine. However, within 4 weeks of starting fluoxetine, Mr. A experienced anorgasmia and an almost total inability to obtain an erection. A 2-week trial of bupropion SR, 150 mg b.i.d., to reverse his sexual dysfunction was unsuccessful. After an attempt on sildenafil, 50 mg, was unsuccessful, the dosage was increased to 100 mg of sildenafil 1 hour prior to anticipated sexual activity. Mr. A described his response as being "80% to 110%" improved ability to achieve erection and orgasm. The reason he reported a "110%" response was because of his perceived diminished refractory stage after orgasm. He noted only minor side effects of elevated heart rate, flushing, and brief instances when it seemed he was looking through a blue filter or haze.

**Case 2.** Mr. B, a 46-year-old white man, had a psychiatric history significant for major depression and attention-deficit/hyperactivity disorder, which had responded to a combination of sertraline, 25 mg b.i.d., and methylphenidate, 50 mg daily in divided doses. He complained of intermittent male erectile disorder and delayed ejaculation beginning with successive prior trials of venlafaxine, bupropion, and nefazodone, none of which controlled the disorders, as well as during his successful trial of sertraline. He also reported hypertension, coronary artery disease, and hypercholesterolemia that had been treated with atorvastatin, 10 mg q.d., and amlodipine, 5 mg q.d., many months prior to the development of sexual dysfunction. Mr. B had no improvement of erectile dysfunction on bupropion, 100 mg at 5 p.m., for 3 weeks. Mr. B did find, however, that 50 mg

of sildenafil 1 hour prior to anticipated sexual activity successfully remitted his erectile dysfunction without side effects. In addition, he noticed that delayed ejaculation that had occurred even in times of adequate erectile functioning during antidepressant treatment was also normalized with sildenafil.

The above cases describe possibly the first patients treated with sildenafil for antidepressant-induced sexual dysfunction. It is not surprising that erectile functioning can be restored using sildenafil, as this is its primary use. What was more interesting was the improvement in delayed ejaculation. This could be explained by an improved erectile capacity that allowed stimulation sufficient for orgasm to occur. However, Mr. B stated that even with adequate erection and stimulation, orgasm could not be reached until sildenafil was added. There is need for further research in this area. Nevertheless, these cases suggest that augmentation with sildenafil may be a treatment strategy for certain patients with iatrogenic sexual dysfunction.

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### Treatment of Intermittent Explosive Disorder With Sertraline in 3 Patients

**Sir:** Underactivity of serotonin systems in the brain has been proposed as a significant factor in patients who have difficulty controlling aggressive impulses.<sup>1,2</sup> Consistent with this theory, the selective serotonin reuptake inhibitor (SSRI) sertraline has been shown to be helpful in reducing impulsive aggressive behaviors in depressed, personality disordered, and developmentally disabled patients.<sup>3-6</sup>

Intermittent explosive disorder, as defined by DSM-IV, is a relatively "pure" condition of difficulty controlling impulsive aggressive behavior that cannot be better accounted for by another mental disorder. Demonstration of the effectiveness of an SSRI in intermittent explosive disorder would therefore be a somewhat more direct form of evidence supporting the role of serotonin in controlling impulsive behavior. A previous study<sup>7</sup> reported a favorable response to sertraline in 1 of 3 patients with intermittent explosive disorder. Two other patients failed to respond to fluoxetine. However, almost all of the subjects in this study had comorbid Axis I disorders, making the results difficult to interpret.

The following 3 cases are the first known reports in the literature of the efficacy of an SSRI in treating intermittent explosive disorder in patients without comorbid Axis I or Axis II disorders.

**Case 1.** Mr. A, a 51-year-old married man, presented for help with his anger. He stated that he had always had a bad temper that was easily set off by minor provocation. He often got upset when he felt people were incompetent or had wronged him in some way. He would usually yell and threaten, and then break or throw something. He stated that such incidents had occurred on at least a weekly basis for most of his adult life. He had no history of substance abuse, affective disorder, or neurologic disorder. At his initial evaluation, Mr. A presented with euthymic mood and no evidence of irritability or anxiety. There was no evidence of psychotic symptoms or cognitive impairment. He denied behavior patterns consistent with any of the major personality disorders and showed no evidence of these to the evaluator.

Mr. A was started on treatment with sertraline, 50 mg in the morning. Within 2 weeks of starting the medication, he reported a decrease in overall irritability and an absence of angry outbursts. His wife also commented on the improvement, which has persisted for over 18 months.

**Case 2.** Ms. B, a 30-year-old divorced woman, was referred by her psychotherapist for psychiatric evaluation. Ms. B had originally sought psychotherapy for help in dealing with her anger, but was finding this only minimally helpful. She described a lifelong problem of controlling her temper. She would become enraged at comments she did not like by others, or by minor frustrations. When angry, she would scream, throw things, or break things. Angry outbursts resulting in broken property had occurred at least twice a week for the past 2 years.

Ms. B's sleep, appetite, weight, and energy level had all been stable over the past several years. She had no history of substance abuse or neurologic disorder. Her psychotherapist had seen no signs of an affective or personality disorder in the 12 months she had been working with her. At her initial examination, Ms. B presented herself calmly without evidence of irritability. Her mood was pleasant, with a good range of appropriate affect. She was mildly anxious. There was no evidence of psychosis, cognitive impairment, or attention problems.

Ms. B was started on sertraline, 50 mg in the morning. She noted a gradual decrease in irritability and anxiety, with a complete elimination of her angry outbursts by the sixth week of treatment. She said that all of her friends were commenting that she was calmer, better controlled, and more pleasant company than they had ever known her to be. She has remained on the medication with ongoing improvement for 2 years.

**Case 3.** Mr. C, a 29-year-old married man, presented for help with irritability and depression. Over the previous 4 months, he had noted the simultaneous onset of "a low frustration tolerance" as well as a mildly depressed mood. He was becoming verbally abusive to his wife on a daily basis when she made the slightest criticism. On several occasions, he had thrown objects or broken them when yelling at his wife. He was becoming increasingly intolerant of his 3-year-old's normal behavior and had recently picked the child up and thrown her into a couch. This incident convinced him to seek help, as he recognized it as abusive and did not wish it to continue.

Mr. C denied any problems with sleep, appetite, concentration, or energy level. He had maintained his usual interest in things. He had no history of symptoms consistent with major depression, nor did he have a history of substance abuse or neurologic disorder. Mr. C presented as a cooperative man with no overt evidence of anger or irritability. His mood was mildly depressed with a slightly constricted range of affect. Anxiety was minimal. There was no evidence of psychosis or cognitive impairment. His history and course during treatment were not consistent with a personality disorder.

Mr. C was started on sertraline treatment, with the daily dosage gradually increased to 100 mg over 6 weeks. At that point, he reported a complete absence of angry outbursts and an improvement in his mood. This improvement was sustained for 5 months until he discontinued sertraline. Within 2 months of discontinuation, he noticed a return of angry outbursts toward his wife and some decrease in mood. He could identify the mood change as secondary to guilt about his loss of control over his anger. He was restarted on sertraline treatment, 100 mg per day, and within 3 weeks again felt in control of his anger, with improved mood. This improvement was sustained for the next 9 months, during which he reported no angry outbursts at his wife despite significant marital stresses. He then again went off sertraline treatment with a return of irritability within 6 weeks. This again responded to restarting the sertraline with sustained results for 6 months, after which the patient dropped out of treatment and was lost to further follow-up.

These 3 patients all met the DSM-IV diagnostic criteria for intermittent explosive disorder, in the absence of any comorbid psychiatric condition. (Although Mr. C presented with a mildly depressed mood, this seemed to be secondary to the intermittent explosive disorder rather than due to a primary affective disorder.) The dramatic reduction in impulsive aggressive behavior in all 3 patients with sertraline adds to the implication of serotonergic systems in controlling aggressive impulsive behavior. Reports in other studies of a high association of intermittent explosive disorder with other major psychiatric disorders has led some investigators to question whether this condition is an inde-

pendent diagnosable disorder or simply a symptom complex seen in other conditions.<sup>3,7,8</sup> Further research will hopefully clarify the diagnosis and treatment of intermittent explosive disorder.

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#### Bupropion Clarification

**Sir:** The recent Glaxo Wellcome-sponsored supplement to the *Journal* entitled "Beyond SSRIs" provides clinicians with useful information regarding the treatment of depression and discusses our bupropion product. I would like to provide clarification on some aspects of the supplement relating to bupropion.

First, Drs. Davidson and Connor<sup>1</sup> refer to evidence supporting the efficacy of bupropion in eating disorders. Although Horne et al.<sup>2</sup> reported a beneficial effect of bupropion in nondepressed bulimic patients, clinicians should be reminded that bupropion is contraindicated in patients with a current diagnosis or past history of bulimia or anorexia nervosa because of a higher

incidence of seizure noted in such patients treated with the immediate-release formulation of bupropion in that trial.

Second, while Dr. Jefferson,<sup>3</sup> in his article on drug interactions, and Drs. Zisook and Downs,<sup>4</sup> in their article on the diagnosis and treatment of depression in the elderly, note the contraindication of the combination of the MAOIs with other antidepressants, it should be noted that this contraindication applies to bupropion as well.

Finally, Dr. Settle,<sup>5</sup> in his overview of the side effect profile of bupropion, and Drs. Zisook and Downs<sup>4</sup> refer to the relative cardiovascular safety of bupropion in patients with preexisting cardiac disease. It should be noted that there is no clinical experience establishing the safety of bupropion in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups.

Bupropion was well tolerated in patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants (TCAs)<sup>6</sup> and was generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure studied by Roose et al.<sup>7</sup> However, bupropion was associated with a rise in supine blood pressure in the study of patients with congestive heart failure, resulting in discontinuation of 2 patients for exacerbation of baseline hypertension.

I hope the above information serves to clarify these issues.

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