Sildenafil for Iatrogenic Serotonergic Antidepressant Medication–Induced Sexual Dysfunction in 4 Patients

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Objective: To evaluate the effect of sildenafil on iatrogenic serotonergic antidepressant–induced sexual dysfunction.

Method: Four outpatients (2 men, 2 women) who developed sexual dysfunction (erectile impotence, anorgasmia) during treatment with a serotonin reuptake inhibitor antidepressant for psychiatric disorder were selected. Each subject was initially prescribed sildenafil 50 mg to be taken approximately 1 hour before sexual activity. The dose was increased to 100 mg for a partial or failed response.

Results: Four cases are detailed in case report fashion. All 4 had rapid reversal of their sexual dysfunction, usually with the first dose. Reversal equates to 1 successful use of sildenafil in each of 2 patients and 3 uses in 2 patients.

Conclusion: Sildenafil may be an effective treatment for serotonergic antidepressant–induced sexual dysfunction and deserves further evaluation in randomized placebo-controlled studies.

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Iatrogenic sexual dysfunction is an adverse event commonly associated with antidepressant pharmacotherapeutic agents, particularly those with serotonergic actions. It has long been underrecognized and underreported for a variety of reasons, i.e., embarrassment, misattribution as a symptom of depression, masking by other adverse events, and inadequate assessment. However, the current widespread use of highly effective thymoleptic serotonergic agents for depression, anxiety, and other psychiatric disorders in both primary care and specialty sectors has increased the awareness of this problem. Unfortunately, 15% to 45% of patients prescribed these medications fail to complete treatment on the initial prescribed agent[1] (approximately two thirds do so because of adverse side effects[2]), and 45% to 60% of patients taking serotonin reuptake inhibitors (SRIs) suffer some form of sexual dysfunction.[3] This high incidence of sexual dysfunction suggests that effective management of this troublesome problem can have a significant impact on outcome, reducing the morbidity and mortality of these common disorders for which they are being prescribed but also commonly discontinued.

The recent introduction of sildenafil citrate, a peripherally acting selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5, as an effective oral treatment for a diverse etiologic spectrum of erectile dysfunction offers an opportunity to examine its ability to alleviate antidepressant-induced sexual dysfunction. Although its current indication is for male erectile dysfunction, analogous dysfunctions and mechanisms may be drawn for female sexual dysfunction.[4] Furthermore, antidepressant-induced sexual dysfunction occurs in both genders. We report the use of sildenafil in open fashion in 4 patients (2 men and 2 women) who developed symptoms of sexual dysfunction as a consequence of treatment with serotonergic-acting antidepressant agents.

CASE REPORTS

The patients were recruited from the outpatient clinical setting. Subjects were capable of and provided informed consent. All 4 experienced sexual dysfunction, particularly erectile impotence in the men or anorgasmia in the women, while being treated with an antidepressant agent. They had been taking a stable dose of an antidepressant for at least 6 weeks, while maintaining improvement of the presenting condition (usually depression and/or anxiety), and had experienced sexual side effects continuously for more than 4 weeks. The patients were required to be free of any concurrent unstable medical illness, poor overall physical health, history of sexual dysfunction (other than antidepressant induced), psychiatric disorder

not under control, previous or current alcohol or substance abuse/dependence, or genital anatomical defects. History of stroke, myocardial infarction, or use or likely use of any nitrate was explicitly considered, and a basis for exclusion.

Each patient was given three 50-mg tablets of sildenafil and instructed to take one 50-mg tablet no more than 2 hours or less than 1 hour before anticipating sexual intercourse. If that dose was unsuccessful in reversing the sexual dysfunction, the patient was instructed to take 100 mg (two tablets) in the same time frame before their next sexual encounter. On at least 1 occasion, all 4 reported a marked reversal of their sexual dysfunction. Three cases were successful with the first 50 mg dose of sildenafil. The fourth patient had 1 failure at 50 mg, but was then successful at 100 mg of sildenafil. There were a total of 8 successful reversals of sexual dysfunction in this trial. This included return of effective duration and intensity of erection and ejaculation for the men and adequate lubrication and orgasm for the women. The only side effects reported were occasional transient mild headaches in 2 subjects. The 4 clinical cases follow.

Case 1

Ms. A, a 36-year-old married Hispanic woman, had a chief complaint of depression. According to the consultation request from her primary physician, she had been prescribed sertraline 50 mg, which "didn't help and caused dizziness." At Ms. A's initial visit to the psychiatric outpatient service, she was diagnosed with recurrent major depression disorder (DSM-IV), and paroxetine 20 mg was prescribed. Six weeks later, at a follow-up appointment, Ms. A reported improved mood and sleep, but complained of sexual problems, specifically, anorgasmia. There was no prior history of this sexual dysfunction. At that point, paroxetine was tapered to 10 mg, without relief of the sexual dysfunction. As a consequence of slowly increasing return of depressive symptoms, nefazodone 50 mg twice a day was started. The nefazodone dosage was increased gradually to 150 mg twice a day, as paroxetine was discontinued, with improvement in mood. At this point, Ms. A again developed anorgasmia. We prescribed sildenafil 50 mg. Ms. A reported reversal of anorgasmia with the first dose. She complained of a mild bifrontal headache for 1 to 3 hours upon waking in the morning. The headache resolved without treatment.

Case 2

Ms. B, a 29-year-old female graduate student, suffered from panic disorder and depression (DSM-IV). Treatment was started at 50 mg of sertraline and 1 mg of lorazepam 4 times daily. At week 4, the lorazepam dosage was tapered and discontinued. The patient was feeling better, had no panic attacks, and described markedly improved mood. However, she reported a corresponding decline in ability to achieve orgasm that progressed to anorgasmia. There was no change in her sexual practices.

With clinical improvement, she described a renewed interest in sexual activity, which had declined while ill. Arousal, lubrication, and orgasm had remained intact while ill. Orgasmic delay and decreased lubrication seemed to correlate with the start of antidepressant medication. Reduction of sertraline to 25 mg was marked by some return of orgasm, although delayed. However, a panic attack recurred. Ms. B insisted on increasing the dose of sertraline back to 50 mg and reported a return to complete anorgasmia. Subsequently, she asked about sildenafil after having read about it in *Time* magazine. Ms. B was given three 50-mg tablets of sildenafil and instructions for their use. She reported by phone that she tried it as instructed and was "amazed" at the immediate return of apparent full orgasm with the first dose. No side effects were noted.

Case 3

Mr. C, a 48-year-old white married man, had a history of recurrent major depression (DSM-IV) for the past 10 years. While he has benefited from antidepressants in the past, he was sensitive to side effects and unable to tolerate most. Notable side effects were an initial loss of potency and subsequently libido. In the past, he was able to have sexual intercourse if he held his medication for a few days, but worried about the return of depression during these drug holidays. He maintained a relatively good level of mood on a combination of fluoxetine and nefazodone; however, his sexual drive and ability to perform were greatly inhibited. Brief drug holidays are not possible owing to fluoxetine's long half-life. The possibility of trying sildenafil, which Mr. C had been considering independently, was brought up. He was given a sample of 3 pills with instructions. The next week, he reported that he had had an erection 40 minutes after using the 50-mg sildenafil dose. He also described waking up the next morning with an erection and was sexually aroused for the first time in a long while. However, he was unsure about continuing sildenafil because its use had been unsettling to his wife.

Case 4

Mr. D, a 50-year-old white married man, had a diagnosis of chronic paranoid schizophrenia and superimposed recurrent depressive episodes (DSM-IV). He was stabilized on risperidone 6 mg and fluoxetine 80 mg. The patient reported a strong sexual drive, but severe impotence. Reduction of fluoxetine improved his potency, but made him very depressed. He quickly asked to have the dose raised. Cyproheptadine had been tried with no effect. Mr. D decided against using yohimbine. After asking about sildenafil, he was given a sample and instructed to take 50 mg 1 hour before his next effort at intercourse. If that was ineffective, to try 100 mg the next time. The patient reported that when he tried 50 mg and it had no effect, he

believed he had been given a sugar pill. The next day he tried 100 mg and was very pleased with the effect of a sustained erection. He returned later that week requesting a prescription for sildenafil.

DISCUSSION

The patients described in this report experienced iatrogenic sexual dysfunction in association with their prescribed antidepressant treatment. The drug effect seemed to parallel improvement in symptoms of their original presenting disorder. Dose reduction to levels that reversed the side effect did not maintain the achieved clinical improvement. In 2 cases, the initial agent was changed and the sexual dysfunction recurred with the second agent. The adverse effects on sexual function were variable and usually involved a variety of intertwined complaints in the domains of libido, sexual arousal (penile tumescence, vaginal engorgement, lubrication), responsivity (ejaculation, orgasm), and experience (pain, discomfort, pleasure). Introduction of sildenafil seemed to be effective for reversing those effects. In addition, the patients were able to continue to use the antidepressant agent that improved the primary psychiatric condition, needed to be continued for maintenance, and, in some cases, would remain for prolonged prophylaxis. With the exception of occasional mild transient headache, no other side effects with sildenafil were observed.

In both men and women, a relationship between sexual dysfunction induced by psychopharmacologic agents, particularly those involving serotonergic activity (SRIs), has been clearly established.[5] Other classes of antidepressants are also implicated, including tricyclics, monamine oxidase inhibitors, and novel agents. Although estimates of the prevalence of this common adverse effect, which contributes to compliance problems, are highly variable, studies indicate that approximately 50% of patients (male and female) taking SRIs experience some degree of sexual dysfunction.[3] With the recent introduction of sildenafil (acting on end organ nitric oxide transmission), a better understanding of the pathophysiologic mechanisms of sexual function is available.[6] Sildenafil is a potential advance over other, generally ineffective approaches with serotonin antagonists (cyproheptadine), cholinergic agonists (bethanechol, neostigmine), α_2 antagonists (yohimbine), and herbals (*Ginkgo biloba*).[4,7]

In conclusion, this report suggests several further considerations. Sildenafil citrate, an oral therapy for erectile dysfunction, may be an effective acute treatment for SRI- and other antidepressant-induced sexual dysfunction in both men and women. We caution against making any overreaching inferences that the effects of sildenafil on sexual dysfunction extend beyond its direct primary action on vascular engorgement with direct stimulation. Considering the interrelated nature of the various domains of the sexual response, it would not be unexpected for improvement in the domain of responsiveness (by direct stimulation) to have secondary or halo effects or placebo effects in the same or other domains of sexual function. Another interesting question is whether improvement in sexual function itself would lead to a faster or more robust improvement in the underlying depression or anxiety disorder. Previous reports suggest that a subset of patients with iatrogenic antidepressant sexual dysfunction have spontaneous remissions and might need only limited treatment.[4] Whether the side effect reversal extends over long-term use for persisting drug-induced sexual dysfunction also remains to be determined. Many patients will not spontaneously discuss sexual concerns and must specifically be asked about changes in sexual function. For the patient who develops sexual problems, careful explanation of the meaning of the symptoms (i.e., reversibility) and the options of watchful waiting versus active treatment, encouragement, and support can be reassuring and maintain compliance. Relationship issues with the patient's significant other and potential for change must be considered and addressed. Replication of these findings in a randomized placebo-controlled study is necessary and underway.

As a final caveat, clinicians must recognize that coverage of this new compound in the lay press has been extensive and has included both informed and misinformed pieces on applications within and beyond its formal indications. It would be prudent to discuss and clarify what awareness and expectations the patient brings to the treatment setting when considering a prescription.

Drug names: bethanechol (Urecholine), cyproheptadine (Periactin and others), fluoxetine (Prozac), lorazepam (Ativan and others), nefazodone (Serzone), neostigmine (Prostigmin), paroxetine (Paxil), risperidone (Risperdal), sertraline (Zoloft), sildenafil citrate (Viagra), yohimbine (Yocon and others).

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