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Persistent Sexual Side Effects after SSRI Discontinuation

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It is well known that the selective serotonin reuptake inhibitors (SSRIs) can cause sexual side effects such as anorgasmia, erectile dysfunction, and diminished libido. Initial studies found that such side effects occur in less than 10% of patients, but those studies relied on unprompted reporting, so the frequency of such problems was underestimated. In more recent studies, doctors have specifically asked about sexual difficulties, and found that they are present in up to 83% of patients [1]. This dysfunction occasionally disappears spontaneously without stopping the SSRI, and is assumed to always resolve after discontinuation. However, one of the authors has noted that sexual functioning does not always return to baseline [2]. Reports on three such cases are presented here.

Case 1

D.K., a 24-year-old male, was prescribed 20 mg q.d. citalopram in February 2001 for depression. He noticed a positive effect on his depression immediately. Within the first month of treatment he noted that sexual desire was reduced and he developed anorgasmia with intact ability to have an erection. After 1 month these side effects subsided. At the end of 2 years he noted that his libido was reduced, ability to have an erection was poor, but his ability to have an orgasm was intact. Towards the end of 2003, he noticed a dramatic decline in libido, inability to have an erection, but with preserved ability to climax. He discontinued the medication without major withdrawal symptoms, but since then his sexual desire has remained very weak and he has severe tactile insensitivity in his penis, chest, and abdomen. His estradiol level was found to be elevated, and he had mild prostatitis, but this was brought under control with 0.5 mg q.d. anastrozole. Attempts were made to reverse the sexual dysfunction with sequential bupropion, cabergoline, and selegiline without success.

Case 2

B.B., a 27-year-old female, presented with chronic insomnia, anxiety and moderate depression in December 1998 and was prescribed 20 mg q.d. fluoxetine. She immediately noticed an improvement in sleep and mood. Within the first 3 days of beginning therapy, she experienced a dramatic loss of libido and a marked reduction of genital and nipple sensitivity with concurrent anorgasmia. She decided to continue with the therapy for a limited time because of the improvement in mood. After 7 months of treatment she discontinued the fluoxetine. Most aspects of sexual dysfunction have never reversed. Orgasmic capacity did return upon discontinuation, but at a dramatically reduced intensity and with a refractory period of several days, and tactile sensitivity only partially returned. Libido loss is almost total, compared to a very high libido since puberty. In July 2000 and February 2005, serum testosterone and estradiol were found to be in the normal range.

Case 3

A.H., a 30-year-old male, was prescribed 50 mg q.d. sertraline for chronic depression and insomnia in 1999. Four to five days after starting the medication, he noticed a severe drop in sexual desire, moderate erectile dysfunction, difficulty reaching orgasm with a long refractory time, reduced ejaculate volume, and genital numbness. He continued to take the medication, hoping that the side effects would subside. Since they did not abate after 5 weeks, he discontinued the sertraline. The side effects did not go away after stopping and remain unchanged to the present. Attempts were made to reverse the sexual dysfunction with sildenafil, supplemental testosterone, and some herbal remedies, without success.

Numerous biochemical and neurochemical changes occur during SSRI use that could account for their sexual side effects [3]. Effects on mood such as 'emotional blunting' have also been associated with sexual dysfunction [4]. We do not know why these changes normalize in the majority of patients discontinuing therapy, but do not in a small minority, such as the cases reported here.

SSRIs cause adaptive changes in neurons that are mediated through alterations in serotonin transporters and receptors [5], and epigenetic expression changes in other genes [6]. This might explain the time delay in clinical response, and protracted discontinuation. The discontinuation syndrome [7] could be a result of abnormal gene expression profiles returning to normal upon medication withdrawal. Although transporter and receptor densities and cerebral gene expression probably normalize in most patients, it is theoretically possible that there are significant delays in some.

Secondly, serotonergic receptors are involved in the negative feedback regulation of the hypothalamic-pituitary-testicular axis [8]. Therefore, elevated serotonin in the hypothalamus could result in downregulation or dysregulation of this axis, creating lowered free testosterone levels [9]. These changes may not fully normalize in some patients.

Finally, although rare, there are reports of SSRIs causing extrapyramidal effects [10], all of which can persistent after drug discontinuance. Perhaps persistent sexual side effects are caused by a similar mechanism to extrapyramidal effects, but in areas of the nervous system responsible for sexual function. For example, treatment of adolescent patients with obsessive-compulsive disorder with paroxetine causes reductions in left amygdala volume [11], a part of the brain shown to be strongly involved in response to visually erotic stimuli [12]. Such structural changes may take a very long time to reverse in some patients.

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Further study needs to be made concerning such prolonged sexual dysfunction from SSRIs. In one study in which patients with SSRI-induced sexual dysfunction were switched to the dopaminergic antidepressant aminpetine, 55% still had at least some type of sexual dysfunction after 6 months compared to 4% in the control group treated with aminpetine alone [13]. More studies are needed to address the frequency, severity and nature of this problem before its neurochemical etiology can be addressed.

These case studies have important clinical implications. They suggest that when patients develop sexual dysfunction as a side effect of SSRIs, clinicians should be alert to the possibility that restoration of sexual function may not correlate temporally with medication cessation. Patients are often willing to continue taking SSRIs despite sexual side effects, but the possibility of increasing the probability of dysfunction remaining after discontinuance should be taken into consideration. Such persistent side effects could even worsen the long-term prognosis of depression [14].

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