Persistent Sexual Dysfunction after Discontinuation of Selective Serotonin Reuptake Inhibitors

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ABSTRACT

Introduction. Sexual dysfunctions such as low libido, anorgasmia, genital anesthesia, and erectile dysfunction are very common in patients taking selective serotonin reuptake inhibitors (SSRIs). It has been assumed that these side effects always resolve after discontinuing treatment, but recently, four cases were presented in which sexual function did not return to baseline. Here, we describe three more cases.

Case #1: A 29-year-old with apparently permanent erectile dysfunction after taking fluoxetine 20 mg once daily for a 4-month period in 1996.

Case #2: A 44-year-old male with persistent loss of libido, genital anesthesia, ejaculatory anhedonia, and erectile dysfunction after taking 20-mg once daily citalopram for 18 months.

Case #3: A 28-year-old male with persistent loss of libido, genital anesthesia, and ejaculatory anhedonia since taking several different SSRIs over a 2-year period from 2003–2005.

Results. No psychological issues related to sexuality were found in any of the three cases, and all common causes of sexual dysfunction such as decreased testosterone, increased prolactin or diabetes were ruled out. Erectile capacity is temporarily restored for Case #1 with injectable alprostadil, and for Case #2 with oral sildenafil, but their other symptoms remain. Case #3 has had some reversal of symptoms with extended-release methylphenidate, although it is not yet known if these prosexual effects will persist when the drug is discontinued.

Conclusion. SSRIs can cause long-term effects on all aspects of the sexual response cycle that may persist after they are discontinued. Mechanistic hypotheses including persistent endocrine and epigenetic gene expression alterations were briefly discussed. **Csoka A, Bahrick A, and Mehtonen O-P. Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors. J Sex Med 2008;5:227–233.**

Key Words. SSRI; Iatrogenesis; Sexual Dysfunction; Persistent; Erectile Dysfunction; Libido

Background

It is now well known that the selective serotonin reuptake inhibitors (SSRIs) can cause sexual side effects such as anorgasmia, erectile dysfunction, diminished libido, and genital anesthesia. The reported frequency of sexual dysfunction varies with how the information is obtained. Premarket studies of the SSRIs found that adverse sexual side effects, such as orgasm problems or lowered libido, occur in less than 10% of patients, but those studies relied on unprompted reporting methods. Spontaneous reporting methods are believed to result in up to 60% differences in sexual dysfunction rates as compared to rates obtained with systematic inquiry [1].

In postmarket studies, clinicians have more systematically solicited information about SSRI-associated sexual problems such as lowered libido and difficulties with arousal or orgasm, via structured clinical interviews or validated sexual functioning questionnaires and found that they are present at dramatically higher rates, at frequencies as high as 98% [2]. While these dysfunctions are very common, and while they typically endure for as long as the individual is taking the medication, it has been generally assumed that these side effects always resolve after discontinuing treatment.

But no studies have specifically tracked SSRI-emergent sexual dysfunction after cessation of use to determine when and to what degree individuals return to their premedication sexual functioning baseline. Recently, there have been four case reports of patients whose sexual function did not return to baseline [3,4]. There have also been reports of SSRI withdrawal causing persistent premature ejaculation [5] and persistent genital arousal disorder [6]. Here, we describe three more cases of persistent sexual dysfunction after cessation of SSRIs, and discuss the theoretical and clinical implications of these findings. The participants have consented to the publication of their case reports under the University of Iowa IRB ID# 200611715. Case information was obtained via a structured clinical interview. It is worth noting that the two instruments most frequently used for assessing medication-related sexual dysfunction, the Changes in Sexual Functioning Questionnaire and the Arizona Sexual Experiences Scale, do not capture the full spectrum of symptoms described by these cases.

Method

An invitation for volunteers to be interviewed was posted to the SSRIsex Internet community (http://health.groups.yahoo.com/group/SSRIsex/), a support and discussion group established in January of 2005, of over 1,300 individuals who have identified themselves as experiencing sexual dysfunctions that began on an SSRI, but which have persisted long after discontinuing the medications. Among the respondents, three, whose cases the authors judged to be highly credible as based on the internal consistency of their posting history to the group over a 2-year period, were selected for and consented to be interviewed as per University of Iowa IRB #200611715. The structured interview protocol included systematic questioning of concerns, symptoms, and changes related to libido, quality of arousal and genital sensitivity, quality of orgasm, and overall sexual satisfaction during four baselines: most typical functioning prior to SSRI use and prior to experiencing the condition treated with SSRIs; during the condition being treated but prior to SSRI use; during SSRI use; and after discontinuing SSRIs. Significant physical and mental health history, history of any evaluations investigating alternative causes for the persisting sexual dysfunctions, and the impact of the persistent sexual problems on quality of life were also explored. Outcomes of physical exams, blood work, and other diagnostic procedures and assessments were reported here based on patient report.

Case #1, currently a 29-year-old male in a long-term relationship, was prescribed 20-mg q.d. fluoxetine in 1996 at age 18, a time during which he reported experiencing a period of anxiety and uncertainty related to academic and career direction. His concerns appear to have been developmentally normative, and his transitory symptoms were not of sufficient severity to warrant a diagnosis of an anxiety disorder. He reported his sexual functioning remained unaffected during this time. Thus, his concerns may best be captured by a diagnosis of a "phase of life problem" or an "adjustment disorder with anxiety." Before taking fluoxetine, prescribed by a family physician, he reported never having had problems getting erections; he had full and lasting erections from erotic thoughts or visual stimuli, regular nocturnal and morning erections, and was easily aroused. Within 3–4 days of initiating the drug, he became impotent. He no longer had nocturnal or morning erections and could not become erect without being physically stimulated, often with much effort. Ejaculation became difficult because it required a great deal of stimulation to achieve even a weak erection, which would immediately diminish once stimulation was withdrawn. His libido was, however, unaffected. He also noticed additional side effects of weight loss, somnolence, and short-term memory problems. As the fluoxetine had not resulted in a therapeutic effect after 2 months, the dosage was increased to 40 mg once daily, which only increased the somnolence. After being on the medication for a total of 4 months, he discontinued it abruptly and without withdrawal problems, but his erectile dysfunction has remained. Over the last 11 years since discontinuing fluoxetine, no psychological or physical health problems have been found in consultations by two family practice physicians, three urologists, two neurologists, an endocrinologist, and a radiologist. All physical examinations and blood work including testosterone, estrogens, prolactin, and glucose have been normal.

A penile Doppler ultrasound showed arterial blood flow to the penis was "extremely good" and a dynamic infusion cavernosal study showed no leakage from the veins. Both these tests were carried out by a radiologist. A somatosensory-evoked potential, carried out by a neurologist, indicated no problems with his spine. He has never had any psychosexual counseling.

In relationships, after becoming impotent, he has sexually satisfied his partner without intercourse. At age 27, he was prescribed 20-μg alprostadil as needed, which has allowed penetrative sex. While intercourse must be prearranged, he finds this more satisfying. He has maintained a long-term, stable relationship and reported a positive vocational adjustment. He has not pursued any counseling related to the persistent sexual dysfunction. He was not informed of the possible sexual side effects of fluoxetine by the prescribing professional.

Case #2, a 44-year-old single male, was diagnosed with a major depressive episode in summer of 2002, at age 39. Prior to being prescribed citalopram 20 mg q.d. by a general practice physician, he reported having experienced feelings of hopelessness, insomnia, impaired work productivity, difficulty concentrating, and social withdrawal. Prior to the depressive episode, he was in good physical health, with no history of sexual difficulties, but during the episode, his libido was mildly lowered. He experienced a resolution of the depressive symptoms after 6 weeks of citalopram treatment and stayed on the citalopram for another 4 weeks, noting that his libido not only remained mildly reduced but was also now experiencing slight difficulty achieving an erection and mildly reduced intensity of orgasm. He experimented with a "drug holiday" and noticed that within days of ceasing the citalopram, his sexual appetite and performance returned. He resumed citalopram 2 weeks later, confident that the side effects were reversible.

With depressive symptoms continuing to be fully remitted, he stopped the drug in spring 2004 and looked forward to resuming a normal sexual life. However, over the ensuing year, he noticed that rather than improvement, there were further declines in libido, genital sensitivity, and ability to achieve an erection. From 2004 to the present day, his sexual functioning has continued to decline. He now reports genital anesthesia and only very rarely being able to reach orgasm, and if he does, it is mechanical and unassociated with pleasure. His depressive symptoms have remained in remission.

Since discontinuing citalopram in 2004, no physical or psychological cause of his sexual dysfunction has been found after consultations with several healthcare professionals, including an endocrinologist, a urologist, and a psychologist. Physical exam and all blood work, including testosterone, estrogens, prolactin, and glucose have been normal, and hyperprolactemia, diabetes, and Cushing's syndrome have been excluded as possible diagnoses. Full erectile capacity can be restored with 100-mg once daily sildenafil, but his erection remains numb and he does not feel mentally connected with his genitals. He explained that given the described sexual difficulties, his relationships have become asexual, frustrating, and much more difficult. He has not pursued any counseling. He was not informed of the possible sexual side effects by the prescribing professional.

Case #3, currently a 28-year-old, married male, suffered from a major depressive episode in 2003 at age 23. He reported a 2-year period of not enjoying formerly satisfying activities, a decline in motivation for his studies, a loss of caring about goals and achievements, excessive sleep, and decreased appetite. He reported having a very strong libido, a highly satisfying sexual life, and no history of problems with sexual functioning prior to beginning medication treatment or associated with his depressive episode. Over a 2-year period, he was prescribed a variety of antidepressants, sequentially: paroxetine 40 mg once daily, sertraline 100 mg once daily, venlafaxine 150 mg once daily, and milnacipran 100 mg once daily, but suffered continuous treatment-emergent sexual problems. While taking the first three medications, his sexual interest remained high, but he experienced a weak erection, a continuous, slow leakage of seminal fluid during sexual activity but prior to ejaculation, significantly decreased genital sensitivity, and anorgasmia. Finally, while on milnacipran, he noticed that he was also losing his libido and had days when he no longer responded to sexual stimuli. He reported minimal therapeutic benefit of the medications, which led to discontinuing them in December 2004 as the sexual side effects had, by then, become intolerable. His erectile dysfunction did reverse, but to the present day, the other aspects of his sexuality have not returned. He is unable to experience sexual pleasure or respond to visual sexual stimuli, has no libido, little to no genital sensitivity, and ejaculatory anhedonia. Physical exam was normal, and numerous tests have failed to reveal any physical or biochemical abnormalities since he discontinued the SSRIs in 2004. In particular, testosterone and prolactin levels have been repeatedly assessed and found to be normal. A magnetic resonance imaging scan was performed to rule out any physical changes in the brain and all results were normal. Psychological factors were ruled out by three different psychiatrists. He received just over 2 years of twice weekly

counseling in which he successfully worked to address his depressive symptoms.

He got married 4 months after discontinuing medication, and both he and his wife assumed that their formerly highly satisfying sexual relationship would soon resume. However, he stated that while his wife remains supportive, over the 2 years of his marriage, the condition has severely compromised the quality of the relationship by depriving him of all physical sensations of pleasure, as well as the emotional bonding connected with sexual intimacy.

Recently, it was found that dopamine agonists (pramipexole, ropinirole, cabergoline) or reuptake inhibitors (bupropion) can improve his symptoms somewhat, but only temporarily for a few weeks, before their effects wear off. Extended-release methylphenidate (Concerta; Alza Corp, Mountainview, CA, USA) 54 mg once daily, appears to have even greater efficacy at reversing his symptoms than the dopamine agonists or bupropion, but again, the prosexual effects are only temporary and go away when the drug is discontinued.

Discussion

It is currently not known what causes the sexual side effects of SSRIs to sometimes persist after discontinuation. Although fluoxetine (Prozac; Eli Lilly, Indianapolis, IN, USA), the prototypical SSRI, is classified as a reproductive toxin [7] by the Center for the Evaluation of Risks to Human Reproduction, an expert panel at the National Institute of Environmental Health Sciences at the National Institutes of Health, and SSRIs were recently shown to cause reversible infertility in some men [8], the long-term effects of SSRIs on sexuality and fertility have scarcely been studied. Most doctors are unaware of the possibility of long-lasting effects or attribute them to psychological causes. However, none of the three cases reported here were found to have any psychological issues related to sexuality, or any other mental health problems that might account for their symptoms.

Various complex hormonal, central, and peripheral nervous system, and neurochemical changes occur during SSRI usage that could account for their sexual side effects. Changes include increased serotonin, decreased dopamine, blockade of cholinergic and alpha-1 adrenergic receptors, inhibition of nitric oxide synthase, elevation of prolactin levels [9,10], decreased oxytocin [11], and decreased testosterone levels [12].

SSRIs change levels of neurotransmitters other than serotonin, likely through indirect mechanisms. A strong case can be made that many of the side effect of SSRIs, both sexual and otherwise, are dopamine dependent [13]. Data suggest that SSRIs can inhibit dopaminergic neurotransmission, not only by their effects on dopamine secretion or recapture, or on dopaminergic receptors, but also indirectly through serotonergic mediation [14]. Complex changes of dopaminergic neurotransmission (mostly antidopaminergic effects) have been described with SSRIs [10]. The partial reversal of symptoms with dopamine agonists or reuptake inhibitors in Case #3 strengthens the case for a role of downregulation of dopaminergic neurotransmission as a cause of persistent SSRI sexual side effects.

More recently, it was shown that SSRIs can induce more complex changes in neurotransmission by forcing dopamine transporters to take up serotonin into dopamine terminals and subsequently corelease dopamine and serotonin signals [15]. It is unknown what long-term neuropsychophamacologic effects these types of synaptic alterations would have on human sexual behavior.

Besides central nervous system (CNS) alterations, it is also possible that peripheral changes are caused by SSRIs. For example, 95% of the serotonin receptors in the body are outside the brain, many in the peripheral nerves [16], and only 1–2% of serotonin is located in the CNS [17]. Thus, it has been postulated that SSRIs, in part, cause sexual problems because of the inhibition of the serotonin receptors in the peripheral nerves [16,17].

While any or all of these changes may be responsible for SSRI sexual side effects, no studies have been performed to validate that these changes are normalized after discontinuation of therapy. It is therefore possible that sometimes, these parameters remain persistently altered. However, at least two of these biomarkers—serum testosterone and prolactin—were normal in the cases reported here.

Second, although rare, many publications point to a role of SSRIs in the occurrence of extrapyrimidal effects such as bradykinesia, rigidity, akathisia, and acute dystonia [18]. These effects can sometimes be persistent even after drug discontinuance [19], an example of other longer-lasting side effects caused by SSRIs. Perhaps, persistent sexual side effects are caused by a similar mechanism to extrapyramidal effects, namely, adverse but unclearly defined neurological alterations in areas of the nervous system responsible for sexual arousal and functioning.

Third, the possibility of structural changes to brain regions involved in sexual response should also be considered. For example, it has been shown that the treatment of adolescent patients with obsessive–compulsive disorder with paroxetine causes significant reductions in the left amygdala volume [20], a part of the brain shown to be strongly involved in response to visually erotic stimuli [21]. Such structural changes may take a very long time to reverse, if at all, in some patients.

Finally, it is becoming increasingly clear that epigenetic changes are involved in human phenotypic expression and disease [22,23]. Antidepressants can cause quite complex changes in gene expression [24], and it is possible that some of these changes are not normalized simply by withdrawing the drugs [25]. It is not unprecedented for medications to cause persistent sexual side effects mediated by such epigenetic gene expression changes. Specifically, it has been hypothesized that persistent female sexual dysfunction caused by the oral contraceptive is caused by long-term or permanent epigenetic upregulation of steroid hormone-binding globulin expression [26]. Also, experiments with rodents have shown that chronic treatment with SSRIs at a young age results in permanently decreased sexual behavior that persists into adulthood and is similar to the cases described here [27,28]. At the cerebral molecular level, there are profound and permanent reductions in both the rate-limiting serotonin synthetic enzyme, tryptophan hydroxylase, and the serotonin transporter, but it is not yet known if the neurochemical situation in rodents is recapitulated in humans.

An extensive search of the literature has not revealed other examples of iatrogenic sexual dysfunction that persist after the causative drug is discontinued, but the authors are aware of many unpublished cases. It is hypothesized that this phenomenon may apply generally to medications that can cause sexual dysfunction, such as antipsychotics (neuroleptics), beta-blockers, histamine-2 receptor blockers, finasteride (Propecia, Proscar; Merck, Whitehouse Station, NJ, USA), antiandrogens such as leuprorelin (Lupron; TAP Pharmaceuticals, Deerfield, IL, USA), tamsulosin (Flomax; Boehringer Ingelheim, Ingelheim, Germany), etc. Although the exact biochemical mechanism may differ between different classes of drug, the persistent sexual dysfunction is postulated to be caused by epigenetic changes in the expression of genes involved in the sexual response cycle. However, apart from the aforementioned contraceptive study [25] and rodent studies [27,28], no experiments have yet been performed to test this theory.

Conclusion

When patients develop sexual dysfunction as a side effect of SSRI antidepressants, clinicians should be alert to the possibility that improvement in this side effect may not correlate temporally with stopping the medication. These three new cases, and the four previously published, suggest that the possibility of persistent sexual dysfunction even after discontinuance should be taken into consideration when patients continue to take SSRIs despite experiencing sexual side effects. For the same reasons, caution may also be warranted when SSRIs are used for the treatment of premature ejaculation [29].

It is important that patients are informed about the high probability of sexual side effects while on SSRI medications. It is worth noting that none of the three patients received adequate informed consent with regards to the known risks of sexual side effects, so as to be able to consider those risks in their decision to take the medications. Patients should also be told that there are indications that in an unknown number of cases, the side effects may not resolve with cessation of the medication, and could be potentially irreversible.

While the Internet source of the cases means we lack the same level of control over verifying the cases' histories in the way that extended in-person interaction would provide, the Internet group membership currently provides the best available source of information about a condition of potential public health importance. Given the lack of awareness of the condition among clinicians, and the lack of follow-up data in the research literature, the problem seems unlikely to be identified either by current research paradigms or by voluntary Medwatch reports. While the patients' accounts of their sexual functioning described here appear reliable, a limitation of these case reports is dependence on patients' retrospective accounts. Until there are more data, it is impossible to know the true level of the risk of persistent SSRI-induced sexual dysfunction.

Further study needs to be made concerning prolonged sexual dysfunction from SSRIs, which we tentatively term "post SSRI sexual dysfunction." Epidemiologic, retrospective, and prospective investigations are necessary to address the

frequency, severity, and quality of this problem, before its biologic and neurochemical etiology can be fully addressed.

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