Prolonged Post-Treatment Genital Anesthesia and Sexual Dysfunction Following Discontinuation of Citalopram and the Atypical Antidepressant Nefazodone

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Abstract: SSRI therapy is commonly associated with sexual side effects, but it is assumed that these distressing symptoms resolve with termination of therapy. The atypical antidepressant nefazodone is infrequently associated with sexual dysfunction and may be substituted for SSRI's when sexual symptoms are intolerable. Recently, scattered case reports of persistent sexual dysfunction and genital anesthesia persisting well after termination of SSRI antidepressant therapy have surfaced. In each case, the underlying depressive disorder was in remission.

Case: A 32-year old women with major depression was treated with citalopram but switched to nefazodone after 4 weeks of therapy due to genital anesthesia and orgasmic dysfunction. These symptoms continued following institution of nefazodone therapy and have persisted for over a year since termination of antidepressant treatment. Her depression remains in full remission.

Discussion: It is likely that persistent post-treatment genital anesthesia and other sexual side effects are underreported, and physicians should be aware of this bothersome phenomenon. Formal post-treatment surveillance for this condition is warranted. Pharmacogenomic research may ultimately allow physicians to predict who is at risk for antidepressant induced sexual side effects.

Keywords: Citalopram, SSRI, nefazodone, sexual dysfunction, genital anesthesia.

INTRODUCTION

The serotonin reuptake inhibitor (SSRI) antidepressants are associated with an array of sexual side effects including diminished libido, delayed orgasm, anorgasmia, erectile dysfunction or vaginal xerosis, and decreased tactile sensitivity in the genital region [1,2]. Activation of the 5-HT_{2A} subclass of serotonin receptors appears to account for these untoward side effects [2,3].

Nefazodone is structurally and pharmacologically distinct form the SSRI class and infrequently associated with sexual side effects. Nefazodone is a potent antagonist at the post-synaptic 5-HT_{2A} receptor site with moderate serotonin and noradrenergic reuptake inhibition. This unique pharmacologic profile likely explains the low order of sexual side effects associated with usage [2-5]. Nefazodone has been administered in conjunction with SSRIs in an effort to counteract the undesirable sexual symptoms associated with the latter [1-3,5,6]. Alternatively, nefazodone may be substituted for a SSRI in patients with major depression. Although exceedingly rare, fulminate hepatotoxicity has been reported following nefazodone administration (one case of death or liver transplant per 250,000 patients treated per year). In fairness, physicians and consumers should be aware that drug induced liver injury (usually reversible) has been rarely associated with essentially all antidepressant agents [7].

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It is expected that sexual functioning rapidly returns to normal once antidepressants are discontinued, but recently, isolated reports of sustained sexual side effects persisting months or years after discontinuation of SSRI's have surfaced in the literature [8,9]. In each case, depressive symptoms were reported to be in remission and no alternative etiology could be identified.

We present a case of persistent genital anesthesia and diminished libido which has persisted for over one year following completion of a brief course of citalopram followed by prolonged nefazodone treatment.

CASE REPORT

A 32 year old woman presented with a six month history of depressed mood, anhedonia, and difficulty falling asleep. A prior history of depression and other psychiatric disorders was absent. The patient denied diminished libido or difficulty achieving orgasm. No significant marital conflicts or other stressors were identified. Her past medical history and physical examination were normal. Citalopram 20 mg daily was prescribed for major depression.

Within days of beginning citalopram therapy, she noted a substantial decrease in libido, difficulty achieving orgasm, and diminished orgasmic intensity. Most distressing to the patient was a sensation of "feeling totally numb" in her genital region with a greatly diminished capacity to respond to clitoral and labial tactile stimulation during intercourse.

Her depressive symptoms improved considerably at 4 weeks but the sexual side effects persisted. She requested a change in drug therapy rather than taking a "wait and see"

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approach. Nefazodone was prescribed and citalopram tapered over one week. She achieved an excellent clinical response to nefazodone 200 mg twice daily, but unfortunately, the sexual side effects and genital anesthesia continued unabated for the duration of therapy. Bupropion (on a continuous basis) and then sildenafil (prior to intercourse) were added to her therapeutic regimen, but the patient failed to experience any improvement.

Nefazodone was discontinued after 14 months, and her depression remained in full remission. One year following completion of drug therapy, she continued to complain of low libido, minimal genital tactile sensation, and orgasmic dysfunction that was essentially unchanged from the time of treatment. Lubrication and genital engorgement remained intact. The patient maintained regular, cyclic menses before, during, and after treatment.

Neurological examination was normal. Thyrotropin, free thyroxine, serum testosterone, sex hormone binding globulin, and calculated free androgen index were within normal limits. Formal psychological consultation and testing were obtained, but no residual psychopathology was identified.

DISCUSSION

Sexual side-effects associated with neuropsychiatric drugs, particularly the SSRI class, are relatively common, and it has been generally assumed that these annoying symptoms abate with discontinuation of treatment. In this regard, the absence of a coordinated post-treatment surveillance study validating this axiom is surprising.

SSRI related sexual side effects have ranged from 58% for fluoxetine to 73% for citalopram [10]. In contrast, studies of nefazodone have consistently reported a low incidence of sexual side effects [3,10,11]. In a series of 593 patients treated with nefazodone from four clinical trials, abnormal orgasm was reported in only 0.2% of the participants [5]. Montejo, *et al*. pinpointed sexual dysfunction in 4 of 50 depressed patients (8%) treated with nefazodone [10].

Although an element of impaired sexual functioning is encountered in approximately 40-50% of depressed individuals [4,12], reduced or absent genital sensation has not been associated with depression or any other common psychiatric entity [13]. Genital anesthesia appears uniquely associated with the use of serotonergic antidepressants [1]. Ordinarily, antidepressant induced sexual side effects rapidly diminish with termination of drug therapy [1,6], but recent case reports suggest that this is not always the case. Bolton, *et al.* described persistence of orgasmic dysfunction, genital anesthesia, and diminished libido in a 26 year old male six years following discontinuation of sertraline [8]. Csoka and Shipko reported three additional cases of sustained genital anesthesia and poor libido following treatment with either fluoxetine, sertraline, or citalopram [9]. In each of these cases, the onset of unwanted sexual side effects first occurred during SSRI therapy, and residual depressive symptoms were absent at follow up. Yet another study at least indirectly implicated paroxetine although patients in that investigation were continued on amineptine, an atypical tricyclic antidepressant not associated with sexual dysfunction, following paroxetine discontinuation [14]. Bahrick has proposed that persistent genital anesthesia and orgasmic hypointensity should be considered putative markers of past SSRI exposure if the condition arose initially during treatment [13].

In addition to these case reports, the emergence of an Internet community comprised of individuals claiming persistent sexual dysfunction following discontinuation of various SSRI's, albeit unsubstantiated, suggests that this phenomenon may not be rare [13]. Plainly, such an event presents a consequential quality of life issue affecting post-depression sexual functioning with the capacity to compromise intimate relationships in men and women alike.

Early studies of fluoxetine concluded that sexual dysfunction occurred in only 2-16% of those receiving the drug, but these numbers were based primarily on patient-based voluntary reporting rather than sophisticated questionnaires or direct interview [15]. In the same vein, lack of long term follow up or failure to inquire about sustained sexual side effects following antidepressant therapy would likely result in underreporting of these events. Accordingly, persistence of orgasmic dysfunction and loss of genital tactile sensation following antidepressant discontinuation may be more common than suspected.

The mechanism of antidepressant induced sexual dysfunction is not fully understood which renders speculation on the psychoneuroendocrinological basis of sustained post-treatment sexual symptoms even more challenging. Permanent changes in serotonin transmission physiology manifested by diminished sexual behavior have been reported in murine models following neonatal or adolescent SSRI exposure [16,17], and hence, it is biologically plausible that an analogous alteration of serotonin receptor neurophysiology might persist in adult humans. Bishop, *et al.* identified an association between a specific 5-HT_{2A} single nucleotide polymorphism (SNP) and sexual side effects in a mixed gender group of individuals receiving SSRIs [18]. This finding raises the possibility that a specific SNP might predispose affected individuals to persistent post-treatment sexual dysfunction.

Persistent sexual dysfunction and genital anesthesia following citalopram administration has been described in one other case report, but there are no published reports of these symptoms following nefazodone therapy [9]. Parenthetically, it is entirely possible that this patient's condition is entirely attributable to citalopram even though her length of exposure was only four weeks. Nevertheless, it is logical to hypothesize that the unusual nefazodone-treated patient who suffers sexual side-effects could also develop prolonged post-treatment sexual side effects similar to individuals treated with traditional SSRIs.

Long term follow up will be crucial in order to determine if antidepressant induced sexual dysfunction remains a permanent phenomenon. Continued research into antidepressant pharmacogenomics may ultimately establish precisely who is predisposed to this perplexing problem and the molecular basis involved. In addition, a multi-institutional long term surveillance project designed to detect the true incidence of persistent post-antidepressant genital anesthesia and sexual dysfunction should be undertaken. If a positive association is found, this would have implications for pre-treatment informed consent and could precipitate yet another "black box" warning by the FDA.

REFERENCES

[1] Zajecka J. Strategies for the treatment of antidepressant-related sexual dysfunction. J Clin Psychiat 2001; 62 Suppl 3: 35.

[2] Clayton AH, Montejo AL. Major depressive disorder, antidepressants, and sexual dysfunction. J Clin Psychiat 2006;67 Suppl 6: 33.

[3] DeVane C, Grothe D, Smith S. Pharmacology of antidepressants: Focus on nefazodone. J Clin Psychiat 2002; 63: 10.

[4] Zajecka J, Dunner DL, Gelenberg AJ, *et al*. Sexual function and satisfaction in the treatment of chronic major depression with nefazodone, psychotherapy, and their combination. J Clin Psychiat 2002; 63: 709.

[5] Augustin B, Cold J, Jann M. Venlafaxine and nefazodone two pharmacologically distinct antidepressants. Pharmacotherapy 1997; 71: 511.

[6] Ferguson JM. The effects of antidepressants on sexual functioning in depressed patients: A review. J Clin Psychiat 2001; 62 Suppl 3: 22.

[7] DeSanty KP, Amabile CM. Antidepressant-induced liver injury. Ann Pharmacother 2007; 41: 1201.

[8] Bolton J, Sareen J, Reiss J. Genital anaesthesia persisting six years after sertraline discontinuation. J Sex Marital Ther 2006; 32: 327.

[9] Csoka A, Shipko S. Persistent sexual side effects after SSRI discontinuation. Psychother Psychosom 2006; 75: 187.

[10] Montejo AL, Llorca G, Izquierdo JA, *et al.* Incidence of sexual dysfunction associated with antidepressant agents: A prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. J Clin Psychiat 2001; 62 Suppl 3: 10.

[11] Taylor MJ, Rudkin L, Hawton K. Strategies for managing antidepressant-induced sexual dysfunction: Systematic review of randomised controlled trials. J Affect Disord 2005; 88: 241.

[12] Kennedy SH, Dickens SE, Eisfeld BS, Bagby RM. Sexual dysfunction before antidepressant therapy in major depression. J Affect Disord 1999; 56: 201.

[13] Bahrick A. Post SSRI sexual dysfunction. ASAP Tablet 2006; 7: 2-3, 10.

[14] Montejo AL, Llorca G, Izquierdo JA, *et al*. Sexual dysfunction with antidepressive agents. Effect of the change to amineptine in patients with sexual dysfunction secondary to SSRI. Actas Esp Psiquiatr 1999; 27: 23.

[15] Zajecka J, Fawcett J, Schaff M, Jeffriess H, Guy C. The role of serotonin in sexual dysfunction: fluoxetine-associated orgasm dysfunction. J Clin Psychiat1991; 52: 66.

[16] Maciag D, Simpson K, Coppinger D, *et al.* Neonatal antidepressant exposure has lasting effects on behavior and serotonin circuitry. Neuropsychopharmacology 2006; 31: 47.

[17] DeJong T, Snaphaan L, Pattij T, *et al.* Effects of chronic treatment with fluvoxamine and paroxetine during adolescence on serotonin-related behavior in adult male rats. Eur Neuropsychopharmacol 2006; 16: 39.

[18] Bishop JR, Moline J, Ellingrod VL, *et al.* Serotonin 2A -1438 G/A and G-protein Beta3 subunit C825T polymorphisms in patients with depression and SSRI-associated sexual side-effects. Neuropsychopharmacology 2006; 31: 2281.

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