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Sexual dysfunction in selective serotonin reuptake inhibitors (SSRIs) and potential solutions: A narrative literature review

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Abstract

Sexual dysfunction is an underdiscussed adverse effect to selective serotonin reuptake inhibitors (SSRIs) and may increase the risk for discontinuation and nonadherence to antidepressant pharmacotherapy. Given the prevalence of depression, health care providers should educate patients about SSRI-associated sexual dysfunction in order to promote patient awareness and medication adherence. This study evaluated primary literature from 1997 to 2015 to identify SSRI-related sexual side effects, therapeutic alternatives, and treatment strategies. The results indicate that paroxetine is associated with the greatest rate of sexual dysfunction among the SSRIs. Potential alternatives to SSRI treatment include bupropion, mirtazapine, vilazodone, vortioxetine, and serotonin-norepinephrine reuptake inhibitors. In the event that a subject responds solely to SSRIs but experiences unwanted sexual side effects, bupropion may be added as an adjunctive medication. Some limited evidence also suggests that saffron may reduce some aspects of sexual dysfunction, excluding ability to reach orgasm.

Keywords: SSRI, selective serotonin reuptake inhibitors, sexual dysfunction, sexual side effect, bupropion, paroxetine, escitalopram, citalopram, venlafaxine, mirtazapine, fluoxetine, sertraline, delayed ejaculation

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Introduction

The prevalence of depression in the United States is approximately 7.9% in men and 12.1% in women.[1] In 2005, an estimated 10% of the US population utilized antidepressant pharmacotherapy.[2] Of the available pharmacotherapies, selective serotonin reuptake inhibitors (SSRIs) are recommended as a component of first-line treatment for depression.[3] Similar to other antidepressants, SSRIs take several weeks to months before optimally relieving the symptoms of depression, making medication adherence crucial for efficacy.

In a 2003 survey, approximately 41.7% of men and 15.4% of women discontinued psychiatric medications due to perceived sexual side effects.[4] Given that SSRIs may cause sexual dysfunction in 40% to 65% of individuals, these side effects may exacerbate depression and create a barrier to medication adherence.[5,6] Other findings indicate that the prevalence of sexual side effects is overestimated because sexual dysfunction may be prevalent before initiation of antidepressant treatment.[7] In treatment-free subjects diagnosed with major depression, greater than 40% of men and 50% of women reported decreased sexual interest. However, in the studied population, subjects were less likely to experience orgasmic or ejaculation difficulties, the most common sexual side effects associated with SSRI therapy.[5] Therefore, although depression may play a role in sexual dysfunction, SSRIs may cause sexual side effects unrelated to depression.[6]

Although sexual dysfunction in SSRIs are far from rare, as many as 50% of people do not discuss these issues with

health care providers.[4,8] In one study, the incidence of individuals who spontaneously reported sexual side effects was 14% compared with 58% of individuals who reported sexual side effects when asked directly by their physicians.[9] Therefore, it is pertinent for health care providers to be proactive on the discussion of these adverse events. Focus should be placed on the most common types of sexual side effects, the risks associated with different SSRIs, and alternative solutions should an SSRI become intolerable. This study seeks to address these concerns in order to facilitate better patient education and treatment.

Methods

This article is a narrative literature review of SSRIs and their potential to cause sexual dysfunction. One reviewer (E.J.) searched Pubmed, Google Scholar, and OVID for articles based on the key words "dose," "delayed ejaculation," "SSRI," "sexual dysfunction," "adjunct," "alternative," and/or "side effects." Inclusion criteria included human trials published in the English and Chinese language between January 1997 and December 2015.

Results

SSRIs Most at Risk for Causing Sexual Side Effects

SSRIs alleviate symptoms of depression primarily by selectively inhibiting the reuptake of serotonin in the central nervous system.[10] It is hypothesized that many side effects of SSRIs are attributed to the increase of serotonin at specific serotonin receptor subtypes, especially in other areas of the body. Specifically, an increase in serotonin may affect other hormones and neurotransmitters, such as testosterone and dopamine.[9-11] This may lead to side effects of sexual dysfunction, as testosterone may affect sexual arousal and dopamine plays a role in achieving orgasm.

Many different categories of sexual side effects are associated with SSRIs, the most common of which is delayed ejaculation.[5,10] Other types of sexual side effects include reduced sexual desire, reduced sexual satisfaction, anorgasmia, and impotence.[5,9] A prospective, descriptive clinical study of 344 subjects found that the incidence of sexual side effects was highest with paroxetine, followed by fluvoxamine, sertraline, and fluoxetine.[9] The incidence of sexual dysfunction was similar between fluoxetine and escitalopram. The frequency of subjects experiencing side effects increased with higher SSRI doses, indicating that subjects should be on the lowest effective dose to decrease the risk of side effects.[9,10] Out of the SSRIs, paroxetine is associated with having the greatest risk for causing delayed ejaculation, reduced desire, and impotence, defined as inability to obtain an erection in men and inadequate lubrication in women.[11-14] An observational cross-sectional study determined that in subjects who experienced sexual side effects from SSRIs, up to 42.5% reacted poorly and seriously considered whether to continue the antidepressant treatment.[11] If SSRI-related sexual dysfunction does not dissipate over time, it is reasonable to switch to an alternative medication or add an adjunctive antidepressant.

These conclusions are in accordance with the findings of a similar study, which found that paroxetine caused more sexual dysfunction than fluvoxamine, sertraline, and fluoxetine.[15] Like paroxetine, citalopram also appears to have a high frequency of sexual dysfunction, but this finding was not replicated in other studies. Arlas et al[16] found that the incidence of sexual dysfunction was 75.5% for paroxetine and 28.9% for citalopram. Arlas et al[16] and Waldinger et al[17] reported similar results, with citalopram resulting less delay in orgasm and ejaculation compared with paroxetine. From these studies, paroxetine appears to have the greatest risk of causing sexual dysfunction compared with other SSRIs.

Alternatives to SSRIs

The sexual side effects of SSRIs are attributed to their mechanism of action, which includes increasing the availability of serotonin.[5,12,18]As such, alternative antidepressants to SSRIs act on other neurotransmitters and receptors to lessen the risk of sexual dysfunction. Specifically, bupropion, mirtazapine, and serotonin-norepinephrine reuptake inhibitors (SNRIs) are antidepressants generally viewed as having less risk for sexual side effects.[9,12,19-21]

Bupropion's mechanism of action involves blocking the reuptake of norepinephrine and dopamine; the SNRI mechanism of action involves blocking the reuptake of serotonin and norepinephrine.[12,22] Both antidepressants are alternative treatments for subjects experiencing sexual dysfunction exacerbated by SSRIs.[20,21] A double-blinded randomized study sought to assess whether once-daily bupropion (XL) or extended-release venlafaxine (XR), an SNRI, was more appropriate for decreasing the risk of sexual side effects.[23] The Hamilton Depression Rating Scale (HAM-D) was used to assess depression while the Changes in Sexual Functioning Questionnaire (CSFQ) was utilized to assess sexual functioning. A lower HAM-D score corresponds to less severe depression, while a lower CSFQ score corresponds to greater sexual dysfunction. The study found that subjects taking bupropion XL had no statistically significant change in their CSFQ scores from baseline ($P = .285$) while subjects taking venlafaxine XR had a decrease in mean CSFQ scores from baseline

($P \leq .002$). A response to treatment was defined as 50% or greater reduction in HAM-D total score from baseline and the response was comparable for bupropion XL (odds ratio, 1.93; 95% confidence interval [CI] 1.07-3.46) and venlafaxine XR (odds ratio, 1.75; 95% CI 1.04-2.93).[24] From this study, it can be concluded that bupropion XL and venlafaxine XR are not inferior in their efficacy for treating depression. However, bupropion XL may have an advantage over venlafaxine XR when it comes to the incidence of sexual dysfunction.

A placebo-controlled, double-blinded experiment utilized sustained-release bupropion 150 mg twice a day versus placebo as an adjunct to SSRI treatment in 55 subjects experiencing SSRI-induced sexual dysfunction.[25] The subjects had previously been stabilized on citalopram, fluoxetine, paroxetine, or sertraline for a minimum of 3 months. After 4 weeks of study treatment, the mean desire and frequency of sexual activity increased significantly in the bupropion group compared with the placebo group (Wilk $F = 5.47$, $df = 1$, $P = .024$). Orgasm and global sexual functioning also improved in both groups, but it was nonsignificant. Another study used adjunct bupropion on an as needed basis, with starting doses of immediate-release bupropion 75 mg taken 1 to 2 hours before sex.[26] Doses were titrated based on the resolution of sexual dysfunction symptoms with the maximum dose being bupropion immediate-release 75 mg 3 times a day. Overall, bupropion reversed sexual dysfunction caused by SSRIs in 66% of the subjects when used consistently. When used on an as needed basis, improvements in sexual symptoms were seen in 38% of subjects. These results imply that bupropion may have a role as an adjunct to SSRI therapy in subjects experiencing a decrease in sexual activity. However, it is significant to note that the improvement in sexual dysfunction may be a by-product of further relief of depressive symptoms, which affect sexual dysfunction.

Mirtazapine, an alpha-2 adrenoceptor and serotonin receptor antagonist, may increase serotonin availability.[18] By indirectly acting as a serotonin receptor agonist, it may decrease the risk of sexual side effects compared with SSRIs. However, because mirtazapine is not selective, this medication may cause sleep disturbance, nausea, and weight gain. Mirtazapine was studied in subjects who were stabilized on an SSRI but experienced SSRI-related sexual dysfunction.[19] In all cases, subjects volunteered to be switched to an alternative antidepressant and were placed on mirtazapine. Mirtazapine was titrated from 7.5 mg to 45 mg daily, depending on individual tolerability. The HAM-D scale was used to measure depression and the Arizona Sexual Experience Scale to assess sexual dysfunction. Mirtazapine treatment led to a significant reduction in the total Arizona Sexual Experience Scale score ($F = 4.856$, $df = 7.16$; $P < .001$), suggesting that mirtazapine reduced the prevalence of sexual dysfunction. There was no significant change in HAM-D scores, indicating that depression remained in remission while on mirtazapine. This result was consistent with the findings of another study, which concluded that the incidence of sexual dysfunction with subjects taking mirtazapine was 24.4% compared with a 59.1% incidence with SSRIs.[26]

Novel antidepressants, vilazodone and vortioxetine, are also being considered as alternative treatments to traditional SSRIs. Vilazodone is an SSRI and a 5HT1A receptor partial agonist.[27] Vilazodone is presumed to have less risk for sexual side effects because of its partial activity at the 5HT1A receptors. In placebo-controlled trials, vilazodone has been reported to have minimal sexual side effects, but few studies directly compared vilazodone to an SSRI. One double-blinded, randomized, control trial compared vilazodone with placebo and utilized citalopram 40 mg as an active control.[28] Analysis evaluated the change in CSFQ score from baseline to week 10 and discovered that sexual dysfunction side effects were most frequent in subjects receiving citalopram, followed by those receiving vilazodone, then those receiving placebo. The most commonly reported adverse effects were loss of libido and anorgasmia, similar to previous findings on SSRIs. Since this study did not indicate whether or not the results were statistically significant, more studies may necessary to determine whether vilazodone is less likely to cause sexual side effects compared with SSRIs.

The mechanism of action of vortioxetine is not fully understood, but it is proposed to function as a serotonin reuptake inhibitor with antagonizing action at several other 5-HT3 receptors.[29] In a pooled study of 7 randomized, placebo-controlled trials, the incidence of treatment-emergent sexual dysfunction was nonsignificant between vortioxetine and placebo. However, sexual dysfunction was more common with increasing doses of vortioxetine, and the study was not powered to detect statistical significance of sexual dysfunction in vortioxetine versus placebo. Additionally, similar to trials assessing sexual side effects of vilazodone, there are few direct comparisons between vortioxetine and SSRIs. Therefore, while vortioxetine may be considered as an alternative pharmacotherapy to SSRIs, additional studies may further elucidate the risks of sexual dysfunction in vortioxetine.

Phosphodiesterase 5 Inhibitor Use in Sexual Dysfunction

A systematic review of randomized control trials found that phosphodiesterase 5 (PDE5) inhibitors, such as sildenafil and tadalafil, improved erectile dysfunction better than placebo in male subjects with sexual

dysfunction as a result of antidepressant treatment.[30] However, it was unclear whether PDE5 inhibitors would be beneficial to treat sexual dysfunction in women. Reviews of the effects of PDE5 inhibitors on sexual dysfunction in women were limited to small studies and case studies and require additional research. The PDE5 inhibitors may play a role in treating men with erectile dysfunction as a result of SSRI therapy, but it does not provide a solution to the most common SSRI-related sexual side effect, difficulty with achieving orgasm.

Saffron Use in Sexual Dysfunction

Saffron, a spice derived from the flower *Crocus sativus*, has implications of producing aphrodisiac effects in animals and humans.[31] The exact mechanism of action has not been elucidated, but there is some evidence that saffron may inhibit serotonin reuptake and affect the levels of nitric oxide in the body, which plays a role in achieving erection.[32] Since it is presumed to work in a similar manner as SSRIs, it may alleviate depression and share common side effects, such as delayed orgasm. Modabbernia et al[31] assessed the efficacy of saffron in fluoxetine-induced sexual dysfunction. The research was a randomized, double-blind, placebo-controlled study of 36 male subjects with stabilized depression. Each subject was enrolled in the study based on complaints of sexual impairment and was assigned to either adjunctive saffron 15 mg twice daily or placebo for 4 weeks. The primary outcome was the measurement of the International Index of Erectile Function scale (IIEF), which has a minimum score of 5 and a maximum score of 25. Lower IIEF scores correlate to greater sexual dysfunction. The study concluded that saffron significantly improved erectile function with the mean difference in IIEF score being 7 points higher in the saffron group than in the placebo group ($P < .001$). Satisfaction with intercourse also improved in the saffron group (mean difference of 2.3, $P = .001$). However, improvements in sexual desire and ability to orgasm remained nonsignificant.

A similar randomized, double blinded, placebo-controlled study looked at saffron's efficacy in women with fluoxetine-induced sexual dysfunction.[33] Thirty-four women were assigned to either adjunctive saffron 15 mg twice daily or placebo for 4 weeks. The results indicated significant improvement in arousal and lubrication at week 4 (mean difference of −0.72, 95% CI −1.36–−0.08 and −1.08; 95% CI −2.07–−0.08, respectively). However, similar to the study by Modabbernia et al,[31] improvements in the ability to achieve orgasm remained nonsignificant. In terms of adverse drug reactions, saffron was comparable to placebo and may serve to reverse some of the sexual side effects created by the SSRI.

Saffron's efficacy in reducing sexual side effects of SSRIs may indicate an alternative or additional mechanism of action, since higher doses of serotonin reuptake inhibitors correspond to greater prevalence of sexual side effects. Alternatively, the conjunction of an additional inhibitor of serotonin reuptake may have improved symptoms of depression, which can subsequently lead to better sexual function. This may explain why improvements in the ability to achieve orgasm, the main sexual side effect of SSRI, were nonsignificant between saffron and placebo. If an unwanted sexual side effect of an SSRI is attributed to arousal, lubrication, erectile function, or satisfaction, it may still be warranted to use saffron as an adjunctive therapy. However, well understood pharmacotherapy approaches should be considered as alternatives before saffron is used.

Discussion

Patient education on the sexual side-effect profiles of SSRIs is critical to medication adherence, resolution of depressive symptoms, and improving quality of life. Delaying this discussion may result in confusion and distrust of pharmacotherapies and health care providers, making it more difficult to adjust and recommend medications later on. This literature review serves as an aid to better facilitate patient education and treatment. However, as with all narrative studies, flaws of this study include potential for selection bias as one reviewer was responsible for article selection. Additionally, given the wide breadth of articles analyzed, there may be some concerns with external validity because subject groups were heterogeneous. Lastly, antidepressants include a wide range of pharmacotherapy and nonpharmacotherapy options and not every facet was explored, potentially contributing to external bias.

Conclusion

Given the prevalence of sexual dysfunction in subjects with depression, it is necessary for health care providers to give a full assessment and explanation of potential side effects of antidepressant pharmacotherapy. For sexually active subjects requiring an SSRI, it is recommended to first try fluoxetine or sertraline, as they have less incidence of causing sexual dysfunction. Paroxetine should be the last SSRI of choice as it has the greatest incidence of causing sexual dysfunction. If an SSRI is chosen, subjects should be maintained on the lowest effective dose to decrease the risk of adverse effects. If sexual side effects occur in subjects stabilized on an SSRI, solutions include switching to an alternative antidepressant or adding an adjunctive antidepressant (eg, bupropion). Novel agents, such as vortioxetine, appear to have limited sexual side effects, but the higher cost may be burdensome. Other

nontraditional methods for alleviating sexual side effects, such as the supplementation of saffron 15 mg twice a day, may improve arousal and erectile function in subjects experiencing SSRI-related sexual dysfunction. However, given the limited research on saffron, other therapies should be tried first. There are many more pharmacologic and nonpharmacologic alternatives not mentioned in this article. As such, health care providers should choose a treatment based on patient need, cost, and clinical evidence.

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