Sildenafil Studied in Women With Antidepressant-Associated Sexual Dysfunction

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Sildenafil (Viagra, Revatio) reduced antidepressant-associated sexual dysfunction in women in a randomized controlled trial, which investigators characterize as the first conducted in women with this adverse drug effect.

The study, recently published in JAMA, was conducted by George Nurnberg, MD, of the department of psychiatry, University of New Mexico, and colleagues.1 This group's 2003 study, also published in JAMA, demonstrated sildenafil's benefit in men with this complaint.2 That study was a departure from the anecdotal or open-label reports that served as an evidence base for a myriad of proposed remedies.3 Although the association between sexual dysfunction and antidepressant therapy has been recognized since the introduction of tricyclics, the incidence of this adverse effect has increased since the advent of serotonin reuptake inhibitors (SRIs). Sexual dysfunction has also played a role in reducing patient adherence to the prescribed medication. Consequently, Nurnberg commented to Psychiatric Times, "treatments have been driven more by opinion than by solid data." Nurnberg and colleagues emphasize this concern in their latest study, warning that "without evidence-based data to treat sexual function associated with SRIs in women, clinicians may lack the confidence to manage it effectively, which leaves patients exposed to excess random pharmacology."

The investigators employed a design and protocol similar to those in their study with men. The data for women indicated that sildenafil reduced adverse sexual effects, specifically including delayed orgasm responses and inadequate lubrication. Nurnberg commented on the relative sparsity of research on the effect of sildenafil on orgasm function, despite the fact that delayed or unachieved orgasm is "the central factor of SRI antidepressant-associated sexual dysfunction." He attributed this to the FDA-approved indication and marketing focus for male erectile dysfunction and to the more complex measures needed to assess orgasm function in women than sexual arousal in men. In addition, he noted, the initial studies of sildenafil had not shown benefit in women with sexual arousal disorder unrelated to antidepressant medication.

Nevertheless, there was good reason to evaluate the effects of a selective phosphodiesterase type 5 inhibitor such as sildenafil in women experiencing sexual dysfunction from antidepressant medication, according to Nurnberg. The initial studies of sildenafil for women with sexual arousal disorder may not have adequately controlled for hormonal factors or level of sexual interest, or measured efficacy in the varied facets of sexual response. Later, more focused studies yielded favorable results. In addition, Nurnberg noted, nitric oxide synthase isoforms, nitric oxide, and phosphodiesterase type 5 inhibitors are present in female genital tissue. Phosphodiesterase type 5 inhibitor enhancement of nitric oxide–cyclic guanosine monophosphate signaling occurs in both women and men.

Studying Drug Treatment of Adverse Drug Effect

Women in the Nurnberg study had to have reported good sexual interest and activity before the onset of depression and antidepressant treatment. Their episodes of sexual dysfunction had to be associated with antidepressant treatment and needed to have remitted with improvement of depression and discontinuation of medication. Baseline endocrine values were obtained in these women to later analyze for possible correlations with treatment response. This analysis indicated that women whose sexual function improved after receiving sildenafil or placebo had higher mean levels of free testosterone and thyroxine.
Ninety-eight women of 145 screened were randomized to receive either sildenafil in a 50-mg starting dosage or matching placebo. They were instructed to take the study medication approximately 1 to 2 hours before anticipated sexual activity but not more than once daily. They were asked to attempt to have sexual activity twice weekly, but not less than once weekly throughout the 8-week trial. Treatment efficacy was measured with 4 validated instruments. The primary outcome measure was the mean improvement on the Clinical Global Impression Scale (CGI) adapted for sexual function. Secondary outcome instruments were the Sexual Function Questionnaire, the Arizona Sexual Experience scale–female version, and the University of New Mexico Sexual Function Inventory–female version. Patients maintained logs that were reviewed for the frequency and percentage of successful intercourse attempts and the number of satisfactory attempts at orgasm. In the intention-to-treat analysis, women receiving sildenafil had a statistically significant higher mean score improvement from baseline of 1.9 on the CGI than the 1.1 mean improved score for those receiving placebo. In the secondary outcome measures, sildenafil was associated with greater improvement on scores in the domain of orgasm function, including the ability to reach orgasm and to experience orgasm satisfaction.

The investigators proclaimed this study important "not only because women experience major depressive disorder at nearly double the rate of men and because they experience greater resulting sexual dysfunction than men, but also because it establishes that selective phosphodiesterase type 5 inhibitors are effective in both sexes for this purpose."

In later discussion, Nurnberg added, "the issue is keeping patients compliant with a medication by actively treating a side effect." Although acknowledging that clinical options include switching adversely affected patients from an SRI to an antidepressant having less incidence of sexual dysfunction, Nurnberg cautioned against discontinuing an effective agent with side effects and substituting another agent, which may or may not be as effective. Instead, he recommended that clinicians "encourage the patient not to stop the medication but to call to discuss which option would be useful—including waiting for it to go away."


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