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Priority Updates from the Research Literature from the Family Physicians Inquiries Network

Antidepressants causing sexual problems? Give her Viagra

Female patients no longer have to choose between relief from depression and a satisfying sex life

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Practice changer

Tell women for whom you prescribe selective and non-selective serotonin reuptake inhibitors (SRIs) to let you know if they develop sexual dysfunction. Offer sildenafil (50 mg with the option to increase to 100 mg) to pre-menopausal women on stable, effective doses of SRIs who experience this common—and treatable—side effect.[1]

Strength of recommendation

B: One high-quality RCT that confirms smaller, open-label studies

Nurnberg HG, Hensley PL, Heiman JR, Croft HA, Debattista C, Paine S. Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial. *JAMA.* 2008;300:395-404.

ILLUSTRATIVE CASE

A 34-year-old woman comes to your office and asks to be taken off the paroxetine you prescribed for her 4 months ago. The medication is working well; her depression has been in remission for at least 12 weeks. But she no longer enjoys sex. She used to have a healthy libido and satisfying arousal and orgasm, but since starting the antidepressant, her sexual interest and pleasure have been low.

Although she's afraid of sinking back into a depression without the medication, she's willing to take the risk. If she were your patient, what alternatives would you suggest?

Sexual dysfunction affects an estimated 30% to 50% of patients on selective and nonselective SRIs, and some studies report rates as high as 70% to 80%.[2] Many patients stop taking these antidepressants prematurely, often because of sexual side effects.[3,4]

Phosphodiesterase type 5 (PDE-5) inhibitors are well established as an effective treatment for erectile dysfunction,[5] and randomized controlled trials (RCTs) have shown sildenafil to be effective in treating male SRI-induced sexual impairment.[6,7] For women, there has been no parallel evidence-based treatment.

Limited options, with little support

Typically, women who reported antidepressant-associated sexual disturbances have been offered options for which there was only weak evidence—dose changes or augmentation with another agent,

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Sildenafil boosted overall sexual function in women on SRIs, but had the greatest impact on orgasmic function

switching to another antidepressant, or taking occasional drug holidays. A 2004 Cochrane review found that there were no RCTs involving dose changes or drug holidays.[8] Among studies of the efficacy of switching to a different drug, nefazodone was the only agent whose use was supported by a double-blind RCT.[9] Augmentation trials of a wide range of medications and supplements—including amantadine, bupropion, buspirone, granisetron, mirtazapine, olanzapine, ephedrine, ginkgo biloba, and yohimbine—yielded mixed results. Indeed, the research found that some were no better than placebo.

PDE-5 inhibitors for women? Inconclusive studies to date

Female sexual dysfunction is generally divided into 4 domains: disorders of desire, arousal, orgasm, or pain. Decreased desire and delayed or absent orgasm are the most common sexual side effects of SRI antidepressants in women.[10] Several studies of PDE-5 inhibitors in this patient population have had positive results,[11-15] so there has been good reason to think that they might help this subset of women. However, all the studies were small and nonblinded, and therefore inconclusive—until now.

FAST TRACK

Some researchers argue that female sexual dysfunction has been defined by drug companies seeking to create new markets for their products

PURLs methodology

This study was selected and evaluated using FPIN's Priority Updates from the Research Literature (PURL) Surveillance System methodology. The criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

STUDY SUMMARY

Finally, a well-done RCT provides some answers

Investigators enrolled 98 premenopausal women from 7 US research centers in a double-blind randomized trial. To qualify, participants had to be diagnosed with major depression in remission, be taking a selective or nonselective SRI for >8 weeks, and be on a stable dose for >4 weeks. They also had to meet *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)* criteria for substance-induced sexual dysfunction lasting >4 weeks, but have no history of sexual impairment independent of antidepressants. Finally, participants had to engage in some form of regular sexual activity—intercourse, oral sex, and masturbation all qualified—at least twice a month, and be willing to continue efforts to have sex at least once a week during the study. Women with other medical, psychiatric, or sexual problems were excluded, as were those who were pregnant, breastfeeding, or able to become pregnant and not using reliable contraception.

Participants were randomized to receive 50 mg of sildenafil (n=49) or a matching placebo tablet (n=49), which they were instructed to take 1 to 2 hours before sexual activity. The dose could be adjusted to 2 tablets (100 mg sildenafil) based on investigator assessment of the patient's response to the initial dose. Participants and all study personnel were blinded to group assignment.

The primary outcome was change from baseline to end-point in the Clinical Global Impression Scale, a clinician-rated scale based on review of patient symptoms that was adapted to evaluate sexual function. Secondary outcomes were changes in 3 other sexual function scales, the Hamilton Rating Scale for Depression, and measured hormone levels.

Investigators followed the women for 8 weeks, measuring outcomes at 2, 4, and 8 weeks.

Sildenafil is better than placebo

Using an intention-to-treat analysis with the last measurement (2, 4, or 8 weeks) as the end-point, both the treatment and placebo groups experienced improvement in sexual function. The sildenafil group improved more than the placebo group. On the Clinical Global Impression Scale (1 to 7, with higher scores indicating worse sexual function), sildenafil users went from a mean of 4.8 to 2.8, while placebo users went from a mean of 4.7 to 3.6. The difference in mean change from baseline was 0.8 (95% confidence interval [CI] 0.6-1.0; P=.001). Using a more conservative analysis in which participants who did not return for the 8-week

follow-up visit were assumed to have returned to baseline, the difference in mean change from baseline was smaller (0.6, 95% CI, 0.3-0.8; *P*=0.03) but still statistically significant.

Orgasmic function shows significant improvement

The sexual function scales used as secondary outcomes provided more detail about which types of sexual dysfunction benefited from sildenafil. On all 3 scales, orgasmic function significantly favored sildenafil over placebo. In the domains of desire, arousal, and pain disorders, small to moderate improvements were seen in both groups, with no statistically significant differences. One potential confounder—a difference in the course of participants' underlying depression— was ruled out because depression scale results remained unchanged from baseline to endpoint in both groups.

Baseline levels of cortisone, estradiol, follicle-stimulating hormone, leuteinizing hormone, progesterone, prolactin, sex hormone-binding globulin, testosterone, thyroid-stimulating hormone, and thyroxine, were normal, with no differences between the sildenafil and placebo groups.

WHAT'S NEW

Women have an evidence-based option

Like their male counterparts, we can now offer women whose depression is effectively treated by SRI antidepressants—and who are motivated to stay sexually active despite medication-associated side effects—an effective pharmacotherapeutic treatment.

CAVEATS

Side effects and study funding are worth noting

Side effects. Significantly more participants in the sildenafil group vs the placebo group experienced the following side effects: headache (43% vs 27%), visual disturbance (14% vs 2%), dyspepsia (12% vs 0%), flushing (24% vs 0%), nasal congestion (37% vs 6%), and palpitations (8% vs 2%). Nausea was the only side effect that was more common in the placebo group, reported by only 2% of those in the intervention group but 16% of those on placebo.

No serious adverse events occurred, however, and the medication appears to have been well tolerated overall, despite relatively high rates of side effects. Participants in the intervention group used an average of 5 doses of sildenafil per 2-week interval, the same number as those in the placebo group.

Small treatment effect. The difference in response between sildenafil and placebo was not large: 0.8 points on a 7-point scale. But this difference is likely a clinically meaningful effect to the women with this problem.

Drug company funding. Pfizer, the maker of Viagra, funded this study through an investigator-initiated grant. Some researchers argue that female sexual dysfunction has been defined, or even invented, by drug companies seeking to create new markets for their products.[16] This concern, coupled with the fact that this is the only double-blind randomized trial to show that sildenafil benefits women with antidepressant-associated sexual impairment, raises the question of whether this finding will be replicated in future trials.

We were reassured by the authors' statement that Pfizer had no role in the study design, implementation, analysis, or manuscript preparation. And we know from clinical practice that women do suffer from SRI-induced sexual side effects, and sometimes stop taking much-needed antidepressants because the medication interferes with their ability to have a satisfying sex life. We believe this study was well done and offers a promising new therapy that deserves consideration. We hope that additional trials will follow and that investigators and journals will not hesitate to publish negative results.

CONTINUED

FAST TRACK

When you prescribe SRI antidepressants to women, let them know that sexual side effects are common—and treatable

Not for all women with sexual dysfunction

It's a safe bet that these findings will be used to market sildenafil to women. It is therefore important for physicians and patients to keep in mind that this trial focused on a well-defined subset of women with sexual dysfunction: those on a stable dose of an SRI, with depression in remission, who were otherwise healthy and not pregnant, breastfeeding, or planning pregnancy, and who were motivated to be sexually active. Although this study does support the use of sildenafil for women in this subset, it does not support the use of PDE-5 inhibitors such as sildenafil for all women with sexual difficulties.

CHALLENGES TO IMPLEMENTATION

You have to ask!

Studies have repeatedly found that many women who experience sexual problems do not broach the subject with their doctors.[17] So don't wait for your female patients to bring it up. Sexual side effects are common enough with SRI antidepressants that all prescribers should mention the possibility in advance. Tell patients to let you know if they develop medication-related sexual dysfunction, and reassure them that there are treatments that can help. ■

FAST TRACK

To find out whether a female patient is experiencing antidepressant-associated sexual dysfunction, you have to ask

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