Does sildenafil improve antidepressant-related sexual dysfunction in women?

Yes In this randomized trial, women who had sexual dysfunction associated with the use of selective or nonselective serotonin reuptake inhibitors (SRIs) experienced a reduction in the number of adverse sexual events after treatment with 50 to 100 mg of sildenafil, compared with placebo.

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.

EXPERT COMMENTARY
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Female sexual dysfunction is a prevalent condition for which there is no medical intervention approved by the US Food and Drug Administration. Approval of sildenafil (Viagra) and other type-5 phosphodiesterase inhibitors (vardenafil and tadalafil) for the treatment of erectile dysfunction in men was followed by a series of studies to determine their efficacy in women. To date, those trials have demonstrated no treatment benefit for women.

Assessment of female sexual dysfunction is difficult

The four areas of potential abnormality in sexual function, as described in the *Diagnostic and Statistical Manual of Mental Disorders–IV*, include desire, arousal, orgasm, and pain and are more difficult to differentiate in women than in men. In addition, the variability of the hormonal environment makes it challenging to study the physiologic mechanisms of some of these conditions.

Nurnberg and colleagues sought to eliminate most of the variables by including only premenopausal women who had normal hormone levels at baseline (mean estradiol level, 67 pg/mL; FSH <10 mIU/mL) and previously normal, satisfying sexual experience before the initiation of antidepressant medication.

Selective and nonselective SRIs have been associated with sexual side effects in up to 70% of women—specifically, delayed or absent orgasm, decreased arousal and lubrication, and diminished libido.

Details of the study

This prospective, randomized, double-blind, placebo-controlled trial aimed to assess the efficacy of 50 to 100 mg of sildenafil in reversing new-onset sexual dysfunction in women adequately treated for their underlying major depression. Ninety-eight women (average age, 37 years) were randomized, with 37 and 39 completing the 8-week trial in the placebo and active treatment arms, respectively.

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

This study shows that treatment with one of the type-5 phosphodiesterase inhibitors for arousal or orgasmic problems, or both, makes sense. It is critical to ensure that baseline hormone levels are well within normal premenopausal ranges and that underlying depression or relationship issues are not contributing to low libido if you are to expect improvement.

Women who have new-onset sexual dysfunction after taking SRIs are most likely to respond. Look for subtle thyroid problems or low testosterone levels in nonresponders.

›› BARBARA S. LEVY, MD

FAST TRACK

50 to 100 mg of sildenafil reduced the number of adverse sexual events in women who had new-onset, antidepressant-related sexual dysfunction

Examining the EVIDENCE

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Utilizing an intent-to-treat statistical analysis, the authors found that women taking an average dosage of 91.7 mg of sildenafil experienced significant improvement in overall sexual satisfaction, lubrication, and ability to reach orgasm. Four different scales of sexual function were utilized in the analysis, each of which has been well validated in previous studies. Of note, 28% of women taking sildenafil and 73% of those taking placebo reported no improvement in sexual function throughout the 8-week study.

In this study, responders had slightly (and statistically significantly) higher levels of both free testosterone (1.44 pg/mL vs 1.04 pg/mL) and thyroxine (8.83 ng/dL vs 7.75 ng/dL) than nonresponders in the treatment arm.

These findings are the first to demonstrate efficacy in women

Physiologically, these findings make sense. In estrogen-replete women, type-5 phosphodiesterase inhibitors are thought to increase blood flow, engorgement, and lubrication to the genitalia, resulting in improved sensation and arousal.

By eliminating or controlling for many of the confounders in earlier studies of sildenafil in women, this well-designed trial has demonstrated, for the first time, significant improvement in women who have sexual complaints related to antidepressant medication.

Is personal distress an important measure when assessing sexual dysfunction?

Yes Although this cross-sectional, industry-funded survey of 50,002 households found a prevalence of any sexual problem of 44.2%, the incidence of personal distress related to the problem was only 12%.

Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women. Obstet Gynecol. 2008;112:970–978.

EXPERT COMMENTARY

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Female sexual function is a common problem, with prevalence estimated in the range of 43%.[1] According to Shifren and colleagues, "Most epidemiologic definitions of female sexual dysfunction refer to sexual problems without requiring sexually related personal distress to be present, whereas current diagnostic guidelines from the American Psychiatric Association and Food and Drug Administration require personal distress as part of the diagnostic criteria for 'dysfunction.'"

In the survey described by this study, which had a response rate of 63% (n = 31,581), female heads of household 18 years of age and older were asked to evaluate their sexual function using the female short-form Changes in Sexual Functioning Questionnaire and the Female Sexual Distress Scale. The prevalence of any sexual problem was 44.2%, with the most common problems being:

- low desire (38.7%)
- low arousal (26.1%)
- orgasmic dysfunction (20.5%).

Dyspareunia was not assessed in this survey because a physical examination is required.

How the findings broke down by age

The **prevalence** of sexual problems increased with age:

- Among women 18 to 44 years old, 27.2% reported a problem with desire, arousal, orgasm, or a combination of the three.
- Among women 45 to 64 years old, the prevalence was 44.6%.
- Among women 65 years and older, the prevalence of one or more of these problems was 80.1%.

As for **personal distress,** it was:

- highest (14.8%) among respondents 45 to 64 years old
- lowest (8.9%) among women 65 years or older
- intermediate (10.8%) in women 18 to 44 years old.

The prevalence of distress associated with desire and arousal problems followed the same pattern. A higher prevalence of distressing desire problems also was seen in women who had health problems and in

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although sexual problems are common among women in the United States, this survey confirms that distress caused by these problems is considerably less widespread. Sexual problems increase with age, but related distress is most common in women at midlife (45 to 64 years old).

Women's health clinicians who elicit a history of sexual dysfunction should determine the level of distress that is present before deciding to address the problem.

›› ANDREW M. KAUNITZ, MD

FAST TRACK

44.2% of respondents reported sexual dysfunction, but only 12% were distressed about it

those who were menopausal. The prevalence of distressful orgasmic dysfunction was similar in middle-aged and older women.

Medical problems associated with a higher prevalence of distressing problems of desire were depression, thyroid dysfunction, anxiety, and urinary incontinence.

Strengths and weaknesses of the study

The large sample size, wide age range, and use of verified instruments to measure sexual problems and related distress were all strengths of this study.

However, to increase response rates to "sensitive" questions, the authors used a research panel that was not randomly chosen. As a result, respondents may have been more health-conscious and self-aware than otherwise would have been the case; they also may have had more time to answer mailed questionnaires.

The fact that sexual problems and distress were self-reported without clinical evaluation also may have biased the findings slightly. Because the study was cross-sectional, cause and effect could not be established.

Reference

1. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors [published erratum appears in JAMA. 1999;281:1174]. JAMA. 1999;281:537–544.