Evaluating medications for women with female sexual dysfunction

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The only medications currently approved for a specific sexual dysfunction are phosphodiesterase type-5 inhibitors, which are used to treat men with erectile dysfunction. Any medications used for female sexual dysfunction (FSD) are used off-label. In the past few years, pharmaceutical companies have presented applications for several FSD medications to the U.S. Food and Drug Administration (FDA). However, the FDA has denied approval for these medications, either because of a paucity of long-term safety data or because of a failure to demonstrate statistically significant improvement in symptoms (ie, “satisfying sexual events”) compared with placebo.

Sexual dysfunction is not life-threatening and does not produce a serious impact on patients’ physical health. Thus, to receive FDA approval for sexual dysfunction, medications must meet the highest levels of quality of evidence in efficacy and safety. My purpose in this article is for it to serve as a review of medications that are either already available for FSD or under investigation for FSD.

Testosterone

Testosterone supplementation has been extensively studied in postmenopausal women, though it remains unapproved by the FDA for use in women with FSD. A twice-weekly testosterone patch designed for use in women has shown efficacy in women with hypoactive sexual desire disorder (HSDD), but availability is pending and dependent on long-term safety data. Interestingly, studies on use of the testosterone patch for FSD have suggested efficacy at moderate doses but little improvement at higher doses.

Testosterone products formulated for men should not be used to treat women with FSD, because such products result in extremely high physiologic levels of testosterone in women and increased risk of androgenic adverse effects, such as hirsutism, voice changes, acne, and clitoromegaly. They also have an adverse impact on lipid levels in women. Compounded 1% testosterone cream in petrolatum has been used historically as a treatment for lichen sclerosis et atrophicus, and it may be appropriate for some women if applied nightly at a dose of 0.5 g. However, although gynecologists may feel comfortable prescribing this cream, it should be kept in mind that no safety or efficacy data exist for this compound’s use in managing FSD.

Hormone therapy

Although anecdotal evidence and some study data suggest that hormone therapy may improve sexual desire in women, such results were not observed in the Women’s Health Initiative (WHI) study. In that randomized controlled trial, women were asked about their overall sexual function—but not desire—and results were tabulated using a Likert scale. The WHI investigators found no differences in sexual function between women taking conjugated equine estrogen/medroxyprogesterone acetate and women taking placebo.

It’s important to note that the WHI did not measure satisfying sexual events, which are now considered the primary endpoint for treatment of patients with FSD. Furthermore, the WHI did not screen study participants for FSD, and many of the participants were older than the typical woman with FSD.

For patients requiring postmenopausal hormone therapy, formulations of esterified estrogens and methyltestosterone may be used.
to increase testosterone levels.\textsuperscript{11,12} These products are not FDA-approved for FSD, though several studies have shown that they can improve sexual functioning in women.\textsuperscript{13,14} Vaginal estrogen therapy—including creams, tablets, and rings—can be used successfully to improve atrophic changes in postmenopausal women. Correcting these changes can reduce vaginal discomfort and improve sensation. Local estrogen therapy does not produce the potentially harmful blood levels of estrogen that can occur with systemic therapy, and, thus, it is viewed as less risky.\textsuperscript{15}

**Other pharmacologic agents**

Laboratory studies and clinical observations have shown that changes in neurotransmitter activity can cause changes in sexual desire. In general, serotonergic activity is inhibitory and dopaminergic activity is facilitatory to sexual desire.\textsuperscript{16} An application to use flibanserin (a 5-HT2 receptor antagonist and 5-HT1 receptor agonist) to modulate neurotransmitter levels in premenopausal women with low sexual desire was recently presented to the FDA. The regulatory agency determined, however, that the drug did not meet criteria for efficacy. The FDA also cited evidence of statistically significant adverse events associated with flibanserin, including depression, syncope, fainting, and accidental injury.\textsuperscript{17-21} The manufacturer has since withdrawn its application for FDA approval of flibanserin.\textsuperscript{22}

Monoamine oxidase inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) have all been shown to inhibit sexual activity in women. Antidepressant-induced FSD may be improved by changing medications. To manage SSRI-related orgasmic dysfunction, some physicians use a short-acting SSRI that a patient can skip for a weekend. This approach is anecdotally effective.

Bupropion hydrochloride has norepinephrine and dopamine reuptake inhibition effects and has been shown to improve sexual satisfaction, arousal, and orgasm.\textsuperscript{23,24} This drug may be considered as an alternative medication for women in whom FSD develops with use of SSRIs for depression.

Sildenafil citrate, approved for male erectile dysfunction, has been studied extensively in women. Results are inconclusive. Although an off-label use, antidepressant-induced sexual desire problems in women have improved with episodic use of sildenafil (50mg) taken one hour before sexual activity.\textsuperscript{25} Other studies have shown some success in using sildenafil for women with sexual arousal disorder, including postmenopausal women and even asymptomatic women.\textsuperscript{25-28}

Local creams and gels are available to improve sensation of the external genitalia. For example, a blend of over-the-counter herbs and vitamins marketed as “feminine massage oil” has been demonstrated to result in improvement in satisfaction and level of interest in women with disorders of sexual desire and arousal.\textsuperscript{29,30} Other kinds of over-the-counter creams or gels lack clinical data establishing their efficacy over placebo.

**Nonpharmacologic therapy**

An FDA-approved clitoral suction device can be used to cause clitoral vascular engorgement. Studies have shown that this device can cause improvement in arousal, genital swelling, vaginal lubrication, and enhancement of orgasm.\textsuperscript{31-33} Originally recommended for use immediately prior to sexual activity, the device is now recommended for use three to four times per week independent of sexual activity to improve genital blood flow and sensation. The device is a prescription item that is available via the Internet.

**Final notes**

There are no FDA-approved pharmacologic treatments for FSD—including HSDD, orgasmic dysfunction, or arousal disorder. Many medications, especially neurotropic drugs, migraine preventatives, and antidepressants can induce sexual dysfunction, especially HSDD and orgasmic dysfunction.

Several medications have been studied for use in women with FSD, with varying results. Most of these studies have had small sample sizes and varying endpoints. None of the studies measured effects of the medications on sexual satisfaction. Testosterone is known to increase sexual desire in women, though formulations designed for men should not be used for women. Knowledge about the role of estrogen therapy in menopausal women remains limited. Hormone therapy is FDA-approved only for the treatment of women with menopausal syndrome.

Physicians should consider off-label treatments only for well-selected patients and after thorough discussion of the risks and benefits with these patients. We can look forward to continued research and development of medications to help women with the distressing disorder of FSD.
References


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