

Managing female sexual dysfunction

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Although about one-third of women report concerns with sexual functioning, many healthcare providers (HCPs) do not feel comfortable screening for, diagnosing, or managing female sexual dysfunction (FSD). The authors offer guidance to HCPs for screening and diagnosing a variety of FSD disorders. In addition, the authors discuss pharmacotherapeutic options for managing these conditions, as well as these agents' benefits, risks, and monitoring parameters.

KEY WORDS: female sexual dysfunction, estrogen, testosterone, bupropion, ospemifene, flibanserin



Female sexual dysfunction (FSD) is highly prevalent among women in the United States, yet patients rarely discuss sexual concerns with their healthcare provider (HCP). Investigators of the Women's International Study of Health and Sexuality sent questionnaires to 2,050 U.S. women regarding health status, sexual desire, and distress caused by low desire.¹ The study showed that 24%-36% of women aged 20-70 years could be classified as having low sexual desire. This prevalence highlights the need for HCPs to know how to communicate with, identify, and manage patients' sexual concerns. To this end, the authors provide evidence-based recommendations drawn from the current literature regarding assessment and diagnosis of FSD, with an emphasis on pharmacologic options available to treat FSD. Most of the pharmacologic options for desire, arousal, and orgasm problems are prescribed *off label*.

Common barriers to identifying and managing FSD

Despite the high prevalence of FSD, many women do not broach the topic with their HCP, and many HCPs do not screen their patients for sexual disorders.² In fact, fewer than 20% of HCPs ask about their patients' sexual activity, including difficulties, enjoyment, and frequency.³

Urologists, gynecologists, and

psychiatrists are the HCPs most likely to inquire about sexual functioning.⁴ However, one study showed that among 187 urologists, only 10% asked every patient about sexual function on a regular basis, as opposed to 87% who asked about sexual activity when the chief complaint was related to abdominal pain, urgency/frequency, incontinence, or a urinary tract infection.⁵ A survey of the attitudes of nurse practitioners (NPs) and physician assistants (PAs) toward management of sexual dysfunction revealed that only one-half felt comfortable discussing the topic and only 21% of NPs and 11% of PAs felt confident in managing FSD.⁶ Nevertheless, most NPs and PAs had a positive attitude toward the possibility of evaluating and managing their female patients' sexual concerns.⁶

Various factors may hinder HCP–patient communication regarding sexual concerns. Potential barriers for HCPs include lack of time, lack of knowledge about FSD management options, and lack of training in how to communicate about FSD; barriers for patients include embarrassment and a belief that their HCP cannot help them.⁷ Some HCPs fear embarrassing or offending patients if they raise the topic,³ although most patients will discuss their sex practices if the HCP initiates the conversation.⁸

Even if a patient does discuss her sexual problems with her HCP, her concerns may not be properly addressed. One survey showed that among 3,807 women who considered seeking help for sexual dysfunction, fewer than half reported feeling hope, relief, validation, or satisfaction after discussing their concerns with a provider.⁹ In addition, patients were disappointed by their HCPs' inability or unwillingness to evaluate, treat, and follow up on their complaints.⁹

Overcoming the barriers

Healthcare providers can increase the likelihood that FSD will be identified and addressed by initiating the conversation with patients, which will strengthen the HCP–patient relationship and help normalize patients' concerns.⁹ Once both parties are comfortable, the HCP can take a sexual history, perform a thorough physical examination, and order appropriate laboratory tests.

HCPs can develop their own unbiased FSD screening questions based on their unique patient population.

History

To transition smoothly into taking a sexual history, HCPs can incorporate questions into the genitourinary/gynecologic/obstetric review of systems.¹⁰ Some patients may feel uneasy answering these questions, so HCPs can explain why such questions are being posed. For example, one can say, "I will be asking you some questions about your sexual activity to get a better idea of you as a whole and to ensure we are providing the most comprehensive care possible." Informing women that FSD is common can facilitate a frank conversation.¹⁰

Screening for FSD with just a few questions can be informative. A literature review by Giraldi et al¹¹

indicated that although multiple FSD screening tools are available, few standardized and culturally acceptable questionnaires are validated in general populations and can be used to assess for FSD in women with or without a partner and independent of the partner's gender. As a result, HCPs can develop their own unbiased FSD screening questions based on their unique patient population. A patient's sexual orientation should not be assumed; instead, HCPs need to ask about any and all sexual partners. Brief questions regarding sexual satisfaction and pain and the ability to reach an orgasm can determine if further screening is warranted.¹² Three targeted questions include the following¹³:

- Do you have any questions or concerns about your sexual activity?
- Have you experienced any changes in sexual response, lubrication, or pain with sexual activity?
- Are you aware of any changes in your level of interest or desire for sexual activities?

If a woman—premenopausal or postmenopausal—answers "yes" to any of these questions, then further investigation is needed.

For a specific problem, HCPs need to explore the nature of the problem, its severity and duration, the degree of distress it causes, and any history of similar problems.¹³ The patient is asked to use her own words to describe any sexual difficulties she may be having.¹⁴ Because sexual functioning is multifaceted, HCPs need to consider a woman's physical, surgical, medication, and social histories to uncover all possible factors causing or contributing to the sexual dysfunction (*Table 1*).¹⁴⁻¹⁶

Table 1. Differential diagnosis for female sexual dysfunction¹⁴⁻¹⁶

History	Differential diagnosis	Rationale
Past health history	Diabetes Hypertension Coronary artery disease Hyperlipidemia	These conditions are all associated with atherosclerosis, which can decrease the amount of blood flow to the vagina and clitoris.
	Thyroid disease Hyperprolactinemia Adrenal insufficiency	These conditions can disrupt the normal hormone milieu and inhibit sexual responsiveness.
	Depression Anxiety	These conditions can create an emotional blockade, thereby preventing normal sexual functioning.
Past surgical history	Pelvic surgeries	Pelvic surgeries can cause underlying nerve damage or leave painful scar tissue.
Medications	Selective serotonin reuptake inhibitors Conventional antipsychotics Statins Hormonal contraception	These medications can cause lack of desire, dyspareunia, lubrication difficulties, and anorgasmia.
Social history	Alcohol or drug use History of intimate partner violence History of sexual or physical assault Life stressors	Alcohol and drug use can diminish sexual responsiveness. A history of abuse may limit a woman's ability to become emotionally close to her partner and may trigger negative emotions during sexual activity.

Physical examination

A physical exam is conducted to identify or exclude conditions that might cause or exacerbate FSD. This exam includes a general systemic survey with a focused cardiovascular exam, which can uncover systemic perfusion abnormalities that might contribute to FSD.¹⁵ A neurologic assessment of the effects of light touch and pressure on the external genitalia may reveal locations with hypersensitivity. A genitourinary exam is done to evaluate for structural abnormalities such as an imperforate hymen or vaginal septum and to look for signs of estrogen depletion (e.g., loss of vaginal rugae, pale mucosa, thin lining).¹⁵ An evaluation of pelvic muscle tone is important; both high tone and low tone can be associated with FSD. This evaluation is best done using a perineometer, a device placed within the vagina

that provides feedback on the tone of the levator ani complex and obturator internus muscles.¹⁷ In the absence of this device, HCPs can evaluate tone during an internal exam by asking the woman to squeeze and relax the vaginal muscles.¹⁷ Of note, many women with FSD have normal physical exam findings.

Laboratory testing

Evaluating certain lab values can aid in identifying health conditions that may be contributing to sexual dysfunction. These lab tests include a complete blood count, fasting prolactin, a lipid profile, blood glucose, and thyroid hormone levels.¹⁸ Abnormal test results may reveal an underlying condition (e.g., anemia, thyroid disease, dyslipidemia, metabolic disorders, hormonal imbalances) causing or exacerbating the FSD.¹⁹ Evaluating the calculated free an-

drogen index can also help in classifying sexual complaints; age-based normative values have been established.²⁰ When a patient's primary complaint is dyspareunia, vaginal, cervical, and/or vulvar cultures can be obtained to rule out infectious causes.¹⁴

DSM-5 changes to FSD diagnoses

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), which was published by the American Psychiatric Association in 2013, includes revisions to previous editions based on new research.²¹ Specific to the category of sexual dysfunction, the *DSM-5* now requires that symptoms be present for at least 6 months. In addition, the *DSM-5* includes gender-specific diagnoses, combines disorders that were previously separate, and removes the subtype of FSD due to psychological

Table 2. Nonpharmacologic treatment options for female sexual dysfunction^{22,23}

Condition	Nonpharmacologic treatment ideas	Rationale
Low sexual desire disorders	Cognitive behavioral therapy	Uncover psychological factors that contribute to low sexual desire disorders
	Sex therapy	Encourage increased intimacy with partner through sexual creativity, partner communication, and self-pleasuring/identifying new activities that are pleasurable.
	Couples therapy	Encourage partners to create a pressure-free, intimate environment and foster communication.
Subjective arousal disorders	Cognitive behavioral therapy, sex therapy	Uncover an underlying cause: sexual boredom, lack of attraction to her partner, inadequate sexual stimulation, and/or negative emotions related to her partner or the sexual situation.
Orgasmic disorder	Self-stimulation, focus on recognizing physiologic signs of arousal and orgasm	Participate in self-stimulation to become more aware of how to elicit these responses and determine personal preferences.
Dyspareunia	Vaginal lubricants and moisturizers	Decrease pain by protecting the delicate vaginal tissue and facilitating penetration.

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factors versus combined factors. Research suggests that sexual response cannot be categorized into specific stages and is not always linear. As a result, the *DSM-5* combines sexual arousal disorder and sexual desire disorder into female sexual interest/arousal disorder. Another combined disorder in the *DSM-5* is genito-pelvic pain/penetration disorder, which was developed because of the difficulty distinguishing between vaginismus and dyspareunia.

Treatment approaches

Initial management of FSD requires treating any contributing underlying physical conditions. If treatment of these conditions does not result in restoration of sexual function, other interventions for FSD are considered. Although this article focuses on pharmacotherapeutic options, patients can try nonpharmacologic interventions such as cognitive behavioral therapy (CBT), sex ther-

apy, self-stimulation, and lubricating gels (*Table 2*).^{22,23} If nonpharmacologic therapies do not offer relief, pharmacologic options are considered.

Estrogen

Declining estrogen levels after menopause can lead to vulvovaginal atrophy (VVA), which can result in vaginal dryness, itching, and pressure and can lead to pain during sexual activity.²⁴ Painful intercourse (dyspareunia) can diminish sexual pleasure and desire for sex. Exogenous estrogen therapies, both systemic and topical, are used to increase vaginal lubrication and promote a more pleasurable sexual experience.²⁵

Compared with systemic estrogen products, vaginal estrogen products have been found to heighten genital vasculature (despite resulting in lower systemic levels of estrogen); systemic estrogen is more useful for relieving vasomotor symptoms (VMS) accom-

panying menopause.²⁵ Conjugated estrogens vaginal cream (Premarin® Vaginal Cream) has an FDA indication for treatment of moderate to severe dyspareunia, a symptom of VVA due to menopause.²⁶ Although estrogen therapies alone have not been found to directly increase sexual desire, they diminish dyspareunia, which may indirectly increase a woman's interest in sexual activity.²⁵

Many formulations of systemic and vaginal estrogen are available. If a woman's FSD complaint is related to VVA, a vaginal formulation is preferred.²⁷ Three vaginal estrogen formulations are available: creams, a ring, and a tablet (*Table 3*).²⁷ For the tablet and creams, a higher dose and/or dosing frequency is typically used for 1–2 weeks until relief is achieved; a tapered dose can then be used for maintenance.²⁷ Whereas most women find relief after 3 weeks of treatment, some may require up to 4–6 weeks.²⁸ Low-dose vaginal

Table 3. Available vaginal estrogen formulations and dosages²⁷

Formulation	Estrogen type/dose	Formulation	FDA-approved dosing
Ring	Estradiol 2 mg	Estring® (Pfizer)	Change ring every 90 days; releases 7.5 mcg daily
Tablet	Estradiol hemihydrate 10 mcg	Vagifem® (Novo Nordisk)	One 10 mcg tablet/day for 2 weeks, then 1 tablet 2x/week
Cream	Estradiol 0.1 mg/g	Estrace Vaginal® (Warner Chilcott)	2-4 g/day for 1-2 weeks, then 1g 1-3x/week
	Conjugated equine estrogens 0.625 mg/g	Premarin® Vaginal Cream (Pfizer)	1-2 g/day for 1-2 weeks, then 0.5-2 g 1-3x/week
	Synthetic conjugated estrogens-A (0.625 mg of SCE-A/g)	SCE-A Vaginal Cream	1 g/day x 2 weeks, then 1 g 1-3x/week

estrogen therapy can be used indefinitely because of the low adverse effect profile; however, given limited data on use beyond 1 year, women should be evaluated annually to determine the need for continued treatment.²⁹

The most common side effects of topical estrogen cream are headache, breast pain, pelvic pain, vasodilation, leukorrhea, metrorrhagia, vaginitis, and vulvovaginal disorder.²⁶ Most side effects subside with ongoing use. Although systemic estrogen use has been linked to an increased risk for endometrial hyperplasia, venous thromboembolism, and breast cancer, little evidence suggests an increased risk with topical estrogen use.²⁷ The North American Menopause Society (NAMS) released new guidelines for prescribing hormone therapy.³⁰ According to these 2012 guidelines, topical estrogen is less likely than standard-dose oral estrogen to cause blood clots or stroke; however, more research is needed to reach definitive conclusions. A Cochrane review showed no increase in endometrial proliferation with vaginal estrogen versus placebo.²⁷ Nevertheless, local es-

trogens can be absorbed into the bloodstream and increase the amount of systemic estrogen. Given the limited research, HCPs need to use clinical judgment when prescribing estrogen and monitor women closely for vaginal spotting/bleeding and other worrisome complaints.

Testosterone

If estrogen alone does not ease FSD symptoms, *off-label* addition of testosterone to estrogen therapy (ET) may increase libido and enhance sexual response.³¹ Use of testosterone in women is off label; this agent is prescribed with caution after patients are educated about the risks. A 2005 Cochrane review of 23 trials concluded that addition of testosterone therapy (TT) to ET improved sexual desire in postmenopausal women.³² The likely mechanism of action of combined therapy was related to the fact that use of exogenous testosterone increases circulating free testosterone and decreases sex hormone-binding globulin (SHBG). The subsequent increase in bioavailable testosterone may correlate with increased sexual desire.

Limited data on the long-term effects of TT led the FDA to reject a proposed testosterone patch for women with FSD. However, a 1% testosterone gel, FDA-approved for use in men only, is often prescribed off label to postmenopausal women with sexual dysfunction.³³ One study showed that a dosage of 10 mg/day, applied in a thin layer to 15 cm² of the inner thigh, led to mean testosterone levels of 3.0 nmol/L, which is in the high-normal range for premenopausal women (≤ 2.5 -3.0 nmol/L).³³ The advantage of the transcutaneous route of administration over other routes (e.g., subcutaneous implant, intramuscular injection) is that it avoids the high hormone levels in the hepatic portal vein, which helps minimize assault to the liver.³³

The most common short-term side effects of TT in women are hirsutism, acne, and a deepened voice, all of which are mild and reversible.³⁴ Long-term side effects of concern are cardiovascular disease (CVD) and breast cancer. Preliminary studies have shown that TT reduces high-density lipoprotein cholesterol levels and increases low-density lipoprotein chole-

terol levels; however, no study has looked at the correlation between TT in women and CVD.³² Studies examining the effects of TT on breast cancer risk are inconclusive.³² Absolute contraindications to TT include a history of breast cancer, endometrial cancer, venothrombotic events, or CVD.¹⁴

When prescribing TT, HCPs should ask women to undergo baseline and annual breast exams and mammography, along with a pelvic exam—with special consideration paid to abnormal bleeding.¹⁴ In addition, women must be regularly evaluated for acne, hirsutism, and androgenic alopecia.¹⁴ Laboratory parameters monitored at baseline, after 3-6 months of use, and then periodically thereafter include SHBG, total testosterone, fasting lipid panel, and liver function tests.¹⁴

In 2005, NAMS published a position statement regarding the role of TT in postmenopausal women. The society concluded that TT is a valuable pharmacologic option for postmenopausal women who present with symptoms of decreased sexual desire.³⁵ Nevertheless, NAMS cautions that insufficient data are available regarding the safety and efficacy of TT in women for longer than 6 months.³⁵ Given these data, testosterone is prescribed with caution, with extensive patient education.

Bupropion

Bupropion is a norepinephrine and dopamine reuptake inhibitor antidepressant without serotonergic effects.³⁶ Although bupropion is most commonly used as an antidepressant, this agent is used *off label* to treat sexual dysfunction in non-depressed women.³⁷ The exact mechanism of bupropion's efficacy for this indication is unknown

but may be related to increased uptake of dopamine and norepinephrine, both of which are correlated with increased sexual responsiveness.³⁶

The prescribed dosage of bupropion should not exceed 400 mg/day for the sustained-release formulation or 450 mg/day for the immediate- or extended release formulations; higher dosages can increase the incidence of side effects such as headache, agitation, insomnia, nausea, and possibly seizures.³⁸ Bupropion is not prescribed to patients with a history

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of anorexia, bulimia, or seizure disorders. Bupropion users must be monitored for neuropsychiatric changes such as hostility, agitation, depression, and suicidality.³⁹ Patients are counseled that treatment efficacy may not occur for 4-6 weeks.

Bupropion is a promising non-hormonal treatment option for FSD. Preliminary studies have shown encouraging results; however, more extensive research is needed before FSD can be listed as an indication for bupropion use.⁴⁰

Ospemifene

In 2013, the FDA approved ospemifene (Osphena™) for treatment of moderate to severe dyspareunia caused by VVA in menopausal women.⁴¹ Ospemifene, an oral selective estrogen receptor modulator, is the only non-estrogen compound approved in the U.S. to treat moderate to severe dyspareunia.⁴² This medication can be offered to women who are not candidates for ET but who have FSD related to dyspareunia. In two 12-week phase III clinical trials, ospemifene significantly improved vaginal dryness and dyspareunia, vaginal maturation index, and vaginal pH.⁴³ The most effective dosage is 60 mg/day.⁴³

The most common adverse effect of ospemifene is VMS.⁴³ This agent is contraindicated in women with genital bleeding of unknown cause, estrogen-dependent neoplasia, personal history of deep vein thrombosis, pulmonary embolism, stroke, or myocardial infarction. Ospemifene should not be prescribed to women with a history of breast cancer or who are at high risk for breast cancer. Pre-clinical and clinical trials show a promising effect of ospemifene on bone density and breast tissue, but long-term data on the safety of this medication are limited.⁴²

Flibanserin

Flibanserin, an oral agent proposed for treatment of premenopausal hypoactive sexual desire disorder, has been shown to significantly increase sexual desire and the number of sexually satisfying events among women taking 100 mg at bedtime.⁴⁴ The FDA initially rejected this medication in 2010.⁴⁴ When Sprout Pharmaceuticals reapplied for approval in 2013, flibanserin was once again

rejected; this time, the FDA indicated that additional studies in healthy subjects were needed to evaluate drug interactions and the drug's possible adverse effect on driving.⁴⁵ Sprout is expecting to resubmit the proposal by the end of the first quarter of 2015.⁴⁵ No more information on the proposal was available as this article went to press.

Conclusion

Given the prevalence of FSD, HCPs must know how to screen for and diagnose FSD, and then manage it or know when to refer. HCPs need to take a short sexual history in all women, and ask them whether they have concerns about their sexual activity or about changes in their sexual desire or response. If the history uncovers a possibility of FSD, a thorough physical exam and lab testing are done. For women in whom FSD is diagnosed, nonpharmacologic interventions include CBT, sex therapy, self-stimulation, and lubricants. Two medications—conjugated estrogens vaginal cream and ospemifene—have a *specific* indication for dyspareunia. Although no pharmacologic agent has been approved by the FDA to treat desire, arousal, or orgasmic dysfunction in women, interest in such agents is growing. In each case, HCPs weigh the risks and benefits of specific treatments, offer extensive patient counseling, and provide close follow-up. ●

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