Concise Review for Clinicians

Female Sexual Dysfunction

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Female sexual dysfunction (FSD) was recently recognized as arising from multiple organic etiologies; it is not primarily a psychological symptom as believed previously. A symptom-related complex resulting in physiologic changes, FSD can respond to either treatment of the underlying condition or supportive measures. A new diagnostic classification allows physicians to perform a clinical evaluation of women with FSD, and recently validated FSD questionnaires allow monitoring of treatment efficacy. This article details the clinical evaluation and physical examination of women with FSD and outlines the fledgling research and treatment options.

Mayo Clin Proc. 2002;77:698-702

FDA = Food and Drug Administration; FSD = female sexual dysfunction; SSRI = selective serotonin reuptake inhibitor

Sexual dysfunction is known to be highly prevalent in both men and women. Traditionally, psychological and interpersonal factors have been thought to be primary in female sexual dysfunction (FSD), whereas male sexual dysfunction is most often attributed to pathophysiologic changes responding to either treatment of the underlying condition or to erectile inductive measures. However, the associated risk factors for both sexes are strikingly similar: peripheral vascular or cardiovascular disease, neurologic disease, endocrine failure, hypertension, and a smoking history. The factors associated with an increased risk of FSD are listed in Table 1. Sexual dysfunction in both sexes is age related and progressive. It is becoming increasingly recognized that FSD is often the result of physiologic changes resulting from disease processes. Treatment of the underlying disorder may reverse the dysfunction, as in renal transplantation for renal failure, or supportive therapy, such as using clitoral vacuum devices for women who have impairment of engorgement, may be helpful. An abundance of basic science and clinical research is under way to define effective therapies for this common problem. The promise for treatment is near.

Physiological and interpersonal difficulties should not be the only factors attributed to the cause of sexual dysfunction; however, these issues cannot be minimized. Recent studies have also shown that socioeconomic factors place people at risk for sexual dysfunction. A particularly prevalent risk is a poor educational background or low socioeconomic class.[1]

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A question-and-answer section appears at the end of this article.

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DIAGNOSTIC CLASSIFICATIONS

Inconsistency between existing diagnostic classifications of FSD and the overarching assumption of a coexisting psychosocial dysfunction led to a new classification of FSD defined by a consensus panel meeting in 1998.[2] This system can be used whether FSD results from medical or psychosocial etiologies and is understood by health care professionals and the lay public. Critical to each diagnosis is the understanding that FSD results in personal distress. Additionally, as is clear from clinical practice, each of these diagnoses is independent of the others, eg, a patient with hypoactive sexual desire may still be arousable and capable of orgasm.

The new and still somewhat controversial diagnostic classification is as follows.

1. Hypoactive sexual desire: the persistent or recurrent lack of sexual thoughts and/or receptivity to sexual activity, which causes personal distress. Hypoactive sexual desire may result from endocrine failure and may be associated with psychological or emotional disorders. Sexual aversion disorder is a subcategory of hypoactive sexual desire.

2. Sexual arousal disorder: the persistent or recurrent inability to attain or maintain sexual excitement, which causes personal distress. This disorder includes poor vaginal lubrication, decreased genital sensation, and poor vaginal smooth muscle relaxation. Arousal disorders are most commonly physiologic and can often result from medications, pelvic disorders, as well as neural and peripheral vascular diseases.

3. Orgasmic disorder: the persistent or recurrent loss of orgasmic potential after sufficient sexual stimulation and arousal, which causes personal distress. Trauma to nerves associated with pelvic surgery and spinal cord injury can be associated with orgasmic failure.

4. Sexual pain disorder: the persistent or recurrent genital pain associated with non–coital sexual stimulation, which causes personal stress. Subcategories include dyspareunia and vaginismus. Operative injury and physical or psychological trauma involving pelvic organs are associated with this disorder.

PREVALENCE

A recent study[3] outlined the prevalence of sexual concerns in women seeking routine gynecologic care. Of almost 1500 women, more than 90% of the respondents (of the 65% of those responding) reported 1 or more sexual concerns. Most frequently described was hypoactive sexual desire in 87.2%, orgasmic disorders in 83.3%, difficulty in lubrication often resulting from a sexual arousal disorder in 74.7%, and dyspareunia indicative of a sexual pain disorder in 71.7%. Of note, FSD is far more common in patients with a history of sexual abuse or coercion, and more than 40% of such women reported a history of sexual coercion.[3] Although such surveys may be unable to distinguish interpersonal dysfunction from organic sexual dysfunction, up to 40% of women are affected.[4]

CLINICAL EVALUATION

Unfortunately, few women volunteer a history of FSD, and therefore information should be actively elicited as part of the routine medical history. The initial question a clinician could ask is, "How is your intimate life?" Questions regarding interest, arousal, orgasm, and pain can also be asked. The evaluation should include the specifics of the patient's FSD, review of over-the-counter, prescription, and street drugs, and tobacco use (Table 2).

Physical evaluation should include a pelvic examination to search for evidence of vaginal atrophy, dryness, and pain-triggering spots. The clinician should refer the patient to other health professionals if she/he does not have the time needed to perform a thorough evaluation and discuss appropriate therapeutic interventions. A sexual therapist should be consulted early because the patient's symptoms may be multifactorial and because sexual education and psychological evaluations are the mainstay of every evaluation and treatment plan.

The clinical assessment of FSD may include the use of questionnaires to monitor treatment efficacy. The Index of Female Sexual Function questionnaire assesses specific domains, including desire, lubrication, and orgasmic potential. Each question is ranked numerically, from 0 to 5; a greater than 60% improvement in the numerical value of this scale was interpreted as representing significant improvement (Table 3).[5] An endocrine evaluation in appropriately selected patients might include measurement of the serum follicle-stimulating hormone, leuteinizing hormone, serum estradiol, dehydroepiandrosterone, total testosterone, free testosterone, and prolactin levels. Vaginal pH, genital blood flow, vaginal wall compliance, vaginal engorgement with use of prestimulation and poststimulation, and genital vibratory sensation thresholds are proving useful in monitoring treatment efficacy. Normative data are being developed for these tools so they can be used as screening devices and specific diagnostic aids.

Table 1. **Increased Risk Factors for Female Sexual Dysfunction**

Neurologic disease
Stroke
Spinal cord injury
Parkinsonism
Genital atrophy
Genital surgery
Endocrinopathies
Diabetes
Hyperprolactinemia
Liver and/or renal failure
Peripheral vascular disease
Sexual abuse
Psychological factors, life stressors
Interpersonal, relationship disorders
Medications (see Table 2)

Research on FSD is proceeding rapidly. The underlying physiologic processes in both normal female sexual function and FSD are being discriminatingly defined. The primary effectors of sexual response in women are anatomical, vascular, and neural. Intact sensation is important in arousal, and therefore poorer levels of sexual functioning may be expected in diabetic women with peripheral neuropathy. Vaginal lubrication is a transudate of serum that results from a normal increase of pelvic blood flow with arousal. Therefore, vascular compromise may result in decreased lubrication and/or dyspareunia. The cavernosal and arteriole smooth muscle relaxation occurring via nitric oxide synthase produces an erectile response in the vestibule and clitoris. Orgasm requires an intact sympathetic outflow tract; hence, orgasmic disorders are common in female patients with spinal cord injuries.

TREATMENT

Educating the patient and partner about normal physiologic response and anatomy is often necessary. Additionally, physiologic changes associated with aging and/or disability and vascular dysfunction should be explained. The clear correlation between the patient's general health and sexual function must be emphasized. Thus, maximizing physical health and avoiding medications likely to produce FSD are prudent. Prescription medications may need to be tapered or changed. The patient should be encouraged to stop smoking and consuming alcohol to maintain or regain

Table 2. **Medications Associated With Female Sexual Dysfunction**

Antihistamines
Sympathomimetic amines
Anticonvulsants
Metronidazole
Metoclopramide
Antihypertensives
Diuretics
Adrenergic antiagonists (terazosin, doxazosin)
β-Blockers
Calcium channel blockers
Antiandrogens
Cimetidine
Spironolactone
Alkylating agents
Cyclophosphamide
Anticholinergics
Oral contraceptives
Drugs with abuse potential
Antidepressants
Hypnotics
Sedatives
Alcohol
Antiestrogens
Tamoxifen
Raloxifen
Gonadotropin-releasing hormone analgesics (leuprolide, goserelin)

sexual function. Furthermore, patients with reversible processes may respond to specific treatment of that disorder, ie, renal transplantation for renal failure.

Because FSD is a common adverse effect of antidepressants of all classes, patients with secondary FSD may respond to a dose reduction, drug holiday, or switch of antidepressants and/or adjunctive pharmacotherapy.[6] In addition, sildenafil with selective serotonin reuptake inhibitor (SSRI) medication has been reported to reverse the FSD associated with the SSRI.[7]

In postmenopausal women, estrogen replacement therapy may be helpful in treating vaginal atrophy, decreasing coital pain, and improving clitoral sensitivity. Thus, estrogen replacement may be helpful in arousal disorders. However, selective estrogen receptor modulators are unlikely to be helpful in treating genital atrophy, and estrogen replacement in the form of local cream is more efficacious.

Androgen levels in women decline substantially before menopause and then plateau. Lower free serum testosterone levels correlate with sexual dysfunction in the aging female. Moreover, although serum endocrine levels may be used to screen for testosterone deficiency, low levels of testosterone/dehydroepiandrosterone are ineffective prognosticators of a therapeutic response to androgen therapy. The widespread use of exogenous replacement androgens for FSD, often erroneously given to women who are menstruating, is not supported by available studies because efficacy has been shown only in patients with known androgen deficiency (premature ovarian failure or menopausal states) and secondary female arousal disorders.[8]

Furthermore, testosterone replacement has associated risks. Oral administration may be associated with hepatic disease. Androgen therapy adversely affects lipid profiles and may cause polycythemia, alopecia, acne, and female hirsutism. Hyperglycemia has been reported in insulin-dependent diabetic women, and fluid retention has been described in compromised patients with cardiac, renal, or hepatic disease. Hence, lipid profiles should be measured every 3 months in androgen-deficient women with secondary FSD, and such women should be given androgen replacement therapy; the medication should be discontinued if it is ineffective. It is inappropriate to use androgen therapy in the absence of a clinical setting consistent with androgen deficiency and supported by laboratory data. Of importance, premenopausal menstruating women are unlikely to have androgen-deficiency–related FSD, and, other than a placebo response do not appear to respond to androgen therapy.

The scientific literature on the value of testosterone replacement therapy for postmenopausal women made substantial gains with the recent publication of a study[9] of 75 healthy women with FSD who had undergone bilateral oophorectomy and hysterectomy. This study suggests that testosterone replacement may be helpful in this small subset of patients. Adequate estrogen replacement therapy had not improved their symptoms, and serum testosterone levels were measurably abnormal because of the lack of ovarian androgen production. This double-blind, placebo-controlled cross-over study evaluated the efficacy of transdermal testosterone at 150 μg/d and 300 μg/d for 12 weeks. The 300-μg dose appeared efficacious, albeit with a large placebo effect seen particularly in younger women. Further trials are awaited with interest.

Knowledge that nitric oxide–mediated stimulation of clitoral cavernosal smooth muscle increases clitoral blood flow and results in genital engorgement important in female sexual arousal has led to pharmaceutical trials with nitric oxide synthase blockade provided by oral sildenafil. An early study[5] showed sildenafil to be safe in women but ineffective because only 20% of these postmenopausal women would have continued sildenafil after the 3-month trial, and 10% dropped out of the trial because of clitoral pain and hypersensitivity. More recent studies[10] suggest that, in selected subpopulations such as premenopausal women with sexual arousal disorder, sildenafil may have a much higher efficacy. Sildenafil has also been reported to be successful in women with spinal cord injury and for FSD secondary to the use of SSRIs.[7] However, sildenafil

Table 3. **Female Sexual Function Index*†‡**

1. Over the past 4 weeks how often did you experience discomfort during sexual intercourse?
   ___Did not attempt sexual intercourse
   ___Almost always or always
   ___Most times (much more than half the time)
   ___Sometimes (about half the time)
   ___A few times (much less than half the time)
   ___Almost never or never
2. Over the past 4 weeks how often did you experience dryness during sexual intercourse?
   ___Did not attempt sexual intercourse
   ___Almost always or always
   ___Most times (much more than half the time)
   ___Sometimes (about half the time)
   ___A few times (much less than half the time)
   ___Almost never or never
3. Over the past 4 weeks how often did you attempt sexual intercourse?
   ___0
   ___1-2
   ___3-4
   ___5-6
   ___7-10
   ___11+
4. Over the past 4 weeks how often have you felt *sexual desire*?
   ___Almost never/never
   ___A few times (much less than half the time)
   ___Sometimes (about half the time)
   ___Most times (much more than half the time)
   ___Almost always/always
5. Over the past 4 weeks how would you rate your level of *sexual desire*?
   ___Very low/none at all
   ___Low
   ___Moderate
   ___High
   ___Very high
6. Over the past 4 weeks how satisfied have you been with your overall *sex life*?
   ___Very dissatisfied
   ___Moderately dissatisfied
   ___About equally satisfied and dissatisfied
   ___Moderately satisfied
   ___Very satisfied
7. Over the past 4 weeks how satisfied have you been with your *sexual relationship* with your partner?
   ___Very dissatisfied
   ___Moderately dissatisfied
   ___About equally satisfied and dissatisfied
   ___Moderately satisfied
   ___Very satisfied
8. Over the past 4 weeks, when you had sexual stimulation *or* intercourse, how often did you have the feeling of orgasm?
   ___Almost never/never
   ___A few times (much less than half the time)
   ___Sometimes (about half the time)
   ___Most times (much more than half the time)
   ___Almost always/always
9. Over the past 4 weeks, when you had sexual stimulation *or* intercourse, how would you rate your degree of *clitoral sensation*?
   ___Very low/none at all
   ___Low
   ___Moderate
   ___High
   ___Very high

*Sexual function includes intercourse, caressing, foreplay, and masturbation. Reprinted from Kaplan et al[5] with permission from Elsevier Science.
†Sexual intercourse is defined as vaginal penetration by your partner. (You were entered by your partner.)
‡Sexual stimulation includes situations like foreplay with a partner, looking at erotic pictures, etc.

has not been approved by the Food and Drug Administration (FDA) for FSD. L-arginine, another nitric oxide precursor, has been used with some success in men, but there are no reports of trials in women.

Yohimbine, a presynaptic α_2-adrenergic antagonist, has not been shown to offer any therapeutic effect beyond placebo in women. Indeed, other more powerful α-antagonists,[11] including labetalol and clonidine, are associated with decreased female sexual function. In contrast, adrenergic stimulants, such as ephedrine[12] and exercise,[13] appear to augment vaginal blood flow, albeit not sexual arousal. Hence, prostaglandin E_1 applied topically to augment blood flow and phentolamine,[14] an orally or vaginally applied α_1- and α_2-adrenergic receptor antagonist, are currently under clinical investigation. Trials of apomorphine, a short-acting dopamine agonist available in sublingual medication, and prostaglandin E_1, used as a intraurethral agent in men with erectile dysfunction, have not yet been reported in women.

Recently, the FDA approved the use of a therapeutic clitoral device for women. This hand-held battery-operated device has a small soft plastic cup that applies a gentle vacuum over the clitoris. When the woman turns on the device, the gentle self-controlled vacuum directly stimulates the clitoral area and causes increased cavernosal blood flow and engorgement, similar to penile vacuum devices used for assisted erections in men. Vaginal lubrica

tion is also increased. It is clinically indicated for those with arousal and orgasmic difficulties.[6]

SUMMARY

Healthy human sexuality is integral to a well-lived life. Newer practical classifications of FSD, research into the mechanisms by which FSD occurs, and the past 50 years of research into the normal female sexual response have resulted in improved treatments and an improvement in the quality of life for many women.

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Questions About FSD

1. Which <u>one</u> of the following is <u>true</u> regarding FSD resulting from physiologic processes?
   a. Is generally irreversible
   b. Treating the underlying cause may reverse the dysfunction
   c. Uniformly responds to patient education and couple psychotherapy
   d. Requires evaluation of genital blood flow and sensation before therapy is initiated
   e. Responds to oral sildenafil
2. Which <u>one</u> of the following is a classification of FSD?
   a. Sexual aversion
   b. Frigidity
   c. Neurogenic cause
   d. Psychiatric cause
   e. Sexual pain
3. Which <u>one</u> of the following groups seeking routine gynecologic care has the <u>*highest*</u> prevalence of FSD?
   a. Women with a low socioeconomic status
   b. Women with a history of sexual abuse or coercion
   c. Women who have had a hysterectomy without bilateral salpingo-oophorectomy for benign disease
   d. Women whose partners have sexual dysfunction
   e. Postmenopausal women receiving hormone replacement therapy
4. Which <u>one</u> of the following is <u>true</u> regarding women with hypoactive sexual desire?
   a. They are unlikely to have androgen deficiency and are unlikely to respond to androgen supplementation
   b. They are unlikely to have low libido related to parenting and childcare issues
   c. They have a high risk of vascular disorders
   d. They should be screened for premature ovarian failure by measurement of follicle-stimulating hormone and leuteinizing hormone levels
   e. They are likely to have a secondary arousal or orgasmic disorder
5. Which <u>one</u> of the following is <u>true</u> regarding sildenafil for the treatment of hypoactive sexual desire disorder?
   a. Sildenafil does not have FDA approval for the treatment of women
   b. Sildenafil is beneficial for treating women with spinal cord injury
   c. Sildenafil is an SSRI that induces FSD
   d. An empirical trial of oral testosterone was unsuccessful
   e. Sildenafil is beneficial in women with surgically induced menopause

Correct answers:
1. *b*, 2. *e*, 3. *b*, 4. *a*, 5. *a*