CME Feature

Managing hypoactive sexual desire in women

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ABSTRACT **Decreased sexual desire afflicts one third of adult women in this country. Difficulty in diagnosing this condition is compounded by the subjective nature of desire, and although many older women attribute their reduced libido to hormonal changes, the etiology is rather complex. Side effects of medications, psychological problems, history of substance abuse, or relationship difficulties can all lead to low libido. Your patient may ask for testosterone replacement therapy, which many today see as the potential "quick fix" for this problem, but such therapy is not always the answer and may cause new medical problems, such as hirsutism or acne. Until clear guidelines for use of testosterone become available, we must exercise caution in administering such therapies. Dr Viera outlines the keys to the correct diagnosis and explores treatment options within the context of the primary care setting.**

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Educational needs addressed: Low sexual desire afflicts many adult women, and primary care clinicians are increasingly seeing patients with this condition. The complex etiology, including psychological and/or relationship problems, drug effects, substance abuse, or hormonal disorders, highlight the need for clearer treatment guidelines.

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Coincident with the advent of effective oral therapy for erectile dysfunction in men, more women have begun seeking medical attention for problems related to their sexual function. One such issue is loss of libido, or hypoactive sexual desire. Hypoactive sexual desire has received a great deal of media attention in recent years, which may have further contributed to the recent surge of female patients seeking medical treatment in the primary care office.

An elusive definition: scope of the problem

Hypoactive sexual desire is the most common female sexual dysfunction, affecting as many as one out of every three women in the United States.[1] It is difficult to clinically define what constitutes hypoactive sexual desire, since "normal" sexual desire obviously differs from person to person. Desire is difficult to measure objectively because it is not simply the equivalent of frequency of intercourse. Women may choose to engage in sexual activity even in the absence of desire; conversely, they may have desire but not engage in sexual activity. An alternative to the model of female sexual response cycle as originally proposed by Masters and Johnson[2] is depicted in the Figure.

The term "desire" encompasses the feelings and sexual wishes surrounding sexual activity. Some have advocated that decrease in a woman's libido is simply a normal change that often accompanies age or menopause. Still,

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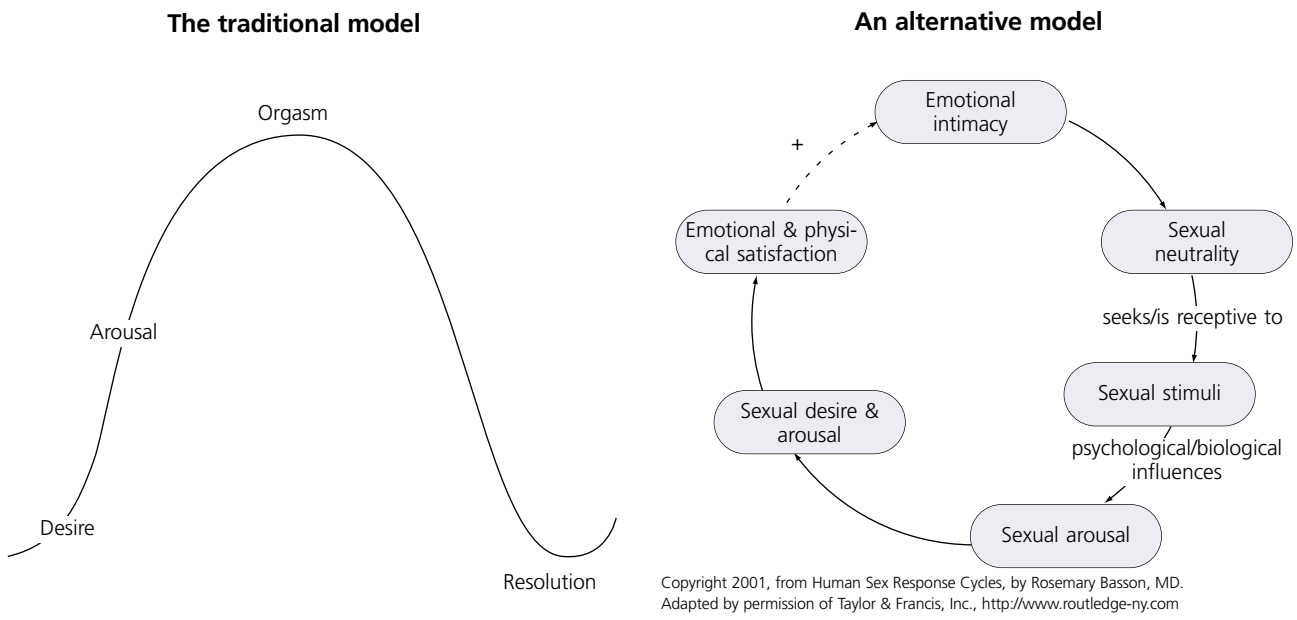
FIGURE **Female sexual response cycle**



The traditional explanation of the human sexual response is derived from Masters and Johnson's work on male sexual arousal. It does not include elements of intimacy or stimuli, and is often referred to as a "mountain." This explanation is echoed in the DSM-IV's definitions of female sexual dysfunction. An alternative model has recently been suggested by Rosemary Basson, MD, who introduces the elements of intimacy and motivation into the cycle of desire in women. Her model shifts the focus from the genitals to intimacy as a major component in female sexuality.

This alternative model begins with the woman's motivation—satisfaction of intimacy needs—which may lead her to respond to sexual stimuli, instead of initiating the cycle with the stimuli itself. Because some women's sexual desire may be based on and motivated by emotions and intimacy rather than pure sexual need, the physical and biological components may permit sexual repercussions that have strong emotional meanings, thereby enhancing the effects of sexual stimuli and provoking a sexual responsive desire.

40 million women in America are estimated to suffer from this so-called normal change. Hence, the most clinically appropriate definition of hypoactive sexual desire is a decreased level of sexual desire that causes distress to the patient. It is the absence of receptive or responsive desire that is so distressing to women. Absence of "spontaneous wanting" is both manageable and likely normal.[3]

Diagnosis

Primary care clinicians should be prepared to evaluate female patients who present with the complaint of decrease or loss of desire. The causes of decreased sexual desire are numerous and complex. The primary task of the physician evaluating a patient with this complaint is to determine if there is an identifiable root cause for the decreased libido. Causes range from medication side effects to depression to the most common cause—relationship problems (Table 1).[4]

The history. When taking the history, ask the patient to describe what has changed regarding her sexual desire. Determine whether the patient's decreased libido is a clear departure from what was once considered her normal libido or whether the patient feels that she never had much libido. Ask whether the loss of sexual desire is toward a specific person or is more general. Also, note whether the decrease in sexual desire has evolved gradually or developed suddenly. Recent stresses (eg, new job, new baby, death in the family) are important to elicit as well as any marital problems or unresolved anger. It is also appropriate for you to use screening questions for depression.

Many medications can interfere with sexual function, some causing decrease in sexual desire (Table 2). Therefore, when taking the history, be sure to review the patient's past medical history and medication use, including over-the-counter and herbal agents. Ask about a history of alcohol or drug abuse, and explore it further if it is likely that the patient may have a current substance abuse problem. The mnemonic device below may be useful in questioning the patient about alcohol abuse.

CAGE: Questions regarding substance abuse

Cut down: Do you feel that you should cut down on your drinking?

Annoy: Does it annoy you when people talk to you about your drinking?

Guilt: Do you feel guilty about your drinking?

Eye opener: Do you ever have a morning eye opener?

Ask the patient if she has any pain with intercourse, difficulty with lubrication, or a history of childhood or adult sexual abuse or trauma (molestation or rape).[5] Anorgasmia, or inhibited orgasm, is probably the most common primary sexual disorder leading to decreased desire,[4] so explore this possibility, but be sure to do so with caution and sensitivity. Although the patient may not volunteer such information if not asked, many will do so when asked directly.[5] A history of gynecologic cancer surgery is also important to note, because up to 75% of patients who have undergone these procedures report decreased libido.[6]

Physical exam/screening. Conduct a general physical examination to determine if there is any detectable general medical condition that may be responsible for decreased libido. Screening lab tests for ruling out common conditions such as diabetes, hypothyroidism, and renal or liver disease may be warranted if suggested by history or physical findings, since decreased sexual desire could be a symptom for any of these conditions. Measuring the plasma testosterone level (especially in premenopausal women) is currently not a routine part of the laboratory evaluation of a woman with the complaint of decreased libido. Checking a testosterone level in a premenopausal woman with functioning ovaries and adrenal glands implies that testosterone supplementation is a possible treatment in this age group, which until very recently was not a valid option. However, new evidence shows a clear connection between decreased levels of free testosterone and low sexual desire even in premenopausal women, likely warranting a revision of the approach to treatment.[7] (Such an approach will be discussed in detail in a forthcoming article by Andre Guay, MD.)

TABLE 1 **Decreased libido: etiological clues gleaned from the history**

Historical clue	Might suggest
Anger or unresolved conflict	Relationship discord
Gradual onset	Relationship discord
CAGE questions (see box)	Alcoholism
Depression screening	Depression
Medication and substance abuse	(See Table 2)
Pain with intercourse	Endometriosis, vaginismus, other pelvic disorder
Difficulty achieving orgasm	Orgasmic disorder
Difficulty with lubrication	Atrophic vaginitis
History of childhood or adult sexual trauma or abuse	Posttraumatic stress disorder
Weight loss	Depression, cancer

Gynecologic examination. The gynecologic examination is perhaps the most important portion of the physical examination of the patient complaining of decreased sexual desire, particularly when hypoactive sexual desire is associated with dyspareunia. In other conditions it offers reassurance to the patient that you have considered all possible causes. You can often detect a primary disorder of sexual function to which the decreased libido is attributable. An exam that is particularly painful to the patient may suggest vaginismus, endometriosis, vulvar vestibulitis, or vaginal mucosal atrophy (in the postmenopausal patient). The decreased desire for sex may simply reflect the fact that sexual activity is painful.

Table 3 lists other possible conditions that may lead to decreased sexual desire. Some suggest that gynecologic exams are not particularly helpful for women with hypoactive sexual desire without pain, other than as a means of reassurance for the patient. However, the value of patient assurance and comfort in the primary care setting is of paramount importance.

Assess for depression. In the premenopausal patient with an initially unremarkable history and a normal

TABLE 2 **Medications that may cause decreased sexual desire**

Drug type	Class/Drug	Examples
Antidepressants and mood stabilizers	Selective serotonin reuptake inhibitors (SSRIs)	citalopram hydrobromide (Celexa™) fluoxetine HCl (Prozac®) sertraline HCl (Zoloft®)
	Tricyclic antidepressants	amitriptyline HCl (Elavil®) lithium (Eskalith®) protriptyline HCl (Vivactil®)
Cerebral depressants and tranquilizers	Antipsychotics	haloperidol (Haldol®) mesoridazine (Serentil®) perphenazine (Trilafon®)
	Benzodiazepines	alprazolam (Xanax®) diazepam (Valium®) halazepam (Paxipam®)
Cardiovascular agents	Antilipids	atorvastatin (Lipitor®) gemfibrozil (Lopid®) simvastatin (Zocor®)
	Beta-blockers	atenolol (Tenormin®) metoprolol (Lopressor®)
	Clonidine HCl (Catapres®) Digoxin (Lanoxin®) Spironolactone (Aldactone®)	
Hormones	Danazol (Danocrine®)	
	GnRH agonists	leuprolide acetate (Lupron®) nafarelin acetate (Synarel®)
	Oral contraceptives	norethindrone, ethinyl estradiol (Midicon®) norethindrone (Micronor®) norgestimate, ethinyl estradiol (Ortho Tri-Cyclen®)
Others	H_2-receptor blockers	cimetidine (Tagamet®) famotidine (Pepcid®) ranitidine (Zantac®)

Based on data from Alexander[4] and Phillips.[26]

physical examination, it may be worthwhile to ask the patient again about her relationship with a partner. Depression may be difficult to recognize when decreased libido (a component of anhedonia) is the predominant symptom. Some depressed premenopausal women seem particularly interested in "getting [their] hormones checked." Such a request may be more than a false alarm triggered by media hype. It may be your only clinical clue to the patient's feelings of guilt, desperation, or fatigue—more commonly recognized signs of depression.

However, keep in mind that other etiologies may be involved. As recent evidence shows, some premenopausal women may indeed be suffering from androgen deficiency, in the form of decreased levels of free testosterone and possibly also dehydroepiandrosterone-sulfate (DHEA-S).[7] A thorough evaluation is therefore necessary, and additional laboratory testing may, at times, be justified.[7]

The postmenopausal woman is certainly not exempt from relationship problems or depression; however, the likelihood of finding other or additional potentially treatable causes of decreased libido in such patients is greater than in premenopausal women. Discomfort secondary to vaginal atrophy and/or dryness may contribute to a woman's decreased desire for sex during this stage in her life. Even women who are on standard-

dose hormone replacement therapy may have poor estrogenization of the vagina, caused by the greater estrogen requirement of the vagina compared to that of bone and blood vessels.[8] Cystoceles, rectoceles, uterine prolapse, or rectal disease may all lead to the complaint of decreased interest in sex. Decreased desire may also be a "normal" physiologic change associated with menopause.[9,10]

Hormones and sexual desire

Estrogen. Whereas premenopausal levels of estrogen are necessary for healthy pelvic tissues, it does not appear that declining levels of estrogen are directly responsible for loss of libido. Rather, loss of interest in sex may be the result of the discomfort experienced during the sexual act caused by inadequate estrogenization of the vulva and vagina. Inadequate levels of estrogen may also weaken the pelvic floor, increasing the risk for cystocele, rectocele, and uterine prolapse.

Testosterone. Testosterone levels also decrease as women reach menopause, and decreased levels of free testosterone have been linked to decreased sexual desire in postmenopausal women[11] and more recently even in premenopausal women.[7] Studies have also shown that oral estrogen-androgen replacement improves sexual desire and satisfaction in these women.[12] However, not all postmenopausal women's testosterone production falls by a clinically significant degree.[13]

Treatment considerations

If you discover an underlying medical disorder that could potentially be responsible for a woman's decreased libido, then treatment should begin there, addressing the specific associated condition. You may need to alter medications if you strongly suspect they are a cause of decreased sexual interest. Other problems may require appropriate referral. Marital or relationship problems are very difficult to treat and are beyond the scope of most primary care clinicians. If faced with this scenario, consider making the appropriate referral to marriage counselors or other professionals. Alcohol or drug abuse also requires appropriate substance abuse treatment or referral.

Depression. When depression is the cause of decreased libido, treatment of the depression will often improve the decrease in sexual desire.[14] Selective serotonin reuptake inhibitors (SSRIs) have become the drugs of choice for most forms of depression treated by primary care clinicians, but decreased libido is a well-known side effect of SSRIs. Therefore, agents less likely to cause decreased libido—such as bupropion, trazodone, and nefazodone—may be better first line medications in patients whose major complaint is loss of sex drive.[14]

TABLE 3 Gynecologic causes of decreased libido secondary to dyspareunia

Causes	Gynecologic sign
Vaginismus	Increased muscle tone, tense levator ani
Atrophy	Decreased skin turgor, thin vaginal mucosa
Infection	Cervical motion tenderness, vaginal discharge, ulcers (herpes simplex)
Endometriosis	Tender adnexa, pain during rectovaginal exam
Cystocele, rectocele, uterine prolapse	Degree of prolapse
Vestibulodynia (vulvar vestibulitis)	Pain elicited by touching the vaginal vestibule with a cotton tip applicator

SSRI-induced decreased libido. If an SSRI has been successful for the condition being treated (eg, depression, anxiety disorder, premenstrual syndrome), both you and your patient may be reluctant to discontinue it. In these cases, you have several options. Reduction of the SSRI dosage may be sufficient to restore sex drive while maintaining treatment of depression.[14] For SSRIs with a short half-life (ie, sertraline, paroxetine), 1- to 2-day "holidays" during which the medication is withheld may be effective.[14] The addition of buspirone in a dose of 20 mg to 60 mg per day may also restore sex drive.[15] Adding 75 mg bupropion per day to the SSRI may also be effective.[16,17] Cyproheptadine, a 5HT-2 antagonist, was shown to be effective in men with SSRI-induced sexual dysfunction.[18] Although there is no reason to believe that it would not be equally effective in women, it may reverse the beneficial effects gained by the SSRI, as well as cause weight gain and sedation. Hence, its use for this purpose should probably be avoided.

Sildenafil and arousal disorder. Although not yet indicated for use in women, several studies suggest that sildenafil (Viagra®) may be effective in treating SSRI-induced sexual dysfunction.[19,20] Sildenafil may find its niche not in the treatment of female sexual desire dis-

order per se, but rather in the treatment of female sexual arousal disorder. Because sildenafil increases blood flow to the clitoris and vagina, some suggest it may also increase genital sexual arousal. However, this issue is still controversial, and more studies are needed to clarify the role of sildenafil in the treatment of sexual arousal in women. There is often considerable overlap among causes of decreased libido and it may be difficult to sort out the exact nature of the sexual complaint. Sexual arousal disorder may lead to or contribute to decreased sexual desire. If it can be established that the sexual dysfunction is not due to emotional or relationship problems, then sildenafil may prove useful in selected patients.

Managing the postmenopausal woman

ERT. If you establish that decreased libido in your patient clearly occurred with menopause and no other cause can be found, your first step is to make sure the patient has adequate estrogen replacement. Estrogen is one hormonal component necessary to maintain normal libido and sexual responsiveness.[11]

Testosterone therapy. Unlike in the case of estrogen, our knowledge regarding the precise nature and extent to which testosterone contributes to female sexual desire is still in its infancy.[7] There is sufficient evidence to affirm that testosterone replacement in women who have inadequate levels of the hormone does improve libido.[11,13,21,22]

This holds true, perhaps even more so, for women with surgical menopause.[22-25] In these women, testosterone replacement should be considered only after a baseline free testosterone level is measured to confirm that it is indeed diminished.

Although no drug treatment is currently FDA approved, some clinicians are now using over-the-counter oral DHEA as a therapy for decreased testosterone associated with decreased libido, as an inexpensive and very accessible form of therapy. Repeat hormonal blood testing on such therapy has been associated with normalization of androgen levels.[7] However, more information in this area is clearly needed concerning the safety and efficacy of androgen replacement therapy.

Risk assessment. Before you initiate off-label testosterone replacement therapy in women, it is imperative that you discuss with the patient all potential risks involved in androgen replacement. And before you consider it as a plausible option, be sure to establish baseline levels of liver enzymes and high-density lipoprotein (HDL), as some forms of testosterone may cause liver damage or lower levels of HDL cholesterol.[13,26] However, these adverse effects are more likely to occur at supraphysiologic levels. You also need to alert your patient to other risks associated with testosterone therapy—these include hirsutism, acne, voice-deepening, and clitorimegaly.

Testosterone administration. There are several preparations and routes of administration available for testosterone. Oral methyltestosterone (1.25 to 2.5 mg per day) in combination with esterified estrogen has been used mainly in the United States and, along with fluoxytestosterone, is an alkylated form of testosterone that has the potential risk of liver damage or reduction of HDL.[13] Testosterone undecenoate is a lipophilic oral formulation that appears to be safer because it avoids first-pass metabolism in the liver. Monthly intramuscular injections of 25 mg of testosterone may also be administered. Transdermal testosterone (300 µg per day) will likely become the favored method for administering testosterone replacement as a result of its ease of use and efficacy. A recent study has shown the beneficial effect of testosterone patch on sexual function in older women who suffered from impaired sexual function after oopherectomy.[25]

Managing the premenopausal woman

Studies showing improved libido in postmenopausal women have led to the consideration of whether decreased sexual desire in premenopausal women might also be treatable with testosterone. However, because functioning ovaries, as well as the adrenal glands, produce testosterone, any testosterone given to women with normally functioning ovaries and adrenals may pose a risk for hormonal excess; such supraphysiologic levels of testosterone could lead to masculinization. Advise premenopausal women with normally functioning ovaries who inquire about the possible use of testosterone that such use would clearly be supplemental therapy, since use as replacement therapy is not currently medically indicated. Still, as is becoming increasingly evident, some premenopausal women may suffer from decreased levels of testosterone[7] and therefore may benefit from replacement therapy. Remember that clear treatment guidelines are still needed before embarking on off-label testosterone therapy in premenopausal women; if you choose to use it, you must monitor results of this therapy closely, to avoid associated risks involved.[7]

If no other cause for decreased libido can be found,

it is possible that in the future premenopausal women may be eligible to enroll in trials of medications for low desire. Clearly, more research is needed in this area. It appears that sildenafil only improves genital response to mental sexual excitement—it has not even been shown to increase desire in men. An alternative may be a trial of bupropion, which is now being investigated in connection with sexual desire. The extended release preparation of bupropion may improve sexual desire and orgasmic disorder in women with hypoactive sexual desire, even in the absence of depression.[27]

Conclusion

Hypoactive sexual desire in women is much more common than once believed. Primary care physicians will frequently encounter women complaining of loss of libido, and many will be asking to have their hormones checked. It is important that you evaluate these patients systematically with a primary goal of detecting any underlying problem. Until recently it was believed that most premenopausal women with the complaint of decreased sex drive had underlying relationship discord or depression; as new evidence suggests, we now have to consider that some premenopausal women may experience decreased libido resulting from testosterone or androgen deficiency. Also, among postmenopausal women, many will have a gynecologic cause that may contribute to their decreased desire for sex. Still, some postmenopausal women, especially those who are surgically menopausal, will have a decreased testosterone level and would likely benefit from testosterone replacement. ⚥

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