

Toward an understanding and a treatment approach Problems of sexual function in menopausal women

► JAMES A. SIMON, MD, CCD, NCMP

Sexual function across the life cycle has, for years, been the subject of intense investigation—and continues to be. Research in this realm is often controversial and clouded by opposing views of what is “normal” female sexual function and behavior. Our psychosocial mores, traditions, and religious and educational background and other points of reference have hampered the investigative process and, in fact, diminished our understanding of sex.

The synopsis that follows is more a “how-I-see-it-and-what-I-do” discussion than an exhaustive systematic review. My aim is to improve clinicians’ understanding of this complex, often neglected, subject and, thereby, improve the care of our menopausal patients.

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Disclosures

Dr Simon’s disclosures are listed on page S6.

What is the “normal” female sexual response?

The female sexual response is a **complicated and dynamic process that is influenced by physiologic, psychological, sociocultural, and interpersonal factors**. In the mid-1960s, Masters and Johnson proposed a linear, male-like, physiologic model of excitement-arousal, plateau, orgasm, and resolution that was derived from direct observations of the physical changes during sexual stimulation in the laboratory. To that model, Kaplan later added the concept of sexual desire and condensed the model into three stages: **desire, arousal, and orgasm**.

In 2005, Basson advanced an alternative, intimacy-based model in which women are motivated to actively seek sexual stimuli, or are receptive to the sexual advances of their partners, and then experience responsive desire and arousal until satisfaction is attained. Any given woman might endorse one of these models on the basis of her personal circumstances and experiences.

Neurobiology of the female sexual response

The sexual response in women involves multiple areas of the brain—from the brain stem and the cerebral cortex to the hypothalamus and the amygdala. Extensive discussion of this topic is beyond the scope of this article; reviews are available elsewhere.^{1,2} Note, however, that much of what we know about the neurobiology of the female sexual response is **based on indirect evidence** that has been extrapolated from research on laboratory animals and neuroimaging studies; such is the state of the art.

In general, it is known that:

- The reproductive hormones estrogen, testosterone, and, even, progesterone all increase desire.¹
- Oxytocin has a beneficial effect on orgasm.¹
- The neurotransmitter serotonin has a negative effect on sexual desire and downstream arousal and orgasm (think: the impact of a selective serotonin reuptake inhibitor [SSRI] antidepressant on sexual function).

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Toward better sex in menopause

As caregivers to menopausal women, we are sometimes asked by patients to “fix” their sexual problems. If menopause is caused by a decline in hormone levels, then we should be able to use hormones to fix disorders of sexual response associated with menopause. Right?

No. Regrettably for those who seek a fix, sexuality is more complicated than that.

In this issue of *Menopausal Medicine*, James A. Simon, MD, CCD, NCMP, reproductive endocrinologist and trained sexual counselor, discusses his approach to the diagnosis and treatment of hypoactive sexual desire disorder. HSDD tends to peak during menopause, and might affect a surprising number of your patients.

So many disorders and medications common in women in this age group can cause sexual dysfunction; simply recognizing what they are can have a positive impact on a patient’s problem. Taking the time to understand the nature of the problem may also pay off. Dr. Simon’s article offers a strategy for recognition and understanding.

There are no FDA-approved products for treating female sexual dysfunction; potentially effective medications are available off-label, however, and other drugs are on the horizon. Again, Dr. Simon reviews the options in his discussion.

In short, menopause need not mark the end of a satisfying sex life.

Cynthia K. Sites, MD

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- Dopamine increases desire and subjective excitement.
- Norepinephrine increases sexual excitement and orgasm.^{1,2}

The causes and kinds of sexual dysfunction

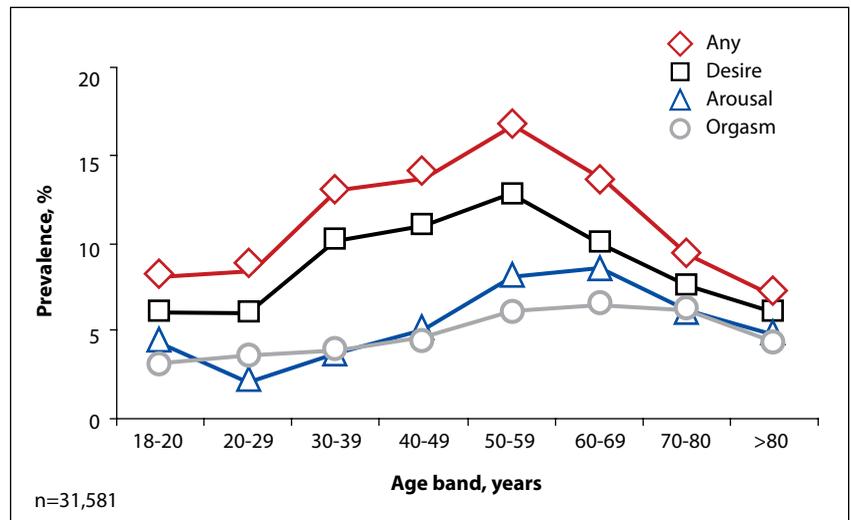
Sexual function waxes and wanes across the life cycle—there should be no doubt about this in the mind of any practitioner of adult medicine. The best information on this subject has come out of the Prevalence and Correlates of Female Sexual Disorders and Determinants of Treatment Seeking (PRESIDE) Study,³ which demonstrated that a small percentage (5%) of reproductive-age women—even young women in their 20s—have low sexual desire and are distressed about it. Although this description doesn't fully satisfy the definition of hypoactive sexual desire disorder (HSDD) in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*, the PRESIDE data clarify the changes in desire, arousal, and orgasm over the life cycle (FIGURE).

Several generalizations seem obvious from this data set:

- **Desire disorder** (actually, low desire with distress) is the most prevalent sexual problem. It has a lower prevalence in young, reproductive-age women that rises progressively, reaching about 12% in early menopausal women.³
- After the fifth and sixth decades of life, **(1) arousal problems** in women with distress and **(2) orgasmic difficulties**, including delay and anorgasmia, *gain* (similar to the increase in the vascular-based prevalence of erectile dysfunction in men during these decades), while the frequency of problems of desire remains stable or declines (FIGURE).

Overall, millions of women, their partners, and their families are affected,

FIGURE How prevalent are sexual problems associated with sexually related personal distress?*



*Sexual pain was not measured in this survey.

Source: Modified from Shifren JL, Monz BU, Russo PA, et al. Sexual problems and distress in United States women: prevalence and correlates. *Obstet Gynecol.* 2008;112(5):970-978.³ Used with permission.

particularly in the early menopausal years.³

Given the age-related changes in hormonal milieu and menstrual function that come with menopause, it is no surprise that changes in levels of endogenous estrogens and androgens might be related to sexual function, particularly in surgically menopausal women. Correlation between sexual function and changes in testosterone concentration have been difficult, if not impossible, to demonstrate, however. The complicated relationship between reproductive hormonal changes and aging has given rise to the possibility that only intracellular testosterone or other androgens are relevant in this context.

Alternatively, other downstream metabolites that give rise to, or are in the pathway related to, intracellular testosterone may be important. Androstenediol (also referred to as hermaphrodiol⁴ because of its mixed estrogenic and androgenic activities) is an intermediate in testosterone biosynthesis and is found in the male testis and the adrenal gland.

It may serve as a biomarker, because it is related to dehydroepiandrosterone (DHEA) production in the adrenal gland. Only DHEA, among other androgens studied, correlates with sexual interest in aging women, although the association is relatively weak.⁵ Other studies, however, have found that sexual function across the menopausal transition might be related to the concentration of endogenous estradiol.^{6,7}

Influence of concurrent diseases and medications

Almost all major medical problems and diseases, and medications for treating them, have a significant impact on sexual function (see a partial list of these problems, diseases, and medications in TABLE 1 and TABLE 2). Discussion of these impacts is, again, beyond the scope of this article; reviews are available elsewhere.^{8,9}

Because these diseases and medications are tremendously prevalent, your approach to any patient who has a problem with sexual functioning

TABLE 1 Female sexual dysfunction can be associated with various medical conditions

THIS CONDITION...	...CAN LEAD TO THIS DYSFUNCTION
Depression	Decreased desire
Diabetes	Impaired arousal and orgasm
Thyroid disease	Decreased desire
Cardiovascular disease	Impaired arousal
Neurologic disease	Impaired arousal and orgasm
Androgen insufficiency	Decreased desire
Estrogen deficiency	Impaired arousal

Source: Modified from Basson R, Schultz WW⁶; Kingsberg SA, Janata JW.⁹

requires careful review of her medical conditions and medications—with particular emphasis on when the sexual symptoms started relative to onset of disease or when the medication was begun. If it appears that the sexual issue and the disease in question, or its treatment, are related temporally, your first step in treatment might be to attempt to modify the disease or the treatment in ways that minimize or eliminate their impact on sexual function (see “Interventions and treatments,” below).

Interventions and treatments

Most time-constrained clinicians would like a quick fix for the sexual dysfunction complaints of postmenopausal women. I assure you: there are no quick fixes. Furthermore, the longer I practice, the less convinced I am that hormonal therapy is the complete answer to these problems. The evolution of my thinking comes from experience as both a trained sexual counselor and a reproductive endocrinologist.

Nevertheless, when a patient complains of a sexual problem to me, I presume that she is likely to have assumed, on some level, that her hormones are at fault. I begin my approach by validating her point of view and, at the least, suggest that her hormones *potentially* are playing a role. I stress, however,

that sexual problems are often, perhaps almost always, multifactorial.

Taking the history

Given the likelihood that the cause of a sexual problem is multifactorial, a careful history is imperative. Such a history cannot, even in the most skilled hands, be completed in 10 minutes. I usually try to divide my questions into several major categories and see where the patient leads the discussion—an approach and taxonomy that were suggested to me years ago by Sandra Leiblum, PhD, an authority on sex therapy; I have used them successfully ever since. Ultimately, many patients require referral to a trained mental health professional who has experience and interest in sexual dysfunction.

These categories of questions (with examples) are:

Biologic and hormonal. Estrogens, androgens, illnesses (TABLE 1), fatigue, and medications (TABLE 2)

Lack of appropriate stimuli. From the partner, personal massager (eg, vibrator), and the partner’s own sexual function

Intrapersonal relationship. Discord and absence of emotional intimacy (ie, the Basson model noted earlier)

Interpersonal development history. Trauma (sexual, physical, medical, and psychological), and negative emotions (anxiety, fear, shame, and guilt)

Contextual. Lack of privacy, safety, emotional rapport

An example: I am amazed at how often my recommendation to a couple who has a small child that they install a lock on their bedroom door, or just put up a door where there is none, is completely “curative.” Such a solution, seemingly obvious, in fact solves the contextual issue of “lack of privacy.” This type of fix, so to speak, is often overlooked.

Expectation of negative outcome. History of disappointing or discomforting encounter.

Providing treatment

The US Food and Drug Administration (FDA) has not approved any drugs specifically to treat female sexual dysfunction, whether for premenopausal or postmenopausal women. Some agents are available outside the United States, however, and others are being developed (see “More options are in development,” below). As such, consider this section an off-label discussion; I’ve provided some key references, but much data from trials remain unpublished.

Estrogens. Prevailing wisdom has it that “if it hurts, most people simply won’t do it.” In the wake of the findings of the Women’s Health Initiative, now 10 years old, we still encounter tremendous fear of hormone therapy—even of local estrogen for vulvovaginal atrophy and, specifically, dyspareunia. (I remain confused by the degree of both undertreatment and absent treatment of this condition.^{7,10})

Absence of a well-estrogenized vagina affects sexual function in many ways. Those effects that are directly related to vulvar and vaginal atrophy include (to name a few):

- Dyspareunia
- Inadequate lubrication
- Elevated pH (which increases the risk of vaginal and urinary tract infection)



- Reduced vaginal relaxation and tissue elasticity
- Reduced size of the vaginal vault.

Other effects of hypoestrogenism on the vaginal vault and, specifically, sexual function include:

- Reduced sensory perception, including vibratory sensation
- Diminished peripheral blood flow (required for the arousal response)
- Altered ability to develop pelvic floor-muscle tension (required to have an orgasm).

With these deleterious effects taken together, it can be easily appreciated how important estrogens are to sexual function.¹¹

Androgens, too, may warrant therapeutic consideration, although understanding of their function remains limited. There is evidence to suggest that testosterone treatment, local (clitoral) and systemic, might increase desire and genital sensitivity and might improve intensity of orgasm.

For example, prospective, randomized, controlled trials of a testosterone patch (Intrinsa) demonstrated a slight but statistically significant increase in the number of what are called satisfying sexual events and improved desire, arousal, orgasm, pleasure, responsiveness, and self-image—while decreasing sexual concerns and distress. These findings were consistent in surgically menopausal women *and* in naturally menopausal women.¹² Further, response to treatment was similar in women taking oral or transdermal estrogen and in women who were not taking estrogen at all. Safety (among a small sample) was demonstrated over as long as 4 years of treatment.¹³ Effects of testosterone patch therapy were usually apparent in 4 to 8 weeks.

Intrinsa failed to garner approval by the FDA because of both long-term safety concerns and the absence of a clearly demonstrable effect; it was,

however, approved for use in surgically menopausal women in nations of the European Union by the European Medicine Agency (EMA). A long-term safety study of testosterone is well under way (Year 4 of 5 years), using a percutaneous testosterone gel for women (Libigel). This study focuses specifically on the risks of breast cancer and cardiovascular disease—the endpoints that were of primary concern to FDA reviewers of Intrinsa in December 2004.

Clinicians in the United States who want to provide testosterone treatment to their postmenopausal patients have no FDA-approved products to offer. Formulated copies of Estratest (esterified estrogens, 1.25 mg, and methyltestosterone, 2.5 mg) and Estratest HS (esterified estrogens, 0.625 mg, and methyltestosterone, 1.25 mg) are available, but the innovator compound was withdrawn from the market by its sponsor. Compounded testosterone therapies remain available but suffer the vagaries of formulation and delivery encountered with all compounded treatments. Consequently, most US clinicians who prescribe testosterone use a reduced dosage of testosterone products that are marketed (and FDA approved) for hypogonadal men.

Knowing that the production rate of testosterone in a premenopausal woman (which is the target rate when treating a postmenopausal woman) is about 10% that of a normal man, efforts to use male products at 10% the dosage have proliferated. These regimens include:

- **Testosterone injection** (testosterone enanthate, testosterone cypionate, or testosterone propionate), 30 to 50 mg intramuscularly every 3 or 4 weeks
- **Testosterone in a hydroalcoholic gel** (Androgel 1%) from a pump—one depression of the pump every other day
- **Testosterone gel** (Testim 1%),

TABLE 2 Some medications put women at risk for sexual dysfunction

PSYCHOTROPIC MEDICATIONS
Antiepileptics
Antipsychotics
Benzodiazepines
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors
Serotonin-neurotransmitter reuptake inhibitors
Tricyclic antidepressants
ANTIHYPERTENSIVES
α-blockers
β-blockers
Diuretics
CARDIOVASCULAR AGENTS
Digoxin
Lipid-lowering agents
HORMONES
Antiandrogens
Estrogens
Gonadotropin-releasing hormone agonists
Oral contraceptives
Progestins
OTHER
Amphetamines
Histamine H ₂ -receptor blockers
Narcotics
Source: Modified from Basson R, Schultz WW ⁶ ; Kingsberg SA, Janata JW. ⁷

approximately 5 or 6 drops a day.

Because some patients grow additional hair at the site of application of a topical testosterone, most of these products are applied to the leg, which many women shave—obviating the risk of localized hirsutism.

Other approaches to treatment

Several central nervous system-active agents already on the market for other indications might have beneficial effects on sexual function as a replacement for a medication in the same therapeutic

class that has deleterious sexual side effects. The antidepressant **bupropion** (Wellbutrin, Wellbutrin SR, Wellbutrin XR), for example, has shown promise for treating arousal and orgasmic dysfunction, and might improve desire. It also appears to have fewer sexual side effects than SSRI agents.¹⁴

Nefazodone (Serzone) appears to have pro-sexual effects on desire¹⁵ and is a perfectly adequate antidepressant (despite recent reports of a risk of associated liver abnormalities).

Bupirone (Buspar) also has pro-sexual effects on desire,¹⁵ and this drug can be substituted for other anxiety-reducing agents in patients who have both anxiety and desire problems. It can also be added to the treatment of depression with bupropion if that therapy creates or augments anxiety.

The common perception that the **phosphodiesterase type 5 (PDE5) inhibitors** (avanafil [Stendra], sildenafil citrate [Viagra], tadalafil [Cialis], and vardenafil [Levitra]) are ineffective in women is not entirely true. Although these agents are ineffective for desire per se, and none are FDA approved for use in women, they may be effective for treating arousal and orgasmic disorders in estrogenized or androgenized postmenopausal women and in women who have an arousal or orgasmic disorder secondary to SSRI-type or serotonin-norepinephrine reuptake inhibitor-type antidepressant therapy or to vascular deficiency.¹⁶

Many otherwise normally functioning women have difficulty achieving orgasm during intercourse only. For them, additional, more direct clitoral stimulation might be required to achieve orgasm outside of intercourse. Oral and manual stimulation are common practices, and personal massagers (vibrators) have entered the mainstream of sexual activity—with approximately one half of

women (and men) between 18 and 60 years of age incorporating a vibrator into solo or partnered sexual activities.¹⁷

More options are in development

A number of compounds are in development for all aspects of female sexual dysfunction, including:

- Nonhormonal therapies gepirone (Ariza, Variza; an anxiolytic and antidepressant) and flibanserin for HSDD
- Androgenic treatments, such as percutaneous testosterone gel (Libigel) for HSDD, intranasal testosterone (Tefina) for anorgasmia, and a DHEA vaginal insert (Vaginorm) for vulvovaginal atrophy and for desire, arousal, orgasm, and pleasure
- Several mixtures of androgens and PDE5 inhibitors for desire and arousal
- The melanocortin agonist bremelanotide for desire, arousal, and orgasm.

Although the FDA approval process has, so far, been complicated—and unsuccessful¹⁸—the future looks promising for approved medical treatments for female sexual dysfunction after menopause. ■

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