Low sexual desire: Appropriate use of testosterone in menopausal women

Low-dose testosterone treatment may be considered for HSDD in carefully selected menopausal women after standard therapies have been tried but symptoms and distress continue. Thorough counseling and close follow-up are essential.

Jan L. Shifren, MD

CASE Midlife woman with low libido causing distress

At her annual gynecologic visit, a 55-year-old woman notes that she has almost no interest in sex. In the past, her libido was good and relations were pleasurable. Since her mid-40s, she has noticed a gradual decline in libido and orgasmic response. Sexual frequency has declined from once or twice weekly to just a few times per month. She has been married for 25 years and describes the relationship as caring and strong. Her husband is healthy with a good libido; his intermittent erectile dysfunction is treated with a phosphodiesterase-5 inhibitor. The patient's low libido is distressing, as the decline in sexual frequency is causing some conflict for the couple. She requests that her testosterone level be checked because she heard that treatment with testosterone cream will solve this problem.

Dr. Shifren is Director, Midlife Women's Health Center, Department of Obstetrics and Gynecology, Massachusetts General Hospital, and Vincent Trustees Professor of Obstetrics, Gynecology and Reproductive Biology; Harvard Medical School, Boston, Massachusetts.

The author reports that she is a consultant for the New England Research Institutes.

Evaluating and treating low libido in menopausal women

Low libido is a very common sexual problem for women. When sexual problems are accompanied by distress, they are classified as sexual dysfunctions. Although ObGyns should discuss sexual concerns at every comprehensive visit, if the patient has no associated distress, treatment is not necessarily indicated. A woman with low libido or anorgasmia who is satisfied with her sex life and is not bothered by these issues does not require any intervention.

Currently, the only indication for testosterone therapy that is supported by clinical trial evidence is low sexual desire with associated distress, known as hypoactive sexual desire disorder (HSDD). Although other sexual problems also commonly occur in menopausal women, such as disorders of orgasm and pain, testosterone is not recommended for these problems. In addition, testosterone is not approved by the US Food and Drug Administration (FDA) for the treatment of female sexual dysfunction.

Routinely inquire about sexual functioning

Ask your patients about sexual concerns at every comprehensive visit. You can easily incorporate into the review of systems a general

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Key points

- Evidence supports low-dose transdermal testosterone in carefully selected menopausal women with HSDD and no other identifiable reason for the sexual dysfunction
- Inform women considering testosterone for HSDD of the limited effectiveness and high placebo responses seen in clinical trials
- Women also must be informed that treatment is off-label (no testosterone formulations are FDA approved for women)
- Review with patients the limitations of compounded medications, and discuss possible adverse effects of androgens. Long-term safety is unknown and, as androgens are converted to estrogens, there may be an effect on breast cancer or cardiovascular risk.

question, such as, "Do you have any sexual concerns?" If the patient does mention a sexual problem, schedule a separate visit (given appointment time constraints) to address it. History and physical examination information you gather during the comprehensive visit will be helpful in the subsequent problem-focused visit.

Taking a thorough history is key when addressing a patient's sexual problems, since identifying possible etiologies guides treatment. Often, the cause of female sexual dysfunction is multifactorial and includes physiologic, psychologic, and relationship issues.

FAST TRACK

Consider the many therapies for low sexual desire prior to initiating a testosterone trial; this should be considered for HSDD only if the disorder persists after addressing all other possible contributing factors

Explore potential causes, recommend standard therapies

Common causes of low libido in menopausal women include vasomotor symptoms, insomnia, urinary incontinence, cancer or another major medical problem, weight gain, poor body image, genitourinary syndrome of menopause (GSM) with dyspareunia, fatigue, stress, aging, relationship duration, lack of novelty, relationship conflict, and a partner's sexual problems. Other common etiologies include depression, anxiety, and substance use disorders, as well as medications used to treat these disorders, including selective serotonin reuptake inhibitors (SSRIs).

There are many effective therapies for low sexual desire to consider prior to initiating a trial of testosterone, which should be considered for HSDD only if the disorder persists after addressing all other possible contributing factors (**TABLE 1**, page 28).

Sex therapy, for example, provides information on sexual functioning and helps improve communication and mutual pleasure and satisfaction. Strongly encourage—if not require—a consultation with a sex therapist before prescribing testosterone for low libido. Any testosterone-derived improvement in sexual functioning will be enhanced by improved communication and additional strategies to achieve mutual pleasure.

Hormone therapy. Vasomotor symptoms, with their associated sleep disruption, fatigue, and reduced quality of life (QOL), often adversely impact sexual desire. Estrogen therapy does not appear to improve libido in otherwise asymptomatic women; however, in women with bothersome vasomotor symptoms treated with estrogen, sexual interest may increase as a result of improved sleep, fatigue, and overall QOL. The benefits of systemic hormone therapy generally outweigh its risks for most healthy women younger than age 60 who have bothersome hot flashes and night sweats.[1]

Nonhormonal and other therapies. GSM with dyspareunia is a principal cause of sexual dysfunction in older women.[2] Many safe and effective treatments are available, including low-dose vaginal estrogen therapy, nonhormonal moisturizers and lubricants, ospemifene, vaginal dehydroepiandrosterone, and pelvic floor physical therapy.[3] Urinary incontinence commonly occurs in midlife women and contributes to low libido.[4]

Lifestyle approaches. Address fatigue and stress by having the patient adjust her work and sleep schedules, obtain help with housework and meals, and engage in mind-body interventions, counseling, or yoga. Sexual function may benefit from yoga practice, likely as a result of the patient experiencing reduced stress and enhanced body image. Improving overall health and body image with regular exercise, optimal diet, and weight management may contribute to a more satisfying sex life after the onset of menopause.

Relationship refresh. Women's sexual interest often declines with relationship duration, and both men and women who are in

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TABLE 1 Common causes of low sexual desire in menopausal women and interventions to consider prior to a trial of testosterone therapy

Common causes of low sexual desire	Interventions
Physical factors	
Vasomotor symptoms	Lifestyle changes, hormone therapy
Dyspareunia, GSM	Lubricants, moisturizers, low-dose vaginal estrogen therapy, vaginal DHEA, ospemifene, pelvic floor PT
Incontinence	Pelvic floor PT, devices, medications, surgery
Weight gain, poor body image	Dietary changes, exercise
Major medical problem, cancer	Treatment, support
Pelvic pain	Treatment
Psychosocial factors	
Fatigue	Lifestyle interventions
Stress	Mind-body interventions, counseling, yoga, exercise
Depression	Psychotherapy, medications
Anxiety	Psychotherapy, medications
Substance use disorders	Treatment
Abuse (current, past)	Psychotherapy, counseling, support
Medications (eg, SSRIs)	Adjust medications (eg, bupropion trial), psychopharmacology consult
Relationship factors	
Relationship conflict	Counseling, sex therapy
Limited quality, novelty	Sex therapy, devices, films, novel experiences, vacations, date nights, counseling
Partner's sexual dysfunction	Treatment, sex therapy

Abbreviations: DHEA, dehydroepiandrosterone; GSM, genitourinary syndrome of menopause; PT, physical therapy; SSRIs, selective serotonin reuptake inhibitors.

new relationships generally have increased libido, affirming the importance of novelty over the long term. Couples will benefit from "date nights," weekends away from home, and trying novel positions, locations, and times for sex. Couple's counseling may address relationship conflict.

Expert referral. Depression, anxiety, and substance use disorders are prevalent in menopausal women and contribute to sexual dysfunction. Effective therapy is available, although some pharmacologic treatments (including SSRIs) may be an additional cause of sexual dysfunction. In addition to recommending appropriate counseling and support, referring the patient to a psychopharmacologist with expertise in managing sexual adverse effects of medications may optimize care.

CASE Sexual function improves, but patient still wants to try testosterone

The patient returns for follow-up visits scheduled specifically to address her sexual concerns. Sex is more comfortable and pleasurable since initiating low-dose vaginal estrogen therapy. Having been on an SSRI since her mid-40s for mild depression, the patient switched to bupropion and notes improved libido and orgasmic response. She is exercising more regularly and working with a nutritionist to address a 15-lb weight gain after menopause. The couple saw a sex therapist and is communicating better about sex with more novelty in their repertoire.

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They are enjoying a regular date night. Although the patient's sex life has improved with these interventions, she is still very interested in trying testosterone.

Testosterone's effects on HSDD in menopausal women

After addressing the many factors that contribute to sexual disinterest, a trial of testosterone may be appropriate for a menopausal woman who continues to experience low libido with associated distress.

Testosterone levels decrease with aging in both men and women. Although testosterone levels decline by approximately 50% with bilateral oophorectomy, there is no decline in androgen levels with natural menopause.[5] Testosterone circulates tightly bound to sex hormone–binding globulin (SHBG), so free or active testosterone will be reduced by oral estrogens, which increase SHBG levels.[6] As most menopausal women will have a low testosterone level due to aging, measuring the testosterone level does not provide information about the etiology of the sexual problem.

Although some studies have identified an association between endogenous androgen levels and sexual function, the associations are modest and are of uncertain clinical significance.[7-9] Not surprisingly, other factors, such as physical and psychologic health and the quality of the relationship, often are reported as more important predictors of sexual satisfaction than androgen levels.[10]

While endogenous testosterone levels may not correlate with sexual function, clinical trials of carefully selected menopausal women with HSDD have shown that androgen treatment generally results in improved sexual function.[11] Studies demonstrate substantial improvements in sexual desire, orgasmic response, and frequency in menopausal women treated with high doses of intramuscular testosterone, which result in supraphysiologic androgen levels.[12,13] While it is interesting that women with testosterone levels in the male low range have sizeable increases in sexual desire and response, long-term use of high-dose testosterone would result in unacceptable androgenic adverse effects and risks.

Testosterone in low doses. It is more relevant to consider the impact on female sexual function of low doses of testosterone, which raise the reduced testosterone levels seen in older women to the higher levels seen in reproductive-aged women.

A series of double-blind, multicenter, randomized, placebo-controlled trials in menopausal women with HSDD examined the impact on sexual function of a transdermal testosterone patch (300 µg) that increased blood testosterone levels to the upper limit of normal for young women.[14-17] In these studies, compared with placebo, women using testosterone reported significant improvements in sexual desire, arousal, orgasmic response, frequency, and sexually related distress. Findings were consistent in surgically and naturally menopausal women, with and without the use of concurrent estrogen therapy. Improvements were clinically limited, however. On average, testosterone-treated women experienced 1 to 1.5 additional satisfying sexual events in a 4-week period compared with those treated with placebo. The percentage of women reporting a clinically meaningful benefit from treatment was significantly greater in women treated with testosterone (52%) compared with the placebo-treated women (31%).[18] An appreciable placebo response was seen, typical of most studies of therapies for sexual dysfunction.

Safety concerns

Potential risks of testosterone treatment include acne, hirsutism, irreversible deepening of the voice, and adverse changes in lipids and liver function (**TABLE 2**).[19] Adverse effects are dose dependent and are unlikely with physiologically dosed testosterone.

A 1-year study of testosterone patches in approximately 800 menopausal women with HSDD (with a subgroup of women followed for an additional year) provides the most comprehensive safety data available.[17] Unwanted hair growth occurred more often in women receiving testosterone, without significant differences in blood biochemistry,

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hematologic parameters, carbohydrate metabolism, or lipids. Breast cancer was diagnosed in more women receiving testosterone than placebo. Although this finding may have been due to chance, the investigators concluded that long-term effects of testosterone treatment remain uncertain.

The FDA reviewed the data from the testosterone patch studies and determined that testosterone patches were effective for the treatment of HSDD in menopausal women, but more information was needed on long-term safety before approval could be granted. Another company then developed a testosterone gel product that produced similar blood levels as the testosterone patch. It was presumed that there would be similar efficacy; the principal goal of these studies was to examine long-term safety, particularly with respect to breast cancer and cardiovascular disease. Unexpectedly, although it raised testosterone blood levels to the upper limit of normal for young women, the testosterone gel product was no more effective than placebo.[20] The clinical trial was ended, with safety data never published.

Availability of testosterone formulations

Currently, no androgen therapies are FDA approved for the treatment of female sexual dysfunction. Although the best evidence regarding testosterone efficacy and safety involves the use of testosterone patches (300 µg), appropriately dosed for women, these patches are not currently available. FDA-approved testosterone patches are approved for the treatment of male hypogonadism, but use of these patches in women is not recommended since they would result in very high circulating testosterone levels.

Testosterone subcutaneous implants, pellets, and intramuscular injections also are not recommended for women because of the risk of excessive dosing. Small trials of menopausal women taking oral estrogen with low sexual desire found that oral formulations of testosterone improved libido in this study population.[21] The combination of esterified estrogens (0.625 mg) and methyltestosterone (1.25 mg) is available as a compounded, non-FDA approved product. Oral androgen formulations generally are not advised, due to potential adverse effects on lipids and liver function.[22]

Compounded testosterone products. Ointments and creams may be compounded by prescription (**TABLE 3**, page 32). Product purity, dose, bioavailability, and quality typically are untested, and substantial variability exists between formulations and batches.[23] Applying 1% testosterone cream or gel (0.5 g/day) topically to the thigh or lower abdomen should increase the low testosterone levels typically seen in menopausal women to the higher levels seen in younger women.[24,25] Application to the vulva or vagina is not advised, as it may cause local irritation and is unpredictably absorbed.

Adapting male testosterone products. High-quality FDA-approved testosterone gel formulations are available for male hypogonadism. However, since women have

TABLE 2 Adverse effects and risks of testosterone treatment in menopausal women

Adverse effects
• Hirsutism
• Acne
• Application site reaction (skin irritation, local hair growth)
Risks with compounded products
• Batch-to-batch variability
• Limited or no testing of product purity and quality
• Variable absorption and bioavailability
• Inadvertent supraphysiologic dosing
Risks with supraphysiologic dosing
• Virilization
• Liver dysfunction
• Lowering of HDL cholesterol
• Psychologic changes
Potential risks with long-term use
• Breast cancer
• Cardiovascular disease

Abbreviation: HDL, high-density lipoprotein.

FAST TRACK

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TABLE 3 Testosterone treatment options for menopausal women

Topical compounded testosterone
1% Testosterone compounded cream or gel
Apply 0.5 g topically to thigh or low abdomen daily
Monitor testosterone level approximately 2 weeks after receiving a new tube or jar of compounded cream or gel to confirm that the testosterone level remains within the normal range for reproductive-aged women
Dose-adjusted topical testosterone product approved for men
1% Testosterone gel (Testim)
Apply 3–4 drops topically to thigh or low abdomen daily (warm gel slightly before use)
Re-cap tube tightly after use
Reduce dose as needed to ensure 1 tube lasts for 10 days
Monitor testosterone level approximately every 3–6 months to confirm testosterone level remains within the normal range for reproductive-aged women
Testosterone formulations not recommended
Due to risk of supraphysiologic dosing
• Testosterone injections
• Testosterone implants or subcutaneous pellets
Due to adverse effects associated with oral administration
• Oral methyltestosterone

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Women who elect to use transdermal testosterone therapy should be seen at 8 to 12 weeks to assess treatment response. Regular follow-up visits are required to assess response, satisfaction, and adverse effects.

approximately one-tenth the circulating testosterone levels of men, supraphysiologic dosing is a risk when these products are prescribed for women. Most testosterone products approved for men are provided in pumps or packets, and they are difficult to dose-adjust for women. Applying one-tenth the male dose of 1% testosterone gel (Testim), which comes in a resealable unit-dose tube, is an alternative to compounding. For men, the dose is 1 tube per day, so women should make 1 tube last for 10 days by using 3 to 4 drops of testosterone gel per day. Close physical contact must be avoided immediately after application, as topical hormone creams and gels are easily transferred to others. The safety and efficacy of compounded or dose-adjusted male testosterone products used in women are unknown.

Follow treated women closely. Women who elect to use transdermal testosterone therapy should be seen at 8 to 12 weeks to assess treatment response. Regular follow-up visits are required to assess response, satisfaction, and adverse effects, including acne and hirsutism. Since there may be little correlation between serum testosterone levels and the prescribed dose of a compounded testosterone product, testosterone levels should be measured regularly as a safety measure. The goal is to keep serum testosterone concentrations within the normal range for reproductive-aged women to reduce the likelihood of adverse effects. Testosterone levels should not be tested as an efficacy measure, however, as there is no testosterone level that will assure a satisfactory sex life.

CASE Conclusion

After a thorough discussion of high placebo response rates, potential adverse effects, unknown long-term risks, and off-label nature of testosterone use, the patient elects a trial of compounded 1% testosterone cream. Her clinician informs her of the limitations of compounded formulations and the need for regular

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testing of testosterone levels to prevent supraphysiologic dosing. At a follow-up visit 8 weeks later, she reports improved sexual desire and elects to continue treatment and monitoring. After using testosterone for 2 years, the patient is uncertain that she still is experiencing a significant benefit, stops testosterone treatment, and remains satisfied with her sex life.

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