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NAMS Practice Pearl

Testosterone use for hypoactive sexual desire disorder in postmenopausal women

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Testosterone is an important evidence-based therapy for hypoactive sexual desire disorder (HSDD) in postmenopausal women. Clinical practice guidelines based on the most comprehensive meta-analysis of benefits and risks of testosterone therapy to date state that the sole evidence-based indication for testosterone therapy is HSDD in postmenopausal women. The guidelines also provide recommendations regarding identification of patients, dosing, monitoring, and follow-up. This *Practice Pearl* will discuss evidence-based testosterone therapy for management of HSDD in postmenopausal women.

DEFINITION, PREVALENCE, AND ASSESSMENT OF HYPOACTIVE SEXUAL DESIRE DISORDER

Decreased sexual desire with distress has an estimated US prevalence of 12% in women aged 45 to 64 years.[1] *Hypoactive sexual desire disorder* (HSDD) is defined as "persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity with marked distress or interpersonal difficulty."[2] A thorough clinical assessment should involve identification, modification, and management of biological, psychological, sociocultural, and interpersonal contributing factors before testosterone therapy is considered.[3] Evaluation includes asking about all aspects of sexual functioning, including arousal, orgasm, and pain, as well as targeted physical and gynecologic examinations and laboratory testing when indicated.

ANDROGENS AND SEXUAL FUNCTION

Testosterone modulates sexual behavior.[4] Testosterone and its precursors are synthesized by the ovaries and adrenal glands, with about 50% of circulating testosterone produced by peripheral conversion of androgen precursors. Androgen levels decline with age and drop abruptly after bilateral oophorectomy. Although serum testosterone levels do not correlate with the presence or absence of HSDD or its severity, there is a correlation between testosterone concentration during therapy and improvement in sexual desire.

EFFICACY AND SAFETY

Transdermal testosterone dosed in a normal premenopause range improves sexual desire and reduces sexually associated personal distress in naturally and surgically menopausal women with HSDD, with and without concurrent estrogen and progestogen therapy.[5] It also improves the frequency of satisfying sexual events, arousal, orgasm frequency, pleasure, responsiveness, and self-image. Transdermal testosterone as a patch releasing 300 μg of testosterone per day or a manufactured cream delivering 5 mg testosterone in 0.5 mL base (10 mg/mL) daily results in levels within the normal premenopause range.

Transdermal testosterone administered in physiologic doses (300 μg/d) for 24 weeks in clinical trials resulted in an increase in acne and hair growth, without other androgenic effects seen with supraphysiologic levels (voice deepening and alopecia).[6,7] Lipid profiles, carbohydrate metabolism, cardiometabolic markers, and renal and liver functions were unaffected.[7] Mammographic breast density did not change with transdermal testosterone, but trials were insufficient to assess long-term breast cancer risk. No serious adverse events were seen with physiologic use, but there is a lack of long-term safety data.

WHOM TO TREAT

Transdermal testosterone is recommended for postmenopausal women with HSDD not related to modifiable factors or comorbidities. Limited data also support use in late reproductive-aged premenopausal women, and expert opinion suggests that management of women with premature and early menopause should be the same as for postmenopausal women presenting with HSDD.[4]

FORMULATION AND INITIATING THERAPY

Clinicians should provide and obtain informed consent, including a comprehensive discussion of off-label use, as well as benefits and risks. Testosterone formulations that deliver a therapeutic dose appropriate for women have generally not been approved by national drug regulatory authorities, except in Australia, where a transdermal 1% testosterone cream is available by prescription.[4] When an approved formulation for women is not available, it is reasonable to prescribe off-label an approved formulation for men at approximately one-tenth

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of the dose for men.[8] Compounded products cannot be recommended because of lack of efficacy and safety data.[9]

Transdermal therapy provides the most physiologic form of replacement; intramuscular injections and subcutaneous implants should be avoided because they result in supraphysiologic levels, and oral preparations are not recommended because of possible adverse lipid effects, including reduction in high-density lipoprotein cholesterol and increase in low-density lipoprotein cholesterol.[4]

DOSING AND ADMINISTRATION

Dosing should be targeted to achieve total testosterone concentrations in the physiologic premenopause range. The starting daily dose for women should be one-tenth of a 1% testosterone tube or packet approved for daily use in men, which typically equates to three tubes or packets per month. Transdermal preparations should be applied to the back of the calf, upper outer thigh, or buttock.[4] Patients should be counseled about potential transference from the application site to the skin of young children, female partners, and pets, whereas the risk of exposure to a male partner is minimal.

RESPONSE TO THERAPY

Patients should be monitored for clinical response to treatment, including increase in sexual desire and decrease in personal distress.[8] Women typically note an improvement in their sexual function 6 to 8 weeks after initiating treatment, although it may occur as early as 4 weeks, with maximal effects on sexual desire and satisfactory sexual events typically occurring at about 12 weeks.[4] Reduction in sexually associated personal distress occurs at about 4 weeks, with a continued downward trend over 6 months. Treatment should be discontinued after 6 months of lack of clinically meaningful improvement, and other causes and treatments for HSDD should be reexplored. If there is improvement, women should continue treatment for 6 to 12 months and then consider taking a drug holiday to see whether treatment is still required. Ongoing therapy may be needed to maintain the improvement in HSDD.

MONITORING

Total testosterone, rather than free or bioavailable testosterone or free androgen index, is the best available measure.[4,8] Total testosterone should not be used to diagnose HSDD but rather to serve as a baseline and to exclude women with midrange to high baseline concentrations. Sex hormone binding globulin (SHBG) also should be measured, because women with levels above the normal range are less likely to benefit from therapy. Total testosterone levels should be monitored to maintain concentrations in the physiologic premenopause range and to ensure that the total testosterone does not significantly exceed the upper limit of the reference range (generally, 27-38.6 ng/dL).[4]

Total testosterone levels should be assessed 3 to 6 weeks after initiating therapy. If the dose is increased, based on clinical response and blood level, total testosterone should be repeated within 6 weeks. When testosterone levels are maintained in the premenopause range, androgenic adverse events are rare. If the level is supraphysiologic, even in the absence of androgenic adverse events, the dose should be reduced, with a repeat blood test after 2 to 3 weeks. Serum testosterone concentrations should be monitored every 4 to 6 months once stable levels are achieved. Increasing the dose and total testosterone levels beyond the physiologic range to overcome elevated SHBG is not recommended, based on evidence on androgen metabolism and short- and long-term safety.[4]

Patients should be assessed for signs of androgen excess; if they occur, the dose should be decreased. Measurement of baseline liver function and a fasting lipid profile is recommended. Guidelines endorse breast and pelvic examinations as clinically indicated; mammography in accordance with country-specific guidance; evaluation of abnormal bleeding; monitoring of lipid profile, liver function tests, and complete blood count semiannually for 1 year and annually each year thereafter.

PEARLS

Transdermal testosterone is recommended for postmenopausal women with HSDD not primarily related to modifiable factors or comorbidities. Clinicians can use the Global Position Statement[8] and the International Society for the Study of Women's Sexual Health clinical practice guideline for more detailed treatment guidance.[4]

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