Transdermal Testosterone (Off-Label) for Hypoactive Sexual Desire Disorder (HSDD) in Postmenopausal Females Summary Guidance March 2025

VA Pharmacy Benefits Management Services and National Formulary Committee

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing.

Objective

Due to increased field interest and questions on the topic, this document provides a summary and clinical guidance focusing on the off-label use of transdermal testosterone in **postmenopausal women with hypoactive sexual desire disorder (HSDD)**, a subset of female sexual dysfunction. *Off-label use of testosterone in women for other indications including HSDD in premenopausal women, improvement in bone mineral density, or mood or cognition enhancement is not recommended due to lack of evidence of benefit.*

Background

There are no FDA approved testosterone products indicated for use in women in the U.S. (or outside of the U.S. except for Australia). FDA declined to approve a transdermal testosterone patch in 2004 due to lack of long term safety data. Clinical studies evaluating transdermal testosterone for the treatment of HSDD in postmenopausal women used doses of approximately 1/10th of the FDA approved products indicated for males, aiming for physiologic premenopausal female hormonal range. Despite uncertain benefits and risks, off-label use of testosterone is increasingly being requested for the treatment of HSDD in postmenopausal women.

In 2019, a global consensus Position Statement on testosterone therapy for women was developed to provide clear guidance on appropriate use of testosterone in the absence of regulatory approvals and problematic dosage forms/need for dose modifications. In 2023, the Menopause Society (formerly known as the North American Menopause Society) published a Practice Pearl summarizing the evidence base and provided practical guidance for use of testosterone in postmenopausal HSDD. International Society for the Study of Women's Sexual Health (ISSWSH) published clinical practice guidelines in 2021.

Key Points:

- **Postmenopausal women (natural or surgically induced)**
  - Most evidence available shows a benefit of transdermal testosterone for the treatment of HSDD in postmenopausal women.
  - Testosterone is generally not recommended in premenopausal women at this time due to insufficient evidence of improvement in symptoms of HSDD.

- **HSDD**
  - Diagnosis of HSDD is characterized as the ***persistent or recurrent*** deficiency or absence of desire for sexual activity ***with marked personal distress*** that is not otherwise accounted for by a general medical or psychiatric condition (Diagnostic and Statistical Manual of Mental Disorders [DSM] IV-TR).
  - HSDD may be primary or secondary; lifelong or acquired; or generalized or situational.
  - Many factors may negatively impact sexual functioning in postmenopausal women including psychosocial, medical conditions, and certain medications.

- Of note, DSM-5 merged female sexual arousal disorder with HSDD into a single category of female sexual interest/arousal disorder (FSAID). Even though there may be overlap, HSDD is a distinct disorder.
- Randomized controlled trials evaluated testosterone in patients with HSDD specifically.

- **Efficacy summary**
  - A 2019 meta-analysis and systematic review on the use of testosterone in women evaluated data from 8,480 participants in 36 randomized controlled trials. Twelve trials studied transdermal testosterone (patch, cream, or gel). Compared to placebo (or other comparator such as estrogen +/- progesterone), testosterone was associated with an overall increase in frequency of satisfying sexual events (~1 additional event per month), reduced personal sexual distress, and augmented sexual desire, arousal, orgasm, pleasure, responsiveness, and self-image in postmenopausal (natural or surgical) women.

- **Safety and adverse effects**
  - Transdermal testosterone administered in physiologic doses may be associated with androgenic effects of increased acne and facial and body hair growth.
  - Data from randomized controlled trials showed no change in breast density or adverse effects on cardiometabolic markers with transdermal testosterone limited to premenopausal physiologic levels (limited to 24 months' duration).
  - Long-term safety data (particularly related to cardiovascular outcomes and breast cancer) are limited and inconclusive.
  - Most studies excluded patients at high cardiometabolic risk.
  - Supraphysiologic testosterone may be associated with dyslipidemia, weight gain, virilization, androgenic alopecia psychologic adverse effects, etc.

- **Dosing and administration**
  - The starting dose for women should be $1/10^{th}$ of a 1% testosterone cream or gel approved for daily use in men. For example, testosterone gel 1% 5 gm tube contains 50 mg of testosterone. The dose for women would be 5 mg (0.5 ml), increasing to 10 mg (1 ml) if needed. A syringe may be provided to patients to help measure the correct dose.
  - Medication should be applied to the back of the calf, upper outer thigh, or buttock. Patients should be counseled about potential transference of drug to the skin of children, pets, female partners, resulting in unintended drug exposure.
  - Injections, pellets, and oral formulations of testosterone are not recommended due to the potential for supraphysiologic levels and risk of adverse effects.

- **VA dispensing guidance**
  - Unit dose tubes of 1% testosterone gel (50 mg testosterone per 5 grams of gel) are available and preferable over unit dose packets. A 5 mg dose would be $1/10^{th}$ of the tube, ~0.5 ml. One tube should last about 10 days.
  - Federal law prohibits dispensing of controlled substances, including testosterone, to no more than 180 days' supply. Unit dose tubes are packaged in boxes of 30. The consolidated mail outpatient pharmacy (CMOP) is unable to break boxes of 30 tubes. VA pharmacies will need to fill testosterone prescriptions for partial boxes at the facility level to limit to no longer than 180 days' supply (e.g., 3 tubes for 30 days, etc.).

- **Monitoring and duration of therapy**
  - Baseline labs: total testosterone level, sex hormone binding globulin (SHBG) level, liver function tests, lipid panel (and other labs as indicated)
  - Testosterone monitoring: Testosterone levels are not used to diagnose HSDD and do not predict treatment efficacy. Total testosterone levels should be used to maintain concentrations in the physiologic premenopausal range and ensure that total testosterone does not exceed these levels (according to local laboratory reference ranges). Baseline mid-range to high total testosterone level indicates symptoms are likely unrelated to testosterone, and therapy should not be initiated. Total testosterone levels should be checked 3 to 6 weeks after starting treatment and after any dose adjustments. Once stable, monitor testosterone every 4 to 6 months.
  - SHBG: Elevated baseline SHBG is typically indicative of nonresponders to testosterone; however, SHBG may be elevated in patients on oral estrogens, thyroid replacement, and untreated hyperthyroidism. For patients with an elevated SHBG who have an unmodifiable risk factor (e.g., thyroid replacement therapy), a trial of testosterone therapy may still be considered. Increasing the dose and total testosterone levels beyond the physiologic range to overcome the elevated SHBG is not recommended.
  - Other monitoring: Additional periodic lab testing (aside from regular testosterone monitoring as above), breast exam, mammography, and pelvic exams should be performed as otherwise clinically indicated.
  - Adverse effects: Signs and symptoms of androgen excess should be monitored.
  - Response to treatment: Noticeable improvements are typically seen within 6 to 8 weeks of treatment. Treatment should be discontinued after 6 months if there is no meaningful improvement. Consider a drug holiday after 6 to 12 months to determine if treatment is still required.

References

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