

Testosterone for Treating Female Sexual Dysfunction

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Abstract: Testosterone levels vary throughout a woman's reproductive life, reaching their lowest level following menopause, and their nadir at about age 60, when they experience higher levels of sexual dysfunction. Testosterone improved the frequency of sexually satisfying events, desire, arousal, and orgasm in several randomized, controlled studies of surgically and naturally postmenopausal women. Available evidence from large cohort and registry studies does not show potentially concerning cardiovascular or breast safety signals with physiological levels of testosterone. Although no female testosterone products are currently approved in most of the world, one-tenth of the male dose can enhance female sexual function.

Key Words: female sexual dysfunction, menopause, testosterone, safety, vagina

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Up to one-half of women worldwide and in the United States have been reported to have sexual problems,^{1–3} including issues with sexual desire, arousal, lubrication, orgasm, sexual satisfaction, and pain, occurring in 21% to 51% of women.^{1,4} Of those who reported a problem, 36% have been found to have severe distress, and 25% a lifetime prevalence with severe distress.² In a sample of 952 premenopausal and naturally or surgically menopausal women who had a sexual partner, the prevalence of low sexual desire was reported as 24% to 36%, with 14% of women aged 20 to 49 and 26% of postmenopausal women of the same age having hypoactive sexual desire disorder (HSDD).⁵

While treatments for female sexual dysfunction (FSD) are limited, testosterone is widely accepted as a modulator of women's sexual desire and is most commonly prescribed for treating FSD in combination with estrogens for postmenopausal women. Use of testosterone for treating FSD is rooted in scientific evidence as previously reviewed.⁶ The normal female sexual response starts in the brain and is mediated by a complex interaction of neurotransmitters,

such as dopamine and norepinephrine, and hormones, including estrogens and testosterone.⁶ Animal models have also shown the complex interplay of testosterone with dopaminergic pathways in the brain.

In women, we know that testosterone decreases with age, and reduced testosterone by several causes has been shown to reduce sexual desire/arousal, receptivity and pleasure.⁶ This circulating testosterone and the presence of androgen receptors throughout a woman's body point to its physiological role in sexual function, as well as cardiovascular, cognitive, and musculoskeletal health.^{7,8} As discussed elsewhere, testosterone levels in women are about one-tenth of those in men (mean: 435 to 600 ng/dL),^{7,9–11} and rise and fall with the menstrual cycle throughout a woman's reproductive life.⁷ In premenopausal women, endogenous testosterone averages ~35 ng/dL, ranging from 27 to 57.5 ng/dL, and peaking in their 20s to 40s.^{7,10} By age 50, as women approach menopause, testosterone falls to about 50% of their highest levels, averaging 25 ng/dL, and continues to decline progressively with age, reaching a nadir at about age 60.^{7,9}

Although testosterone is widely used by clinicians to treat FSD, testosterone is not approved by the US Food and Drug Administration (FDA) for such an indication in women, compared with a plethora of such products approved for men. In fact, the only country with an approved testosterone product for women is Australia (Androfeme 1; Lawley Pharmaceuticals Pty Ltd, West Leederville, Australia).¹² Despite the lack of approved testosterone products for women, guidelines and consensus documents from the International Society for the Study of Women's Sexual Health (ISSWSH) and the International Menopause Society (IMS) have been developed based on the significant amount of relevant evidence in the medical literature, consensus of many women's health clinicians, and evidence of its clinical use for HSDD.^{13–15} Recent analysis of a US claims database (TriNetX Diamond) containing over 33,000 women with HSDD found that 850 of these women received a testosterone prescription,¹⁶ although such data may be biased by lack of insurance coverage for testosterone in women. Nonetheless, up to 2015, the rate of testosterone use for HSDD has grown linearly, and prescriptions have varied highly by duration, route of delivery, and coadministration with estrogen.¹⁶ The greatest increase in testosterone use for HSDD has been in women aged 41 to 55 years.¹⁶

Here we review physiological and clinical evidence supporting the use of testosterone to treat FSD.

VAGINAL EFFECTS OF TESTOSTERONE

Androgen receptors are found in the mucosa, submucosa, stroma, smooth muscle, and vascular endothelium of the vagina.^{17,18} Although the density of these vaginal receptors declines with age and postmenopausal status, testosterone administration increases their expression.^{7,17,18}

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While many would prefer to describe these tissues as the vaginal epithelium, subepithelium, stroma, etc., collective evidence shows that androgens help maintain tissue structure and function of the vagina, bladder/urethra, and clitoris/labia/vestibule.⁷ With insufficient levels of sex steroids, the genitourinary organs essentially return to prepubertal-like structure and function.⁷

A direct physiological response of testosterone was reported in a small, observational study of women with FSD (N = 81). When transdermal testosterone (2% gel, 300 µg/day) was given alone (n = 23) or with local estrogens (n = 9), improvements were observed on clitoral blood flow and sexual function [total Female Sexual Function Index (FSFI) score, and FSFI desire, pain, arousal, lubrication, and/or orgasm].¹⁹ Increases in clitoral blood flow were also significantly greater than those in women taking estrogens alone (n = 12).¹⁹ A small (n = 10), randomized, double-blind, crossover, placebo-controlled trial in postmenopausal women without sexual dysfunction also showed a significant effect of methyltestosterone (5 mg) on vaginal pulse amplitude, which significantly correlated ($r = -0.6$) with mental and physical sexual arousal scales.²⁰

Effects of testosterone on the vagina have also been reported clinically. In an earlier, larger study, Barrett-Connor reported similar vaginal dryness for surgically menopausal women (N = 311) taking esterified estrogens with methyltestosterone or conjugated estrogens alone, with no significant difference in the androgenic side effect of hirsutism, in a 2-year, double-blind trial.²¹ A more recent, smaller randomized, controlled, 12-week study assessed vaginal cream with testosterone propionate, conjugated estrogens, or polyacrylic acid versus vaginal lubricant in 80 postmenopausal women.^{22–24} Vaginal testosterone cream significantly improved the vaginal health score and lactobacilli in the vagina, and increased the proportion of women with a vaginal pH ≤ 5 , without affecting the vaginal maturation index.²³ In other reports of the same study, this vaginal testosterone cream improved sexual function without androgenic, metabolic, or endometrial effects.^{23,24} Direct vaginal effects were also shown from a retrospective chart review of 50 premenopausal women experiencing vestibular pain while using combined hormonal contraceptives. When they applied a compounded preparation of topical estradiol 0.03% and testosterone 0.01% to the vestibule twice daily, their vestibular pain decreased by almost 75%.²⁵

While to our knowledge, no vaginal testosterone products are being developed, use of vaginal testosterone in breast cancer patients may be a safe and effective alternative to local vaginal estrogens. Some studies of vaginal testosterone use have been reported in breast cancer survivors using aromatase inhibitors (AIs). In a randomized, double-blind, placebo-controlled trial, intravaginal testosterone cream (300 µg/mL) in postmenopausal women with invasive breast cancer and vulvar-vaginal symptoms taking an AI (N = 37), vaginal dryness, dyspareunia, and vaginal surface thickness improved after 26 weeks of treatment.²⁶ Sexual satisfaction as measured by the FSFI, and sexual concerns and sexual responsiveness on the Profile of Female Sexual Function also improved, and serum levels of sex steroids in the testosterone group were the same as those with placebo at week 26.²⁶ In another study, in early-stage breast cancer patients taking AIs (N = 69), vaginal testosterone (0.5 mg of 1% cream daily for 2 wk, then 0.5 mg 3 times a week) or a vaginal estradiol ring (7.5 µg/d) for 12

weeks, both treatments improved vaginal atrophy (including improvements in vaginal rugae, pallor, petechiae, elasticity, and dryness), as well as, sexual interest and dysfunction.²⁷ Systemic testosterone levels were elevated in more women using the local testosterone (24% of patients) than the vaginal estradiol ring (11%). A smaller pilot study of breast cancer patients taking AIs and having symptoms of sexual dysfunction, showed that daily vaginal testosterone cream (300 µg) for 4 weeks improved FSFI domains of pain, lubrication, desire, arousal, orgasm, and satisfaction.²⁸ When 300 or 150 µg vaginal testosterone was given daily for 4 weeks to women with breast cancer taking AIs (N = 20) in a phase 1/2 study, their vaginal symptoms, including vaginal dryness and dyspareunia improved from baseline.²⁹ Serum estradiol levels in these women were the same pretreatment and post-treatment and between doses, and were nondetectable in all except 2 patients, in which they were ~ 7 pg/mL; median serum testosterone levels were 15.5 ng/dL pretreatment and 21.5 ng/dL after 4 weeks of testosterone.²⁹

Since testosterone is aromatized to estradiol, one might expect serum levels of estradiol to increase given the increase in systemic testosterone levels. Another option to treat vaginal symptoms in breast cancer patients taking AIs that may keep systemic sex steroids low is dehydroepiandrosterone [DHEA; Intrarosa (prasterone), Endoceutics, Quebec, Canada and Millicent Pharma, Dundalk, Ireland]. With vaginal application of DHEA, it is converted to estradiol and testosterone intracellularly, so that systemic absorption of hormones can be avoided.

CLINICAL USE OF SYSTEMIC TESTOSTERONE FOR FSD

Formulations and exposure

Early studies examined testosterone in women given as a pellet, implant³⁰ or injection.³¹ Since testosterone implants and intramuscular and oral formulations can result in wide variations of serum testosterone concentrations, transdermal formulations of testosterone were later developed for a more consistent testosterone level, and to avoid first-pass liver metabolism. Currently, transdermal delivery of testosterone results in the most physiological route of administration for women.³² Transdermal testosterone options that have been studied include a patch (releasing 300 µg of testosterone/day) or a cream [delivering 5 mg testosterone in 0.5 mL (10 mg/mL) a day], the latter of which is the cream approved in Australia for use in menopausal women. Since there is not an approved testosterone therapy for treating postmenopausal women in the United States, physicians are prescribing testosterone products formulated for men off-label (usually at one-tenth of the male dose) or pharmacist-compounded testosterone (1%), both of which may put women at risk given their lack of safety data.³² Current guidelines recommend using male formulations given testosterone levels are maintained in the physiological range for women.¹⁴

While intuitive to measure serum testosterone in women for androgen deficiency, deciding to use testosterone therapy in women should not be based on her testosterone level since there is no biochemical definition of androgen deficiency in women, nor a minimum androgen level that can be used to identify women with HSDD.^{13,14,32} Also important to note is that testosterone assays have their

limitations, which are complicated by the low concentrations in women, and because it is cyclically and diurnally regulated and highly bound to plasma proteins in the circulation.⁹ However, baseline total testosterone, measured by liquid or gas chromatography with mass spectrometry, not direct assays, and sex hormone binding globulin (SHBG) should be evaluated if a patient and her health care professional decide to begin testosterone therapy, which would help exclude women at risk for hyperandrogenism/overtreatment.^{13,32} Women should then have regular blood testosterone measurements during testosterone use to avoid supraphysiological serum levels and their associated side effects.^{13,14}

Testosterone Use in Postmenopausal Women

Consistent evidence from randomized, controlled trials (RCTs) shows that testosterone therapy, with or without estrogens, is more effective than placebo for the treatment of HSDD in postmenopausal women. Here we summarize larger, placebo-controlled studies in various populations of menopausal women. Other smaller, RCTs supporting a positive effect of testosterone on sexual function in women are reviewed elsewhere.^{33–35}

Surgically Menopausal Women

In the multicenter, 24-week, INTIMATE SM1 study of women with surgically induced menopause who lost sexual desire after surgery ($n = 562$), Simon et al³⁶ reported that the testosterone patch (combined with exogenous oral estrogen) when compared with placebo had a better increase from baseline in total satisfying sexual activity frequency (0.98 vs. 2.10 from baseline; $P = 0.0003$) and significantly improved sexual desire and orgasm, with decreased sexually related personal distress ($P \leq 0.0006$ for all). Another placebo-controlled, randomized trial evaluated the testosterone patch (300 $\mu\text{g/day}$) in 533 surgically menopausal women with HSDD taking estrogens in 2005.³⁷ In this study, testosterone increased total satisfying sexual activity versus placebo (1.56 vs. 0.73 episodes per 4 wk; $P < 0.001$), total sexual activity, orgasm, and all 7 measured domains of sexual function (including sexual desire, pleasure, arousal, orgasm, concerns, responsiveness, and self-image) improving after 24 weeks of therapy. Braunstein et al³⁸ also reported increased sexual desire, mean frequency of total satisfying episodes, and sexual arousal in surgically menopausal women with HSDD (taking estrogens).

Naturally Menopausal Women

In 2006, Shifren et al³⁹ assessed the testosterone patch combined with estrogen \pm progestin versus placebo in 549 naturally menopausal women in the randomized, 24-week, INTIMATE NM1 study. The number of satisfying sexual events (2.1 vs. 0.5 episodes per 4 wk; $P < 0.0001$), number of orgasms, and sexual desire increased, and personal distress decreased with testosterone compared with placebo.³⁹ Similarly, in the placebo-controlled, randomized, double-blind ADORE study of 272 naturally menopausal women with or without estrogens, the testosterone patch (300 $\mu\text{g/d}$) versus placebo increased satisfying sexual events (1.69 vs. 0.53 episodes per 4 wk; $P = 0.0089$), improved libido ($P = 0.0007$) and orgasm ($P = 0.0152$), and reduced personal distress ($P = 0.0024$).⁴⁰ In an earlier double-blind, randomized, 16-week study reported by Lobo et al⁴¹ in naturally ($\sim 70\%$) or surgically menopausal women with HSDD ($N = 221$), those taking the oral combination of esterified

estrogen plus methyltestosterone had better scores for sexual desire, frequency of interest/desire, responsiveness, and total scores on the Sexual Interest Questionnaire than those taking oral esterified estrogens alone.

Testosterone Therapy Without Estrogens

Evidence for the benefits and safety of testosterone in women not taking estrogens is limited. Davis et al⁴² found in 814 mostly naturally ($\sim 75\%$) or surgically menopausal women with HSDD not taking estrogens that the testosterone patch at 300 $\mu\text{g/day}$, but not 150 $\mu\text{g/day}$, tripled the number of satisfying sexual events (2.1 vs. 0.7 episodes per 4 wk, $P < 0.001$), increased desire, and decreased distress compared with placebo in a 24-week study. Treatment effects did not differ between women who were surgically or naturally menopausal.⁴²

Testosterone Use in Premenopausal Women

While evidence is strong for the use of testosterone in postmenopausal women, evidence in premenopausal women is limited, even though low sexual desire has been reported in 25% of premenopausal women, of whom 59% were distressed over that low sexual desire.⁵ Evidence in women defined as premenopausal (mean age ~ 40 y, regular menstrual cycles, FSH levels < 20 to 40 mIU/mL) was shown in 2 multicenter, randomized, placebo-controlled, double-blind trials.^{43,44} The first study was of a metered-dose testosterone spray (56, 90, or 180 μL of a 50 $\mu\text{g}/\mu\text{L}$ spray) in 261 premenopausal women with sexual dysfunction. In this study, testosterone helped to provide a significantly greater number of satisfying sexual events with the 90- μL dose versus placebo (1.8 vs. 3.4 events), without a significant difference between testosterone doses.⁴³ In the second multicenter, but smaller, study of premenopausal women with low libido ($n = 34$), transdermal testosterone versus placebo found that 12 weeks of testosterone (10 mg testosterone 1% cream) significantly improved sexual interest, sexual activity, sex-life satisfaction, sexual fantasy, orgasm, and importance of sex.⁴⁵ In a single-center, randomized, controlled study, transdermal testosterone (300 $\mu\text{g/day}$) increased the frequency of satisfying sexual events versus placebo in women taking selective serotonin (SSRI) or serotonin-noradrenalin reuptake inhibitors (SNRI; $N = 44$), the majority (77%) of whom were premenopausal.⁴⁴ However, in this study, testosterone did not improve measures of sexual dysfunction or distress.⁴⁴

A much earlier, small, crossover study that compared premenopausal women requiring a hysterectomy with ($n = 43$) and without ($n = 10$) a bilateral salpingo-oophorectomy found that women who received testosterone enanthate (200 mg) or testosterone enanthate (150 mg) plus estradiol (7.5 mg) and estradiol benzoate (1 mg) had significantly higher scores for sexual desire and fantasies versus women in the estrogen and placebo groups ($P < 0.01$). Improved scores coincided with higher levels of plasma testosterone that later fell below levels of those with placebo when hormones were withdrawn ($P < 0.01$).⁴⁶ When transdermal testosterone (150 $\mu\text{g/d}$; $n = 67$) or placebo ($n = 61$) was added to transdermal estradiol (150 $\mu\text{g/d}$) plus cyclical oral medroxyprogesterone acetate (10 mg/d for 12 d/28-d cycle) in premenopausal women with primary ovarian insufficiency (age: 18 to 42 y), no significant differences in outcomes related to QoL, depression and mood, or self-esteem were observed (sexual function not studied).⁴⁷ A recent study in premenopausal patients with breast cancer

undergoing ovarian suppression and AI therapy found that low-dose topical testosterone (3 mg/mL; daily gel) improved desire, arousal, lubrication, orgasm, satisfaction, and total scores of the FSFI after 12 weeks of treatment.⁴⁸

SAFETY OF TESTOSTERONE USE IN WOMEN

Short-term and long-term safety is the main concern of using testosterone in women. Although the safety of testosterone therapy in women has been studied in many placebo-controlled trials, the duration of therapy in these studies is typically 6 months,^{37,42} such data are not powered to detect longer-term safety, such cardiovascular and breast cancer risks.

Cardiovascular and Breast Safety

The longer-term safety of testosterone treatment in women has not been extensively studied, so is largely unknown. While women with excess endogenous androgens (such as in polycystic ovarian syndrome) are known to be at risk for cardiovascular disease, the same is unknown for exogenous testosterone resulting in physiological levels. Evidence in women treated with testosterone are limited to studies with data inadequate to assess longer-term, cardiovascular events (ie, acute myocardial infarction, stroke, deep vein thrombosis, and death) or breast cancer risk, and are largely inconclusive.

Cardiovascular Safety

While testosterone is generally thought to increase the risk of cardiovascular disease,⁸ low levels of endogenous testosterone in women may be detrimental to cardiovascular function.⁴⁹ Clinical data from larger studies are conflicting. A multiethnic study of over 2800 postmenopausal women (mean age 65 y) without cardiovascular published in 2018 found a higher risk of cardiovascular disease, coronary heart disease, and heart failure events in those with a higher testosterone/estradiol ratio after 12 years of follow up.⁵⁰ However, after that study, opposite results were reported in over 5500 Australian women (mean age: 74 y), which showed lower testosterone values were associated with lower risk of major adverse cardiovascular events, including fatal coronary heart disease, nonfatal myocardial infarction, and fatal or nonfatal ischemic stroke.⁵¹ Data from these studies do not address the effects of exogenous testosterone on cardiovascular risk, and their inconsistent risk results suggests there are many confounders in these observational data.

A claims-based analysis (Optum's deidentified Clinformatics Data Mart Database; 2007 to 2021) of premenopausal and postmenopausal women with cardiovascular disease (N = 6288) suggested higher rates of coronary artery disease and stroke, but not myocardial infarction in testosterone users versus nonusers.⁵² A more recent claims-data analysis (TriNetX Diamond Network; 2009 to 2022) did not find an increased risk of major adverse cardiac events or deep vein thrombosis with testosterone use regardless of menopause status.⁵³ In general, claims-data cannot adequately capture risks of testosterone in women as the majority of women taking testosterone therapy are not captured in insurance claims as insurance rarely covers testosterone use for women.

Nachtigall et al⁵⁴ reported direct evidence of the longest observation of exogenous testosterone safety in healthy, surgically menopausal women (n = 967; age: 20 to

70 y) taking oral or transdermal estrogens for up to 4 years in an extension of the randomized, placebo-controlled, INTIMATE SM1 and 2 studies evaluating use of a testosterone patch (300 µg/d). In this study, women were randomized to the testosterone patch or placebo for 6 months, after which, patients receiving placebo were switched to the testosterone patch.⁵⁴ Few cardiovascular events were reported as would be expected in that healthy population.⁵⁴ During the 4 years of transdermal testosterone, angina was reported in 2 women, myocardial infarctions in none, and stroke in one woman who was also receiving 1.25 mg of conjugated equine estrogens.⁵⁴ Palpitations, the most frequently reported cardiovascular event, were reported in 12 women, the rate and severity of which did not increase with testosterone exposure over time.⁵⁴

The largest, randomized, controlled trial on cardiovascular and breast safety, as required by FDA to establish safety of a testosterone gel (LibiGel; BioSante Pharmaceuticals Inc., Lincolnshire, IL), evaluated 3656 postmenopausal women (> 50 y of age) who had at least 2 cardiovascular risk factors at baseline (eg, hypertension, dyslipidemia) and an HSDD diagnosis.⁵⁵ After 4 years, with over 7300 women-years of exposure, a lower than anticipated rate of 53 adjudicated cardiovascular events (0.72%) were reported by the company.⁵⁶ Although these data were reviewed by an independent data safety and monitoring board which allowed the trial to continue, these 4-year data have never been peer reviewed or published. From other placebo-controlled, randomized data from a large study (TRAVERSE; N = 5204) of cis males (age: 40 to 80 y; hypogonadism symptoms; and low testosterone levels) with pre-existing cardiovascular disease or elevated cardiovascular risk, authors concluded that exogenous testosterone therapy did not increase cardiovascular events in these men.⁵⁷ Indeed, the Androgen Society recently published their position that testosterone was not associated with increased risks of heart attack, stroke, or cardiovascular death based on the results of the TRAVERSE study.⁵⁸ Collectively, these data should prove to be very reassuring regarding the safety of testosterone therapy and cardiovascular health when given at physiological concentrations.

Some,³⁶ but not all,^{40,42,43} smaller placebo-controlled efficacy studies observed cardiovascular events. In the INTIMATE SM1 (N = 562), 2 women had cardiovascular related, serious AEs considered treatment related (transient ischemic attack in one woman; diaphoresis, increased heart rate, nausea, and other symptoms in another woman), which resolved while continuing to use testosterone.³⁶

Other evidence alluding to the effects of testosterone on cardiovascular safety in postmenopausal women focuses on biomarkers of cardiovascular risk. Meta-analyses found that oral testosterone (methyltestosterone or testosterone undecanoate) significantly lowers total cholesterol, HDL cholesterol and triglycerides, but increases LDL-cholesterol.^{35,59} In contrast, nonoral testosterone does not affect these lipid parameters, blood pressure, glucose, insulin, or C-reactive protein.^{35,59} Placebo-controlled trials on transdermal testosterone showed no clinically meaningful changes in lipids, lipoproteins, and carbohydrate metabolism,^{36,37,43,60} homocysteine,⁴³ or C-reactive protein.^{43,60} One randomized, controlled study of oral methyltestosterone combined with esterified estrogens showed a decrease in total cholesterol, HDL cholesterol, and triglycerides;⁴¹ however, contribution of the estrogens complicates the interpretation of these

findings. A small study of 40 postmenopausal women found an overall decrease in plasma viscosity and an increase in fibrinogen with esterified estrogen plus methyltestosterone; however, plasma viscosity increased in older women.⁶¹

Breast Safety

Because testosterone is aromatized to estradiol, the possibility for an increased risk of breast cancer with testosterone therapy is a potential concern. Breast safety was examined over the 4 years of testosterone patch use by Nachtigall et al.⁵⁴ During the more than 1250 patient-years of testosterone use, invasive breast cancer was reported in 3 women; 1 metastatic adenocarcinoma after 5 weeks, whose origin was diagnosed as breast and thought to be pre-existing, 1 infiltrating tubulolobular mammary carcinoma after 47 weeks, and 1 infiltrating lobular and ductal carcinoma in situ after ~2.5 years.⁵⁴ Ductal carcinoma in situ was also diagnosed in 1 woman after 6 months and in 2 women after 3 years.⁵⁴ Another woman who received 6 months of open-label testosterone was diagnosed with ductal carcinoma in situ 1 year after discontinuing therapy.⁵⁴ Since 6 of these 7 patients diagnosed with breast cancer were initially randomized to placebo during the initial 6 months of the study,⁵⁴ it would be important to note that any presence of breast cancer in these patients after completing placebo, before testosterone therapy, was not known as breast exams and mammograms were not protocol specified at that time.⁵⁴ In the randomized, controlled trial required by FDA to establish safety of testosterone gel, 27 breast cancers were reported in 3656 postmenopausal women with HSDD over 7300 women-years of exposure, yielding a rate of ~0.37%, which is in line with the expected, age-appropriate rate of the enrolled patients.^{55,56} In the recent claims-data analysis (TriNetX Diamond Network), while risk of malignant breast neoplasm did not increase with testosterone use regardless of menopause status, prescription reporting bias needs to be considered in the interpretation of these data.⁵³

In randomized, controlled studies of shorter duration that are not powered to determine risk for breast cancer, some cases of breast cancer were reported. In naturally and surgically menopausal women, Davis et al⁴² observed 1 case with 150 µg/day of testosterone and 2 cases with 300 µg/day testosterone (between weeks 4 and 12), one of which had prior-study bloody nipple discharge she reported after randomization. In an extension of the same study, another woman treated for 104 weeks had an infiltrating ductal breast cancer detected by mammography 3 months after study end; her mammogram was normal after 52 weeks of treatment, she used estrogen for 27 years, and she had a sister who had breast cancer.⁴² Other randomized, controlled studies reporting on testosterone patch efficacy did not report any cases of breast cancer.^{36,40,43}

Breast density, when used as a surrogate marker for breast cancer risk, did not change with transdermal testosterone in a meta-analysis of data from over 3000 women using transdermal testosterone, alone or with concomitant estrogen and progestin hormone therapy.³⁵

Androgenic Adverse Effects

Adverse effects related to androgens might be expected in women taking extra testosterone, mostly commonly oily skin, acne, and hirsutism. These have been evaluated or reported in randomized, controlled trials. However, such effects are infrequent and mild, if present at all, when

testosterone therapies result in premenopausal physiological concentrations.

In the randomized, controlled trial reported by Buster et al,³⁷ the overall incidence of androgenic AEs (mostly mild) was higher for the testosterone patch versus placebo (19.5% vs. 11.3%), and 6 versus 2 women withdrew from the study due to androgenic AEs, respectively; however, facial hair and acne were not significantly different between groups. Panay et al⁴⁰ found a higher incidence of acne (4.6% vs. 1.4%) and increased hair growth (18.5% vs. 12%) with testosterone versus placebo, and overall, most androgenic AEs were mild (≥87%), and women discontinuing due to androgenic AEs was similar between groups (3.1% vs. 2.8%).

In postmenopausal women with HSDD using a testosterone patch without concomitant estrogens, Davis et al⁴² reported increased hair growth. It was the only androgenic side effect reported at a higher incidence with 300 µg/day testosterone, and 3 women developed clitoral enlargement; none of these events lead to a higher rate of study discontinuation.

During the 24-week treatment period in surgically menopausal women of the INTIMATE SM1 study, the risk of experiencing at least 1 type of androgenic event (acne, alopecia, unwanted hair growth, or voice deepening) was lower in the testosterone versus placebo group (12.7% vs. 15.8%), few women (1.1% vs. 0.4%, respectively) discontinued treatment, and facial hair and acne were similar in the testosterone and placebo groups.³⁶ Similarly, in the INTIMATE NM1 study, naturally menopausal women using the patch with oral estrogens versus placebo had more androgen-related events, mostly due to increased hair growth.³⁹

For the most part, androgenic side effects were similar in the limited randomized, controlled data from premenopausal women. In the study of testosterone spray in premenopausal women with sexual dysfunction (n=261), the most frequently reported AE was hypertrichosis mostly at the application site followed by headache, nausea, acne, and dysmenorrhea. Acne severity, but not incidence, increased slightly after testosterone, and body weight did not change.⁴³

PRESCRIBING TESTOSTERONE FOR FSD

How to prescribe testosterone to treat women with sexual dysfunction is reviewed by ISSWSH in their testosterone guidelines for treating HSDD.¹³ In brief, they recommend first diagnosis, which considers screening tools, sexual history, partner relationships, and other potential confounders.¹³ Therapy should only begin after a full biopsychosocial evaluation and other conditions like dyspareunia, fatigue, anemia, thyroid disease, anxiety, depression, medication side effects, and relationship issues are addressed.¹³ Given the multifactorial nature of FSD, psychological and pharmacologic therapy may also be considered with testosterone treatment, especially when psychosocial and interpersonal factors are involved.¹³ Because testosterone use in women is off-label in all but one country (Australia),¹² before prescribing it, clinicians should obtain informed consent from their patient and make shared decisions based on risks and benefits, as well as patient's goals and concerns.¹³

Testosterone therapy is suitable for postmenopausal women with low sexual desire causing distress.¹³

Management of women with surgically induced menopause or premature ovarian insufficiency is similar to that of postmenopausal women with HSDD.¹³ Since an approved female testosterone formulation is not available, prescribing an approved male formulation off-label at approximately one-tenth of the male dose is reasonable and targets physiological concentrations in women.¹³ While one can prescribe compounded products, their efficacy and safety evidence are lacking, and quality control concerns arise from their variable testosterone concentrations.¹³

Logistically, testosterone therapy in women means prescribing 1% testosterone gel at one-tenth that of the prescription for men with hypogonadism.¹³ For example, these men are given 30 tubes or packets per month of 1% generic testosterone gel for daily use, so women would utilize 3 tubes per month (one-tenth a tube/day).¹³ One-tenth of a male dose using resealable tubes (preferred over packets) at room temperature is ~4 to 6 drops per day.¹³ The recommended starting dose with the 1% cream available in Australia is 5 mg/day testosterone (0.5 mL), but this may be titrated to 10 mg/day (1.0 mL) if needed.^{12,13} Patients should apply topical testosterone to skin on the back of the calf or upper outer thigh (> 1 h after shaving) or buttock, immediately washing hands thoroughly afterward.^{12,13} They should also be advised about potential testosterone transference from the application site to the skin of young children, female partners, and pets in close contact.^{12,13} Such transfer is uncommon and usually restricted by allowing the preparation to dry before contact.

Once using testosterone therapy, patients should be monitored, as reviewed in ISSWSH guidelines,¹³ for a clinically meaningful response, such as an increase in sexual desire and a decrease in personal distress, as well as for testosterone and SHBG levels. Efficacy expectations should be initially discussed and later, clinical response subjectively assessed based on clinician-patient dialog.¹³ While average efficacy is typically observed 6 to 8 weeks after initiating therapy, many women feel improvement after 4 weeks, with maximal effects on sexual desire and satisfying sexual events at 12 weeks. Reduced sexually associated personal distress is seen at about 4 weeks, with this distress continuing to decline over the next 5 to 6 months of therapy. With improved HSDD, testosterone therapy is recommended for 6 to 12 months, followed by a drug holiday to assess the need to continue treatment, as ongoing therapy may be required to maintain HSDD improvements.¹³ When symptoms do not improve, calculating free testosterone might provide insight into the lack of efficacy when total testosterone levels are in the upper end of the physiological range.¹³ Also consider measuring 5 α -reductase, as low activity of this enzyme may lower women's response to physiological doses of testosterone.^{13,62}

Total testosterone levels should be checked before initiating therapy to exclude women with midrange to high pretreatment testosterone concentrations.¹³ Total testosterone levels should also be measured after 3 to 6 weeks of initiating therapy, not to treat to a target blood level, but for determining the need for dose titration or an excessive dose (not significantly above the upper normal premenopausal range limit).¹³ If testosterone dose is increased, total testosterone measurement should be repeated within 6 weeks.¹³ If supraphysiological testosterone levels are found, even without androgenic side effects, testosterone should be titrated and blood levels remeasured in 2 to 3 weeks based on little available safety data.¹³ The dose of testosterone should also be decreased if androgenic side effects occur.

SHBG should be measured as higher SHBG will bind free testosterone, making it inactive.^{13,39} In women with very high SHBG (ie, >170 nmol/L), and unmodifiable factors, a trial of testosterone therapy is still worthwhile. If elevated SHBG results in reduced free testosterone leading to lack of efficacy, and the contributing factor cannot be addressed, a different approach to manage HSDD is recommended.¹³ Increasing the dose of testosterone to attain total testosterone levels above women's physiological range to overcome elevated SHBG is not supported by current evidence.¹³

Women not appropriate for testosterone therapy are those who have excess androgens (presenting with acne, hirsutism, androgenic alopecia) or those who are using antiandrogenic medication.¹³ In addition, women with hormone-dependent neoplasia should consult cancer specialists before both estrogen or testosterone therapy. Testosterone is also not advised for women who are or might become pregnant due to risk of fetal masculinization, albeit limited to supraphysiological concentrations. Evidence is insufficient to recommend testosterone for treatment-emergent sexual dysfunction with SSRIs or SNRIs, given that data are limited to one small trial (N=44)⁴⁴ showing a positive effect of testosterone on satisfying sexual events only in women taking these medications.

CONCLUSIONS

Testosterone is abundant in women, particularly compared with estradiol, and is essential for developing and maintaining female sexual anatomy and physiology and modulating sexual behavior. Low or absent circulating testosterone is associated with reduced sexual desire, although there is no absolute testosterone level associated with HSDD. While no FDA-approved testosterone formulation exists for women, about one-tenth of the male dose can restore blood level of testosterone to that of the normal premenopausal level in perimenopausal and postmenopausal women. Randomized, controlled data show that testosterone treatment improves symptoms of HSDD, including desire, arousal, orgasm, and others, while reducing its associated distress.

REFERENCES

1. Alidost F, Pakzad R, Dolatian M, et al. Sexual dysfunction among women of reproductive age: a systematic review and meta-analysis. *Int J Reprod Biomed*. 2021;19:421-432.
2. Briken P, Matthiesen S, Pietras L, et al. Estimating the prevalence of sexual dysfunction using the new ICD-11 guidelines. *Dtsch Arztebl Int*. 2020;117:653-658.
3. Koops TU, Briken P. Prevalence of female sexual function difficulties and sexual pain assessed by the Female Sexual Function Index: a systematic review. *J Sex Med*. 2018;15:1591-1599.
4. Shifren JL, Monz BU, Russo PA, et al. Sexual problems and distress in United States women: prevalence and correlates. *Obstet Gynecol*. 2008;112:970-978.
5. Leiblum SR, Koochaki PE, Rodenberg CA, et al. Hypoactive sexual desire disorder in postmenopausal women: US results from the Women's International Study of Health and Sexuality (WISHS). *Menopause*. 2006;13:46-56.
6. Kingsberg SA, Clayton AH, Pfau JG. The female sexual response: current models, neurobiological underpinnings and agents currently approved or under investigation for the treatment of hypoactive sexual desire disorder. *CNS Drugs*. 2015;29:915-933.

7. Traish AM, Vignozzi L, Simon JA, et al. Role of androgens in female genitourinary tissue structure and function: implications in the genitourinary syndrome of menopause. *Sex Med Rev*. 2018;6:558–571.
8. Davis SR, Wahlin-Jacobsen S. Testosterone in women—the clinical significance. *Lancet Diabetes Endocrinol*. 2015;3:980–992.
9. Simon JA, Kapner MD. The saga of testosterone for menopausal women at the Food and Drug Administration (FDA). *J Sex Med*. 2020;17:826–829.
10. Guay A, Munarriz R, Jacobson J, et al. Serum androgen levels in healthy premenopausal women with and without sexual dysfunction: Part A. Serum androgen levels in women aged 20–49 years with no complaints of sexual dysfunction. *Int J Impot Res*. 2004;16:112–120.
11. Platz EA, Barber JR, Chadid S, et al. Nationally representative estimates of serum testosterone concentration in never-smoking, lean men without aging-associated comorbidities. *J Endocr Soc*. 2019;3:1759–1770.
12. *Androfeme 1® (testosterone) 1% w/v Cream Prescribing Information*. West Leederville, Western Australia: Lawley Pharmaceuticals Pty Ltd; 2023.
13. Parish SJ, Simon JA, Davis SR, et al. International Society for the Study of Women's Sexual Health clinical practice guideline for the use of systemic testosterone for hypoactive sexual desire disorder in women. *J Sex Med*. 2021;18:849–867.
14. Davis SR, Baber R, Panay N, et al. Global Consensus Position Statement on the use of testosterone therapy for women. *Climacteric*. 2019;22:429–434.
15. Goldstein I, Kim NN, Clayton AH, et al. Hypoactive sexual desire disorder: International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. *Mayo Clin Proc*. 2017;92:114–128.
16. Agrawal P, Lee YS, Grutman AJ, et al. Characteristics of systemic testosterone therapy for female hypoactive sexual desire disorder—a claims database analysis. *J Sex Med*. 2024;21:288–293.
17. Baldassarre M, Perrone AM, Giannone FA, et al. Androgen receptor expression in the human vagina under different physiological and treatment conditions. *Int J Impot Res*. 2013;25:7–11.
18. Berman JR, Almeida FG, Jolin J, et al. Correlation of androgen receptors, aromatase, and 5- α reductase in the human vagina with menopausal status. *Fertil Steril*. 2003;79:925–931.
19. Cipriani S, Maseroli E, Di Stasi V, et al. Effects of testosterone treatment on clitoral haemodynamics in women with sexual dysfunction. *J Endocrinol Invest*. 2021;44:2765–2776.
20. Heard-Davison A, Heiman JR, Kuffel S. Genital and subjective measurement of the time course effects of an acute dose of testosterone vs. placebo in postmenopausal women. *J Sex Med*. 2007;4:209–217.
21. Barrett-Connor E, Young R, Notelovitz M, et al. A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. Effects on bone mineral density, symptoms and lipid profiles. *J Reprod Med*. 1999;44:1012–1020.
22. Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial. *J Sex Med*. 2014;11:1262–1270.
23. Fernandes T, Costa-Paiva LH, Pedro AO, et al. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on vaginal atrophy: a randomized controlled trial. *Menopause*. 2016;23:792–798.
24. Fernandes T, Pedro AO, Baccaro LF, et al. Hormonal, metabolic, and endometrial safety of testosterone vaginal cream versus estrogens for the treatment of vulvovaginal atrophy in postmenopausal women: a randomized, placebo-controlled study. *Menopause*. 2018;25:641–647.
25. Burrows LJ, Goldstein AT. The treatment of vestibulodynia with topical estradiol and testosterone. *Sex Med*. 2013;1:30–33.
26. Davis SR, Robinson PJ, Jane F, et al. Intravaginal testosterone improves sexual satisfaction and vaginal symptoms associated with aromatase inhibitors. *J Clin Endocrinol Metab*. 2018;103:4146–4154.
27. Melisko ME, Goldman ME, Hwang J, et al. Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. *JAMA Oncol*. 2017;3:313–319.
28. Dahir M, Travers-Gustafson D. Breast cancer, aromatase inhibitor therapy, and sexual functioning: a pilot study of the effects of vaginal testosterone therapy. *Sex Med*. 2014;2:8–15.
29. Witherby S, Johnson J, Demers L, et al. Topical testosterone for breast cancer patients with vaginal atrophy related to aromatase inhibitors: a phase I/II study. *Oncologist*. 2011;16:424–431.
30. Burger H, Hailes J, Nelson J, et al. Effect of combined implants of oestradiol and testosterone on libido in postmenopausal women. *Br Med J (Clin Res Ed)*. 1987;294:936–937.
31. Sherwin BB, Gelfand MM. The role of androgen in the maintenance of sexual functioning in oophorectomized women. *Psychosom Med*. 1987;49:397–409.
32. Davis SR, Worsley R. Androgen treatment of postmenopausal women. *J Steroid Biochem Mol Biol*. 2014;142:107–114.
33. Jayasena CN, Alkaabi FM, Liebers CS, et al. A systematic review of randomized controlled trials investigating the efficacy and safety of testosterone therapy for female sexual dysfunction in postmenopausal women. *Clin Endocrinol (Oxf)*. 2019;90:391–414.
34. Achilli C, Pundir J, Ramanathan P, et al. Efficacy and safety of transdermal testosterone in postmenopausal women with hypoactive sexual desire disorder: a systematic review and meta-analysis. *Fertil Steril*. 2017;107:475–482.e415.
35. Islam RM, Bell RJ, Green S, et al. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. *Lancet Diabetes Endocrinol*. 2019;7:754–766.
36. Simon J, Braunstein G, Nachtigall L, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab*. 2005;90:5226–5233.
37. Buster JE, Kingsberg SA, Aguirre O, et al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol*. 2005;105:944–952.
38. Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med*. 2005;165:1582–1589.
39. Shifren JL, Davis SR, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. *Menopause*. 2006;13:770–779.
40. Panay N, Al-Azzawi F, Bouchard C, et al. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. *Climacteric*. 2010;13:121–131.
41. Lobo RA, Rosen RC, Yang HM, Katz M, et al. Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. *Fertil Steril*. 2003;79:1341–1352.
42. Davis SR, Moreau M, Kroll R, et al. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med*. 2008;359:2005–2017.
43. Davis S, Papalia MA, Norman RJ, et al. Safety and efficacy of a testosterone metered-dose transdermal spray for treating decreased sexual satisfaction in premenopausal women: a randomized trial. *Ann Intern Med*. 2008;148:569–577.
44. Fooladi E, Bell RJ, Jane F, et al. Testosterone improves antidepressant-emergent loss of libido in women: findings from a randomized, double-blind, placebo-controlled trial. *J Sex Med*. 2014;11:831–839.

45. Goldstat R, Briganti E, Tran J, et al. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. *Menopause*. 2003;10:390–398.
46. Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females: a prospective, crossover study of sex steroid administration in the surgical menopause. *Psychosom Med*. 1985;47:339–351.
47. Guerrieri GM, Martinez PE, Klug SP, et al. Effects of physiologic testosterone therapy on quality of life, self-esteem, and mood in women with primary ovarian insufficiency. *Menopause*. 2014;21:952–961.
48. Taranto P, de Brito Sales D, Maluf FC, et al. Safety and efficacy of topical testosterone in breast cancer patients receiving ovarian suppression and aromatase inhibitor therapy. *Breast Cancer Res*. 2024;26:133.
49. Davis SR. Testosterone and the heart: friend or foe? *Climacteric*. 2024;27:53–59.
50. Zhao D, Guallar E, Ouyang P, et al. Endogenous sex hormones and incident cardiovascular disease in post-menopausal women. *J Am Coll Cardiol*. 2018;71:2555–2566.
51. Islam RM, Bell RJ, Handelsman DJ, et al. Associations between blood sex steroid concentrations and risk of major adverse cardiovascular events in healthy older women in Australia: a prospective cohort substudy of the ASPREE trial. *Lancet Healthy Longev*. 2022;3:e109–e118.
52. Lopez DS, Mulla JS, El Haddad D, et al. Testosterone replacement therapy in relation with cardiovascular disease in cisgender women and transgender people. *J Clin Endocrinol Metab*. 2023;108:e1515–e1523.
53. Agrawal P, Singh SM, Hsueh J, et al. Testosterone therapy in females is not associated with increased cardiovascular or breast cancer risk: a claims database analysis. *J Sex Med*. 2024;21:414–419.
54. Nachtigall L, Casson P, Lucas J, et al. Safety and tolerability of testosterone patch therapy for up to 4 years in surgically menopausal women receiving oral or transdermal oestrogen. *Gynecol Endocrinol*. 2011;27:39–48.
55. White WB, Grady D, Giudice LC, et al. A cardiovascular safety study of LibiGel (testosterone gel) in postmenopausal women with elevated cardiovascular risk and hypoactive sexual desire disorder. *Am Heart J*. 2012;163:27–32.
56. businesswire. BioSante Pharmaceuticals Announces Positive LibiGel® Phase III Safety Data Review and Decision to Conclude the Safety Study 2012. Accessed October 24, 2024. <https://www.businesswire.com/news/home/20120904005404/cn/BioSan>
57. Lincoff AM, Bhasin S, Flevaris P, et al. Cardiovascular safety of testosterone-replacement therapy. *N Engl J Med*. 2023;389:107–117.
58. Morgentaler A, Dhindsa S, Dobs AS, et al. Androgen society position paper on cardiovascular risk with testosterone therapy. *Mayo Clin Proc*. 2024;99:1785–1801.
59. Elraiyah T, Sonbol MB, Wang Z, et al. Clinical review: the benefits and harms of systemic testosterone therapy in postmenopausal women with normal adrenal function: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2014;99:3543–3550.
60. Huang G, Tang E, Aakil A, et al. Testosterone dose-response relationships with cardiovascular risk markers in androgen-deficient women: a randomized, placebo-controlled trial. *J Clin Endocrinol Metab*. 2014;99:E1287–E1293.
61. Basaria S, Nguyen T, Rosenson RS, et al. Effect of methyl testosterone administration on plasma viscosity in postmenopausal women. *Clin Endocrinol (Oxf)*. 2002;57:209–214.
62. Kennedy RG, Davies T, Al-Azzawi F. Sexual interest in postmenopausal women is related to 5 α -reductase activity. *Hum Reprod*. 1997;12:209–213.