

NAMS PRACTICE PEARL

Testosterone for Midlife Women: The Hormone of Desire?

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Testosterone declines with aging, so most midlife women have “low” testosterone levels. Because libido also declines with aging, and distressing sexual problems peak at midlife, should midlife women with low libido and associated distress be treated with testosterone? This *Practice Pearl* reports clinical trial evidence, reviews the risks, and explains how testosterone might be used in a clinical setting. For women who may be considering a trial of testosterone therapy, limitations and adverse effects should be disclosed and appropriate monitoring instituted once treatment has begun.

Sexual problems are highly prevalent, reported in approximately 40% of US women, with 12% reporting a sexual problem associated with personal distress.¹ Although sexual problems generally increase with aging, distressing sexual problems peak in midlife women (aged 45-64 y) and are lowest in women aged 65 years or older. Hypoactive sexual desire disorder (HSDD), low desire with associated distress, is the most common sexual problem for women.

The etiology of sexual dysfunction is generally multifactorial, including psychological and social factors such as depression or anxiety, fatigue, stress, lack of privacy, conflict within the relationship, partner performance, relationship duration, and prior physical or sexual abuse. Medical and gynecologic problems also play a role, including medications, especially antidepressants, and conditions that make sexual activity uncomfortable, such as endometriosis or arthritis. For perimenopausal and postmenopausal women, genitourinary syndrome of menopause (GSM), encompassing symptomatic vulvovaginal atrophy, and night sweats with associated sleep disruption and fatigue contribute to sexual problems at this stage of life.

Low androgen states occur in the settings of oophorectomy, hypopituitarism, adrenal insufficiency, oral estrogen therapy, and aging. Although decreased testosterone concentrations may contribute to sexual dysfunction in midlife women, results from large observational studies generally have found no association between androgen levels and female sexual function. Rather than androgen levels, physical and psychological well-being and the partner relationship appear to be significant predictors of a distressing sexual problem for women.

Clinical trials of testosterone therapy. Although low testosterone levels do not clearly correlate with sexual function, in some but not all studies, testosterone therapy has been shown to be an effective treatment for HSDD in carefully selected postmenopausal women.² Early randomized, controlled trials confirmed that administration of supraphysiologic doses of testosterone improved sexual interest, frequency, and orgasmic response in surgically menopausal women.³ As supraphysiologic dosing of testosterone results in androgenic adverse effects, and oral

androgens can have adverse effects on lipids and liver function, recent research has investigated the safety and efficacy of transdermal testosterone in postmenopausal women with HSDD. A large series of multicenter, randomized, placebo-controlled trials used a testosterone patch (300 µg/d) that raised testosterone levels to the upper limits of normal for reproductive-aged women. The testosterone patch significantly improved libido and the frequency of satisfactory sexual events (SSEs) and lowered sexually related distress in carefully selected postmenopausal women with HSDD.⁴⁻⁶

Initial clinical trials involved surgically menopausal women on concurrent estrogen therapy. Subsequent studies confirmed similar efficacy in naturally menopausal women⁷ and in women not using concurrent estrogen.⁸ Although sexual desire and activity were significantly improved with testosterone compared with placebo, placebo responses were high. On average, in menopausal women with HSDD, placebo increased SSEs by approximately one event per month compared with an increase of approximately two events per month with testosterone treatment.

Although no significant safety concerns were identified, the studies were too brief to assess potential long-term risks of testosterone, including cardiovascular disease (CVD) or breast cancer. In the only long-term study (52 wk), there were four cases of breast cancer in women who received testosterone and no cases in placebo-treated women, with authors stating that the possibility of a causal relationship must be considered.⁸ Transdermal testosterone patches were not approved by FDA after an advisory panel expressed concerns regarding long-term safety. The patches were approved in Europe and available for several years but are no longer being marketed.

In contrast to the improvement in sexual function observed with the testosterone patch, two large, phase III, randomized trials of a testosterone gel in postmenopausal women with HSDD failed to demonstrate any improvement in sexual function compared with placebo. Satisfactory sexual events increased by approximately one event per month in women treated with both testosterone and placebo gel. Likewise, sexual desire increased and associated distress decreased similarly in both groups. Of note, treatment with the testosterone gel achieved serum free testosterone levels similar to those achieved with the testosterone patch.⁹ Safety data collected in this study to assess long-term outcomes of testosterone treatment, including CVD and breast cancer, have not been published.

A study of intramuscular (IM) testosterone administration in 71 estrogen-treated, hysterectomized women aged 45 to 70 years suggests that significant increases in sexual desire and activity with testosterone occur only with supraphysiologic dosing. Women were randomized to receive weekly IM injections of placebo or testosterone (3 mg, 6.25 mg, 12.5 mg, or 25 mg) for 24 weeks.¹⁰ Total testosterone levels ranged from 19 ng/dL with placebo to 210 ng/dL with 25-mg IM testosterone, with the highest doses of testosterone resulting in hormone concentrations approaching the lower limit of normal for men. Significant increases compared with placebo for libido and frequency of sexual activity were seen only in women assigned to the 25-mg testosterone group. Sexual encounters per week increased by approximately 0.5 in women treated with placebo and lower testosterone doses compared with an increase of 2.7 per week in women assigned to the highest testosterone dose.

Use of testosterone in clinical practice. Although no testosterone product is currently approved for the treatment of HSDD in women in the United States, it is commonly prescribed off-label,

often as a compounded topical cream or as a reduced dose of a testosterone gel (1%) FDA approved for men (eg, AndroGel, Testim). As serum testosterone levels in women are approximately one-tenth those in men, prescribing one-tenth of a standard dose used for male hypogonadism typically raises blood testosterone levels in postmenopausal women to those seen in women of reproductive age. A popular but untested treatment is the use of custom-compounded testosterone ointment or cream (1%), 0.5 g daily, applied topically to the arms, thighs, or low abdomen. Topical testosterone also may be applied to the vulva or vagina, but absorption in this area is erratic, and local irritation common. Clinical trials have not evaluated the safety or efficacy of compounded testosterone for any indication, including improvement of female sexual function.

Women using government-approved testosterone gel products formulated for men are at increased risk of excessive dosing, as are women using testosterone IM injections or testosterone implants. Using compounding testosterone cream also has drawbacks because compounded products are not subject to strict government oversight, so quality, purity, batch-to-batch consistency, and bioavailability are variable and typically untested. Methyltestosterone is a potent oral androgen with potential adverse effects on lipids and liver function.

Risks. Potential risks of androgen therapy include hirsutism, acne, irreversible deepening of the voice, and adverse changes in liver function and lipids. Topical androgen creams and gels may be absorbed by others after close physical contact after application. Limited data are available on the risks associated with long-term androgen use in women. Because most androgens are aromatized to estrogens, the risks of estrogen therapy also are possible with androgen treatment, including an increased risk of CVD and breast cancer.

Monitoring therapy. Women should be advised to stop therapy if a clinically significant improvement in libido and associated distress is not seen within 3 to 6 months of initiating testosterone or if adverse effects occur. Women should be monitored for androgenic adverse effects, including acne and increased facial and body hair. Liver function tests and a fasting lipid profile should be checked before initiating treatment. Although these tests are unaffected by physiologically dosed transdermal testosterone, underlying liver disease or hyperlipidemia would be a contraindication to androgen therapy. Testosterone levels should be measured before initiating therapy to rule out a hyperandrogenic state. Because there is a risk of excessive dosing with the use both of compounded topical testosterone and products approved for men, testosterone levels should be measured intermittently during treatment to be certain that they remain in the normal range for reproductive-aged women. Assays for total testosterone are generally more reliable than those for free testosterone in the low concentrations seen in women.

Summary

The only current indication for testosterone therapy supported by clinical trial evidence is the treatment of HSDD in carefully selected postmenopausal women with no other possible etiology for the sexual problem. Androgens may have a role in muscle function, lean body mass, mood, energy, and bone strength, but testosterone use for any of these potential indications is not supported by research.

Female sexual dysfunction after menopause is a complex problem with many etiologies. Careful evaluation of physiological, psychological, lifestyle, and relationship variables is required to optimize treatment. Based on findings from a detailed sexual history and physical exam,

established safe and effective interventions should be tried before considering androgen therapy. Options may include treatment of anxiety and depression, adjusting antidepressant medication, date nights, relationship counseling, stress reduction, sex therapy, and treatment of GSM and disruptive night sweats.

Postmenopausal women with HSDD considering a trial of testosterone must be informed of limitations of available formulations, off-label nature of use, potential risks and adverse effects, and lack of long-term safety data. The high placebo response seen in trials of testosterone therapy should be discussed, with efficacy beyond placebo seen in some but not all studies. Women should try available safe and effective alternative interventions before considering a trial of testosterone.

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Disclosure

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