

Decreased Sexual Desire

Navigating the complexities of diagnosis and treatment

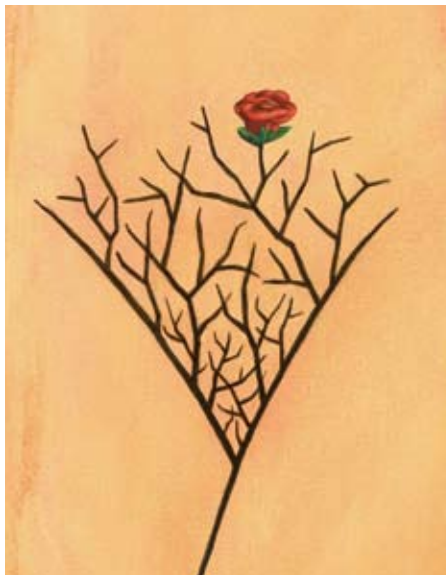
PART 1
OF A 3-PART
SERIES

Low libido after menopause: Considerations and therapy

If the treatment of low sexual desire in postmenopausal women confounds clinicians, it is no surprise. Criteria and diagnostic tools to define androgen deficiency remain elusive; extant therapeutic agents are not approved by the US Food and Drug Administration (FDA). Statements from medical associations provide conflicting guidance: the Endocrine Society recommends against the diagnosis of androgen deficiency, citing the absence of a well-defined clinical syndrome and lack of data on normal total or free testosterone levels, and also discourages the generalized use of testosterone until more data are available.¹ Conversely, the North American Menopause Society stands by its 2005 position that it is appropriate to treat sexual dysfunction that causes distress with exogenous testosterone after other conditions have been ruled out.²

Regardless of the controversy surrounding diagnosis and treatment, clinicians report that low libido is a frequently heard complaint. Supporting data from epidemiologic studies show that sexual dysfunction is an important public health concern. Low sexual desire among women was the most prevalent complaint in the National Health and Social Life Survey of sexual function in 1749 women and 1410 men aged 18 to 59 years.³ This survey revealed that sexual dysfunction is more prevalent for women (43%) than for men (31%).

Sexual dysfunction results from physiological and psychological factors, interpersonal relationships, and sociocultural influences (TABLE 1). Sexual dysfunction is divided into 4 categories: hypoactive sexual desire disorder (HSDD), sexual arousal



disorder, sexual orgasmic disorder, and sexual pain disorder. HSDD is the persistent recurrent deficiency or absence of sexual fantasies, thoughts, and desire, which causes personal distress. The factors that contribute to decreased sexual desire or receptivity to sexual activity are not well defined. Nevertheless, good evidence supports the role of low androgen production, particularly testosterone, in HSDD.⁴ In such cases, administration of exogenous testosterone may be an effective treatment. Strategies to identify and treat postmenopausal women who might benefit from testosterone therapy are discussed below.

Potential role of testosterone in female sexual function

Biological and clinical evidence shows that testosterone has a significant role in sexual desire in postmenopausal women,^{5,6} even if serum testosterone levels have not been clearly linked to sexual function in postmenopausal women.⁷

John E. Buster, MD

Professor, Obstetrics and Gynecology
Division of Reproductive Endocrinology
Department of Obstetrics
and Gynecology
Warren Alpert Medical School
of Brown University
Women and Infants Hospital
of Rhode Island
Providence, Rhode Island

Paula Amato, MD

Adjunct Associate Professor
Division of Reproductive
Endocrinology and Infertility
Department of Obstetrics and
Gynecology
Oregon Health & Science University
Portland, Oregon

Dr Buster reports that he is a consultant to Procter & Gamble and Vivus, Inc.

Dr Amato reports that she is on the speakers' bureau of Procter & Gamble.



KEY POINT

The adrenal cortex shrinks with age, producing less testosterone in peri- and postmenopause.

TABLE 1

Factors in Female Sexual Dysfunction

Physiological

- Cancer
- Cardiovascular disease
- Fatigue
- Hormonal loss or abnormality
- Medications
- Neurological problems
- Urogenital disorders

Psychological

- Alcohol/substance abuse
- Depression/anxiety
- Prior sexual or physical abuse
- Stress

Interpersonal relationships

- Lack of partner
- Lack of privacy
- Partner performance and technique
- Relationship quality and conflict

Sociocultural influences

- Conflict with religious, personal, or family values
- Inadequate education
- Societal taboos

In healthy, premenopausal women, the adrenal cortex and ovaries produce 5 major androgens important for sexual function, namely, testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate.⁴ As the adrenal cortex decreases in size with aging, dehydroepiandrosterone sulfate production and testosterone levels decrease (FIGURE 1). Although the ovaries continue to secrete testosterone postmenopausally, testosterone levels in 40-year-old women are half of what they are in 20-year-old women.⁸

Women who undergo oophorectomy experience a sharp further decline in androgen levels: testosterone and androstenedione levels drop to about 50% after oophorectomy.⁹ The results of one study suggested that this loss of testosterone due to the removal of the ovaries adversely affects sexual function.¹⁰ Oophorectomized women (n=66) and women with intact ovaries reported on

their sexual experience in a structured interview. Sexual function was impaired in women without ovaries, regardless of whether or not they had been treated with estrogen therapy, which indicates that testosterone—rather than estrogen therapy—may be beneficial in preserving sexual function.

This rationale is borne out by trials of testosterone therapy in oral or transdermal formulations that show significant improvements in measures of sexual function on validated questionnaires.¹¹⁻¹⁶

Identifying possible causes of sexual dysfunction

The diagnosis of HSDD is established based on symptoms and circumstances (FIGURE 2).^{17,18} A clinical evaluation of sexual dysfunction must include a complete medical and psychosocial history that identifies intrapersonal, contextual, interpersonal, and biological factors that contribute to sexual health; if possible, both partners should be evaluated. This interview is important to identify causative psychosocial factors, such as mental health issues (depression, self-esteem, anxiety, fatigue) and social factors (partners, work, and family). HSDD refers exclusively to diminished sexual desire.

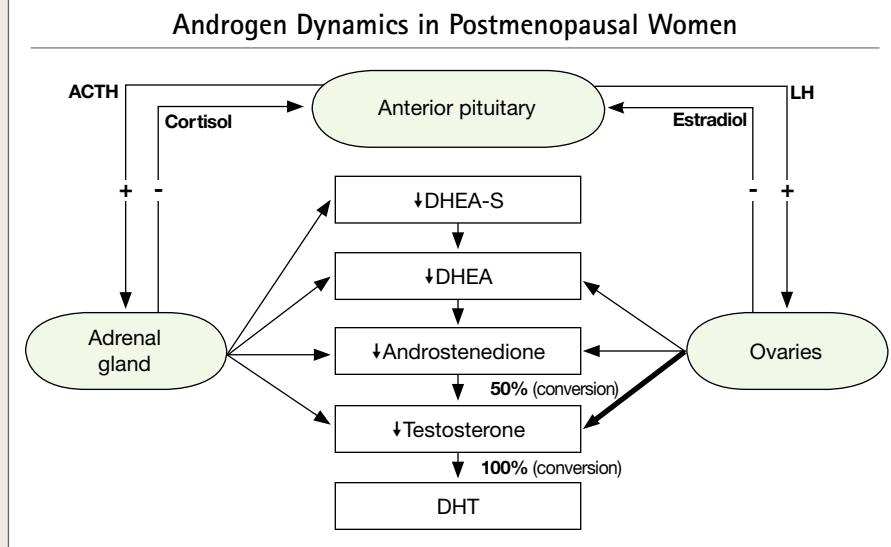
It is necessary to investigate the use of any medications that may adversely affect female sexual desire, such as selective serotonin reuptake inhibitors (SSRIs). Clinicians should review with patients the reasons that SSRIs were prescribed and explore the options for switching to another agent. Corticosteroids suppress the adrenal cortex and, therefore, suppress androgens. Finally, oral estrogen preparations decrease bioavailability of testosterone by increasing circulating sex hormone-binding globulin (SHBG), which increases testosterone binding.

Evaluating sexual dysfunction: Laboratory tests

Measurement of testosterone levels can support the diagnosis of HSDD, but is not in itself diagnostic.

Laboratory tests for ovarian failure or adrenal insufficiency may be indicated, as these conditions may lead to decreased androgen. Thyroid disease, adrenal disease, pituitary disease, metabolic or nutritional disorders, depression,

FIGURE 1



ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; LH, luteinizing hormone.
Reprinted from Buster JE, et al. In: Lobo RA, ed. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects*. 2nd ed. Philadelphia, PA: Lippincott, Williams and Wilkins; 1999:142.

immunologic disorders, or hypothalamic disease should be ruled out as the cause of sexual dysfunction.

Assays for total testosterone level, SHBG level, and the free androgen index (the total testosterone/SHBG ratio) are insensitive at low ranges, which limits the value of these tests. Additionally, without normative data on total or free testosterone levels in women, it is not possible to diagnose a woman as androgen deficient.¹

Clinicians should determine clinically if the patient is adequately estrogenized because menopausal symptoms and vaginal dryness can affect desire.¹⁹ However, because oral—not transdermal—estrogen therapy may decrease testosterone bioavailability by increasing the levels of SHBG, nonoral estrogen may be preferable for women who experience low sexual desire.²⁰

The decision to treat a patient with testosterone is simplified when the patient has a concomitant condition that is a known etiology of sexual dysfunction. These include oophorectomy, ovarian failure, adrenal insufficiency, hypopituitarism, or chronic illness. Women who had normal sexual function prior to one of these diagnoses respond well to testosterone therapy,¹³⁻¹⁵ because for them, the cause of diminished libido is often hormonal.

For women whose low libido is of unknown etiology, once psychosocial or medical causes are ruled out, a diagnosis of HSDD may be made and a trial of androgen therapy may be warranted.

Testosterone therapies under investigation

There are no FDA-approved treatments for HSDD. Nevertheless, a number of testosterone products approved for different indications or not approved by the FDA have been investigated for use in women (TABLE 2).

Methyltestosterone, 1.25 mg, is administered orally in combination with esterified estrogen, 0.625 mg. In one trial, estrogen-methyltestosterone therapy significantly improved scores for sexual interest or desire and frequency of desire in postmenopausal women compared with estrogen-only therapy, as measured by the Sexual Interest Questionnaire.¹¹ In another trial, estrogen-methyltestosterone therapy significantly improved scores for sensation and desire compared with estrogen alone.¹² Methyltestosterone has been associated with a decrease in high-density lipoprotein (HDL) cholesterol and an increase in total cholesterol/HDL cholesterol ratio.

Transdermal testosterone, 300 mcg, has been shown to significantly increase

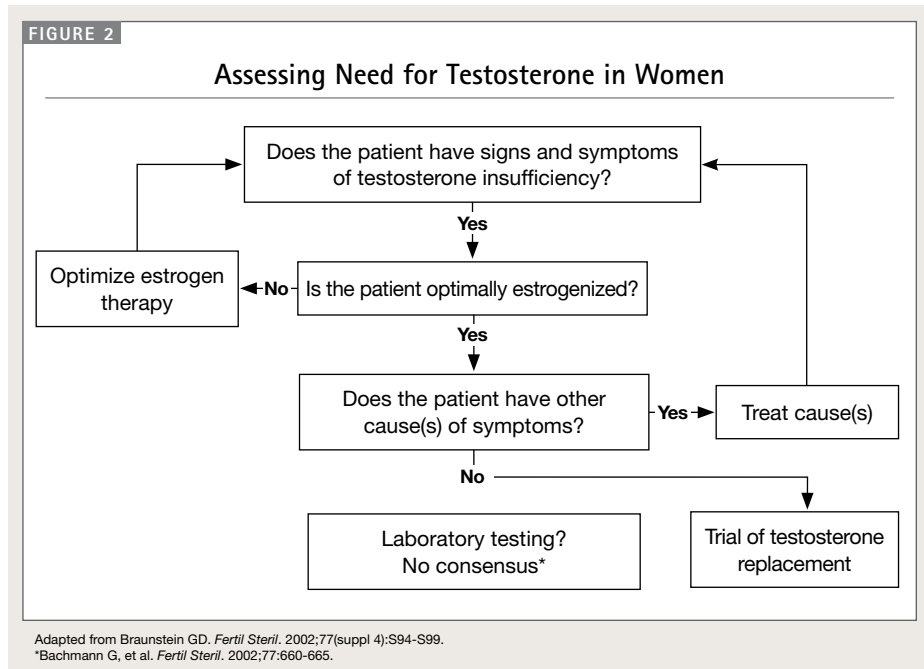
KEY POINT

Nonoral estrogen may benefit women who experience menopausal symptoms and vaginal dryness, which can reduce desire.



KEY POINT

Sexual desire increased and personal distress decreased in a clinical trial of transdermal testosterone.



sexual thoughts and desires, arousal, and frequency of satisfying sexual activity in women, though it is only approved for men.¹³⁻¹⁵ In a study of 75 surgically menopausal women, a 300-mcg testosterone patch increased scores for frequency of sexual activity and pleasure-orgasm in the Brief Index of Sexual Functioning for Women.¹³ With this therapy, the percentages of women who had sexual fantasies, masturbated, or engaged in sexual intercourse at least once a week increased 2- to 3-fold from baseline. In a 12-week trial of 533 surgically menopausal women using a testosterone patch, 300 mcg/d, total satisfying sexual activity increased by 1.56 episodes per 4 weeks from baseline with the patch, compared with an increase of 0.73 episodes per 4 weeks without therapy ($P = .001$).¹⁴ Treatment with testosterone significantly improved sexual desire and decreased personal distress. A similar trial reported by another group confirmed these results.¹⁵

Testosterone that is administered transdermally avoids first-pass hepatic metabolism and, therefore, does not cause any significant change in lipids or lipoprotein levels.¹⁴

Compounded testosterone creams are available from compounding pharmacies and are not regulated by the FDA. Dosing is not standardized and absorption of the hormone varies by patient, so their use

requires diligent monitoring. Individualized dosing can be achieved by applying a known dose to a woman's wrist. Serum hormone levels should be measured 4 to 6 weeks later, at which time a clinician can document how much of the hormone is in the bloodstream and adjust the formulation accordingly.

Using and monitoring testosterone therapy

The goal of treatment should be to increase sexual desire without producing the side effects of hirsutism, acne, or virilization. Other possible but rare effects (if doses are monitored) are alopecia, liver toxicity, adverse effects on lipoproteins, and clitoromegaly.

Patients should be counseled about these side effects and told that the available data on testosterone therapy are for 6 months' duration in postmenopausal women taking concomitant estrogen. They should understand that testosterone therapy is not approved by the FDA for decreased female sexual desire and that the effects of testosterone therapy on the risk of breast cancer and cardiovascular disease or on thromboembolic events are unknown.

Conclusion

Without a clear definition of androgen deficiency or approved therapeutic agents,

treatment of low libido in women remains a clinical challenge. The first part of this challenge is the dearth of tools available to diagnose androgen insufficiency. There are no clinical methods for measuring testosterone transformation and action in target tissue.

The second necessity is having approved therapeutic agents. Patients would benefit if there were a therapy available with standardized, uniform dosing. There is better surveillance and reporting with approved agents, and long-term safety data could be collected. The testosterone patch has been approved for use in Europe. It is hoped that long-term safety data will emerge with this experience and will be encouraging.

Other drugs that do not contain testosterone are being developed in response to patient need. Flibanserin, currently in phase 3 clinical trials, acts on the central serotonin and dopamine systems. Bremelanotide, a nasal inhalant, is in phase 2a and 2b trials. Tibolone, a hormone-based drug approved in Europe, is being tested in the United States.

In the meantime, clinicians must nonetheless provide the best possible care for their patients with off-label testosterone therapies, which may have been modified to approximate delivery systems for which clinical trial data are available. ■

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TABLE 2

Therapies Available and Under Investigation*

Oral

- Methyltestosterone
- Testosterone undecanoate

Intramuscular

- Testosterone propionate
- Testosterone cypionate
- Testosterone enanthate

Subcutaneous (implant)

- Testosterone propionate pellets*
- Testosterone crystalline pellets*

Transdermal

- Transdermal testosterone patch*
- Testosterone gel*
- Testosterone emulsion*
- Testosterone spray*

Other testosterone agents

- Testosterone-containing vaginal ring*
- Sublingual testosterone in propylene glycol*

Non-testosterone agents

- Bremelanotide*
- Flibanserin*
- Tibolone*

*Not approved by US Food and Drug Administration for use in women.

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KEY POINT

Testosterone levels do not correlate with sexual functioning because the most significant androgen actions and transformations occur in target tissues—not in blood.