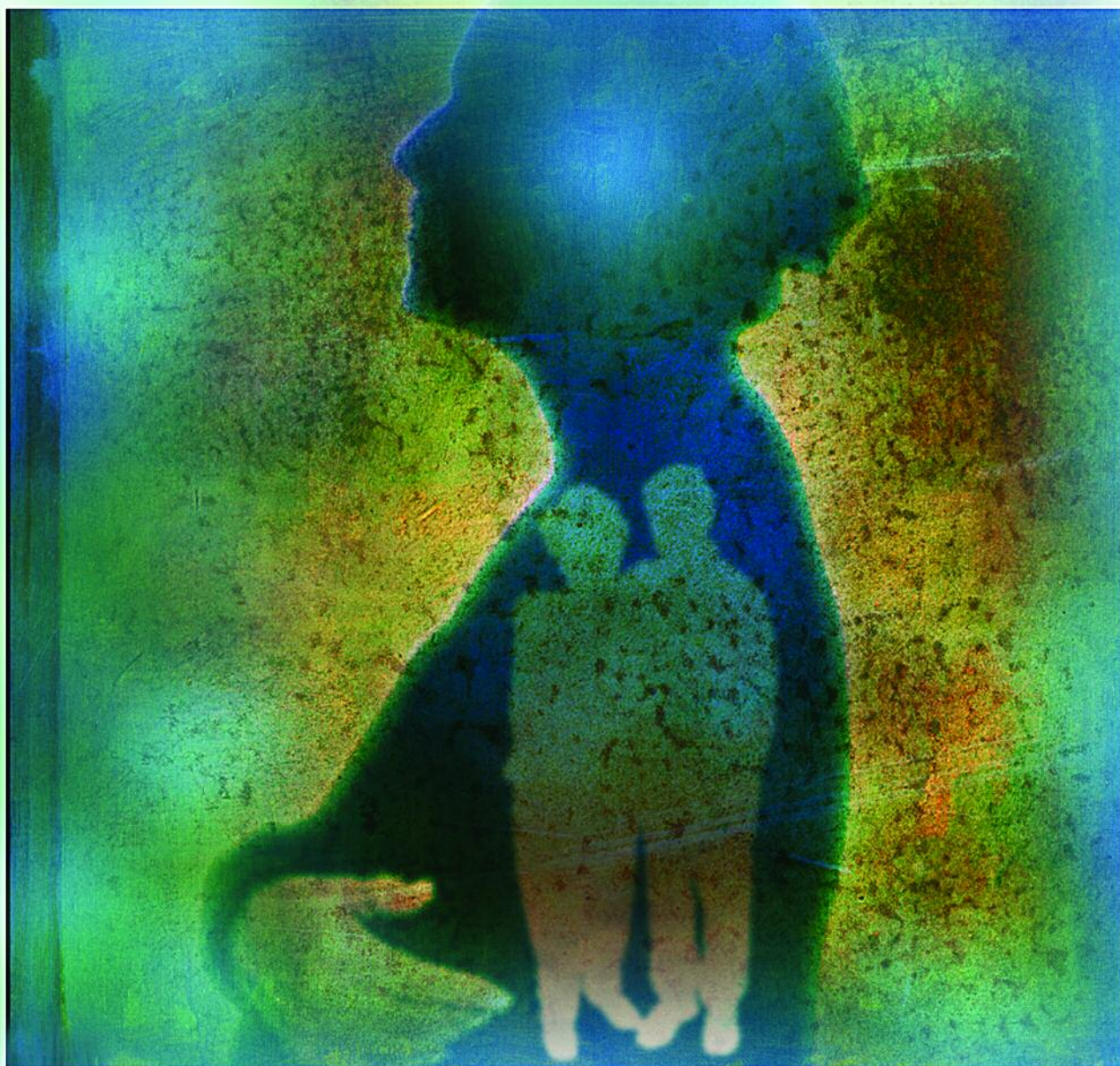

The Role of Testosterone in the Treatment of Hypoactive Sexual Desire Disorder in Postmenopausal Women

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Introduction

Sexual dysfunctions are common in women of all ages, but aging and menopause—both natural and surgically induced—are associated with an increased risk of dysfunction due to declining levels of estrogen and testosterone. Although estrogen therapy (ET) improves vaginal dryness and pain, it does not directly affect sexual desire. Accumulating data suggest that testosterone improves sexual function, including desire, in postmenopausal women. This article reviews the etiology and treatment of hypoactive sexual desire disorder (HSDD), with a particular focus on emerging testosterone therapies.

Hypoactive Sexual Desire Disorder

The American Foundation of Urologic Disease (AFUD) defined HSDD as persistent or recurrent deficiency (or absence) of sexual fantasies, thoughts, and/or desire for, or receptivity to, sexual activity, which causes personal distress.¹ Recently, an international committee organized by AFUD revised and expanded this definition.² The newly defined sexual desire/interest disorder is characterized by a woman's absent or diminished feelings of sexual interest or desire, absent sexual thoughts/fantasies, lack of responsive desire, and absent or scarce motivation for attempting to become sexually aroused. Both the absence of responsive desire and lack of spontaneous sexual thinking and desire are required to establish the disorder. In addition, the reductions in sexual desire or interest should be considered greater than the normative changes expected with aging or relationship duration. Although the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* has not updated its definition of HSDD in women,³ a new code has been added to the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* for decreased libido outside of a mental health diagnosis.⁴

Low desire is a common female sexual complaint. In the National Health and Social Life Survey (NHSLs) of 1,749 women and 1,410 men ages 18 to 59 years, lack of interest in sex was the most prevalent female sexual dysfunction, with one-third of the women reporting lack of interest.⁵ A longitudinal study of women ages 45 to 55 years demonstrated that frequency of sexual activity and libido decreased significantly in women after menopause.⁶ Other studies indicate that approximately 40% of women experience low sexual desire after menopause.^{7,8}

Recent definitions of HSDD indicate that, in most cases, this disorder has a mixed etiology of biological and psychological factors. Aging, illness, depression, the use of certain medications, abnormal hormone levels, or interpersonal problems may lead to low sexual desire. Declining ovarian function and resulting hormone insufficiencies characteristic of menopause are associated with changes in sexual function, including loss of desire. Some studies have found that psychosocial factors, such as marital status and mental health, can have a greater impact on sexual function in menopause than hormone levels.^{6,9} In the Global Study of Sexual Attitudes and Behaviors,¹⁰ an international survey conducted among adults 40 to 80 years of age, Laumann et al found that women's lack of sexual interest was associated with the following factors: the belief that aging reduces sexual desire or activity, infrequent sexual thinking, low expectations for their relationships' future, and infrequent sex.

It is important to determine the originating cause of low sexual desire. Both biological and psychosocial factors can play a role, and these factors may be closely related. Women who reported low sexual desire in the NHSLs also reported feelings of low physical and emotional satisfaction and low general happiness.⁵ The Women's International Study of Health and Sexuality (WISHeS), a mail survey of 2,050 premenopausal, perimenopausal, and postmenopausal

women ages 20 to 70 years in the United States, showed that approximately 30% of women reported having low sexual desire, with 50% experiencing distress due to their low desire.¹¹ It is possible that the loss of sexual desire caused by biological factors result in distress, and that distress can, in turn, lower sexual drive.

Evaluation of HSDD

Discussions surrounding sexuality are often uncomfortable for patients and physicians. A few open-ended questions regarding sexual activity can be used to increase comfort and help initiate a discussion about sexual concerns. Specific questions can be used to assess the presence of low sexual desire and any associated distress in patients at risk for HSDD, such as women who have undergone oophorectomy. Similarly, as women encounter menopause, it is a good time to discuss any concerns relative to their sexuality.

A diagnosis of HSDD should be based on complete medical and sexual histories. Comorbid illnesses or concomitant medications that may interfere with sexual function should be identified and addressed. The duration of low sexual desire also can provide clues to the cause of HSDD. A decrease in desire occurring with age or the transition to menopause can be a clue to an underlying physiologic basis for low desire. Because psychological factors may be involved, partner relationships, past sexual experiences and emotional problems should be considered as well.

Postmenopausal Hormone Levels and Sexual Function

Testosterone levels progressively decrease with age. Women in their forties have approximately half the level of testosterone of women in their 20s.¹² Women who undergo bilateral oophorectomy experience a precipitous decline in circulating testosterone levels, decreasing to half of the levels prior to oophorectomy.¹³ A small longitudinal study that followed still-cycling

perimenopausal women until 1 year after their last menstrual period found that postmenopausal status was associated with fewer sexual thoughts, increased pain resulting from lack of vaginal lubrication, and decreased satisfaction with one's partner.¹⁴ Declining testosterone levels also were linked to decreased coital frequency in this study. Another longitudinal study that followed 326 women, ages 35 to 47 years, through the transition to menopause for 4 years found that although mean testosterone levels were not associated with decreased libido, women whose testosterone levels fluctuated significantly during the study period were two to four times more likely to report decreased libido.¹⁵ Larger studies of approximately 3,000 women¹⁶ and 1,400 women,¹⁷ respectively, did not find correlations between testosterone levels and sexual function in women at midlife and beyond. These data suggest that measuring testosterone levels is not an effective way to diagnose low female sexual desire.

Menopause-related decreases in estrogen levels have a negative impact on sexual function but not a direct effect on desire. Studies suggest a significant relationship between low levels of estradiol (<50 pg/mL) and vaginal dryness, dyspareunia and pain, and ET has been shown to increase vaginal lubrication and decrease vaginal atrophy.⁸ Declining estradiol levels also are associated with reduced blood flow in the non-sexually aroused state, which may adversely affect sexual function.¹⁸ While estrogen impacts the urogenital and vascular systems, it does not appear to play a role in arousal or frequency of activity.¹⁹

Treatment of Sexual Dysfunction after Menopause

The importance of testosterone in female sexual function, particularly after menopause, has gained increasing attention. Accumulating evidence indicates that testosterone treatment improves sexual function, including low desire, with a low incidence of androgenic adverse events. Although long-term data are not yet available, studies

are ongoing to establish the safety of prolonged testosterone therapy in women. Several published trials are outlined below (a full review of the literature is beyond the scope of this article) and research in this area continues.

Davis et al²⁰ conducted a randomized, single-blind trial of 32 postmenopausal women to investigate the effects of implanted estrogen (50 mg) and combined estrogen (50 mg) plus androgen pellets (50 mg) on sexual function and bone mineral density. Pellets were implanted every 3 months over 2 years. Women receiving combined estrogen-testosterone therapy experienced significantly greater improvement in sexual activity, satisfaction, orgasm, relevancy (the sense of being connected to one's partner), and pleasure compared with those receiving estrogen alone.

A placebo-controlled, double-blind study investigated the effects of 12 weeks' treatment with a transdermal testosterone patch (150 µg/d and 300 µg/d) in 65 oophorectomized women with impaired sexual function.²¹ Women in the study also received concomitant ET. After 12 weeks of treatment, sexual frequency and pleasure-orgasm, but not sexual thoughts/desires, increased significantly in the group receiving estrogen plus the higher dose of testosterone.

In a larger 24-week, double-blind study of 340 women with surgically induced menopause who had HSDD and were receiving concomitant ET or estrogen-plus-progestogen therapy (HT), transdermal testosterone (300 µg/d) was shown to increase sexual desire and total satisfying sexual activity compared with placebo ($P < 0.05$).²² The 150 µg/d dose of transdermal testosterone showed no evidence of a treatment effect, and 450 µg/d was not statistically different from 300 µg/d. No serious adverse events were identified during the study.

Additionally, in two 24-week, phase III studies conducted in approximately 1,100 women with surgically induced menopause who had HSDD and who also received concomitant ET or HT, treatment with transdermal testos-

terone (300 µg/d) resulted in increased sexual desire, increased total satisfying sexual activity, and decreased distress compared with placebo ($P < 0.05$).^{23,24} The safety profile was similar between the testosterone treatment and placebo groups, with slightly higher androgenic adverse events in the testosterone group. Most of these adverse events were mild in severity.

A randomized, double-blind study of 218 postmenopausal women compared the use of oral estrogen monotherapy (0.625 mg esterified estrogen) to oral estrogen-testosterone therapy (0.625 mg esterified estrogen and 1.25 mg methyltestosterone) for 4 months.²⁵ At the end of the study, mean levels of sexual interest or desire, but not frequency of desire, as measured on the sexual interest questionnaire, increased significantly in the estrogen-testosterone group compared with those receiving estrogen alone. Changes in the Brief-Index of Sexual Functioning in Women did not reach statistical significance with oral estrogen plus testosterone versus estrogen alone. The improvements in sexual function in the estrogen-testosterone group were correlated with significant increases in serum testosterone and significant decreases in sex hormone-binding globulin (SHBG) levels.

These studies support the role of testosterone in female sexual function, and a number of trials indicate that the addition of testosterone to ET improves sexual function in postmenopausal women. Furthermore, these trials demonstrate that in the short-term, the risk of virilizing effects, such as acne and hirsutism, is generally low and the majority of cases, when they do occur, are mild. It is important to note that the effects of testosterone in postmenopausal women not receiving estrogen are unknown. Of the studies conducted to date, several have demonstrated testosterone levels within or close to the normal range.²¹⁻²⁴ When methyltestosterone is administered, methyltestosterone concentrations cannot be measured, but it is

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active at the androgen receptor. Ongoing studies are focused on evaluating high-normal premenopausal testosterone levels.

While estrogens can be helpful in improving vaginal health, they can further depress testosterone levels when given orally. The differential effects of estrogen monotherapy and methyltestosterone-estrogen combination therapy are most likely due to differences in circulating SHBG, the protein that binds estrogen and testosterone in the blood.²⁵ In a study by Simon et al,²⁶ SHBG levels were significantly increased with both doses of estrogen but were significantly decreased in the methyltestosterone-estrogen groups after 3 months of treatment. Nachtigall et al²⁷ found that postmenopausal women receiving ET—either oral conjugated equine estrogens, oral micronized estradiol, or transdermal estradiol—had increased SHBG levels compared with baseline. Concentrations of SHBG increased 100% and 45% in the conjugated and micronized estrogen groups, respectively. Transdermal administration increased SHBG levels to a lesser extent (12%). Therefore, treatment with estrogen alone may lower testosterone levels and adversely affect sexual function. The formulation of estrogen needs to be considered when treating women for low sexual desire.

The impact of psychological, emotional, and relationship factors must be considered when making a diagnosis and initiating treatment. Education about sexual function and sex and/or couples therapy in conjunction with medical interventions may be necessary for treatment of HSDD.

Testosterone Treatment in Women

An FDA Advisory Committee for reproductive health drugs recently voted not to recommend approval for a transder-

Table 1. Routes of Administration and Formulations of Testosterone

Route of administration	Testosterone formulation
Oral	<ul style="list-style-type: none"> • Methyltestosterone • Testosterone undecanoate
Intramuscular	<ul style="list-style-type: none"> • Testosterone propionate • Testosterone cypionate • Testosterone enanthate
Subcutaneous	<ul style="list-style-type: none"> • Testosterone propionate pellets
Transdermal patch	<ul style="list-style-type: none"> • Testosterone
Gel	<ul style="list-style-type: none"> • Testosterone
Emulsion	<ul style="list-style-type: none"> • Testosterone
Sublingual/buccal	<ul style="list-style-type: none"> • Testosterone in propylene

*Not all testosterone formulations and routes of administration are approved by the FDA for use in women.

mal testosterone patch based on the need for longer-term safety data. There are currently no testosterone formulations approved by the FDA for HSDD. If physicians decide to prescribe testosterone products “off-label” for menopausal women with HSDD, they must weigh the risks and benefits for individual patients. Because clinical studies of testosterone included patients on concomitant ET, physicians must determine the appropriate duration of treatment, bearing in mind that estrogen is recommended for short-term use only. Careful follow-up is necessary for all women prescribed any of the testosterone formulations not approved for the intended use.

There are multiple viable routes of administration for testosterone (as shown in Table 1), most of which were developed for men, and some of which are used off-label for treating women. The dosing requirements of these agents when used by women may be unknown or may require suboptimal methods of administration, such as pill-splitting, which can result in increased or inadequate testosterone levels. Compounded formulations of testosterone are available from some pharmacies but are not subject to stringent quality control. As a result, these formulations may have inconsistent dosing and variable efficacy and safety. The following section

profiles the strengths and weaknesses of the different testosterone formulations.

Oral testosterone. Oral testosterone products undergo first-pass hepatic metabolism, which may lead to decreases in high-density lipoprotein levels.^{25,28} An oral formulation of methyltestosterone in combination with estrogen is approved for treating vasomotor symptoms in postmenopausal women and has been demonstrated to improve sexual function compared to estrogen alone, as discussed.²⁵ Testosterone undecanoate, a unique oral formulation that is absorbed via the lymphatic system, is available in the European Union and Canada for male androgen deficiency. It is characterized by rapid absorption and turnover, and dosing requirements for women are unknown.²⁹

Sublingual/buccal testosterone. Sublingual/buccal testosterone does not undergo first-pass metabolism but results in rapid absorption and turnover, requiring increased doses for an effect. Patients also complain that sublingual preparations have an unpleasant taste. In the United States, buccal testosterone is approved for use in men; sublingual formulations are not approved.

Intramuscular testosterone. Intramuscular testosterone preparations bypass the liver but are associated with peaks and valleys of testosterone levels. Consequently, increased doses may be required

Table 2.
Testosterone Therapies in Development for Women

Company	Route of administration	Status
Procter & Gamble Pharmaceuticals	Patch	Phase III
BioSante Pharmaceuticals	Gel (also estrogen + testosterone gel)	Phase II/III
Cellegy Pharmaceuticals, Inc.	Gel	Phase II/III
Vivus, Inc.	Spray	Phase II
Warner Chilcott PLC	Vaginal ring	Phase II
Unimed Pharmaceuticals, Inc.	Gel	Phase I
Novavax, Inc.	Lotion	Phase I

for an effect, and there is an increased risk of hormone accumulation.³⁰ The injectable products can result in temporary supraphysiologic testosterone levels during the first 1 to 2 weeks of intramuscular administration, which can result in androgen-excess side effects.

Subcutaneous testosterone pellets. The metabolism of pelleted forms of testosterone bypass the liver, and although pelleted forms of testosterone deliver stable levels of hormone, studies indicate that there is a risk of achieving supraphysiologic levels in women.³¹ In addition, minor surgery is required for insertion and removal.

Transdermal testosterone patches. The metabolism of transdermal testosterone bypasses the liver and is a well-accepted method of delivery in men; however, no testosterone patches with appropriate doses for women are available at this time.³⁰

Testosterone gels and emulsions. The available gels and emulsions, designed for use in men, are used in women because testosterone exposure can be regulated by the amount applied. Absorption and response may be erratic or unpredictable in some patients, necessitating physician monitoring. Furthermore, there is a risk of transferring testosterone from gels and emulsions to another person via skin contact, and some patients find these formulations messy.

Several testosterone formulations are in development for the treatment of HSDD (Table 2), and several have

demonstrated significant improvements in sexual function and desire.^{22-24,31,32}

Conclusions

Declining levels of estradiol and testosterone characteristic of menopause are associated with sexual dysfunction, including HSDD. Postmenopausal ET improves symptoms of vaginal atrophy and dryness, which negatively impact sexual function, but does not affect sexual desire. Accumulating evidence confirms a role for testosterone in female sexual health and suggests that the addition of testosterone to ET improves sexual function and desire. There are currently no FDA-approved treatments for HSDD, and long-term safety data are needed, but several testosterone therapies are in late-stage clinical trials. The availability of physiologic testosterone therapy is expected to be an advance in the management of HSDD, which should be based on a holistic approach addressing biological and psychological factors and encouraging patient education on sexual function and therapies. ■

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References

- Basson R, Berman J, Burnett A, et al. Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. *J Urol* 2000;163:888-93.
- Basson R, Leiblum SL, Brotto L, et al. Definitions of women's sexual dysfunctions reconsidered: advocating expansion and revision. *J Psychosom Obstet Gynecol* 2003;24:221-9.
- American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Press, 2000.
- Practice Management Information Corporation. *International Classification of Diseases, 9th Revision, Clinical Modification*. Los Angeles, CA, 2000.
- Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999;281:537-44.
- Dennerstein L, Dudley E, Burger H. Are changes in sexual functioning during midlife due to aging or menopause? *Fertil Steril* 2001;76:456-60.
- Harris Interactive, PRIME PLUS, Red Hot Mamas. Sexual communications survey. Available at: <http://www.siecus.org/pubs/fact/fact0018.html>. Accessed September 15, 2005.
- Sarrel PM. Sexuality and menopause. *Obstet Gynecol* 1990;75(4 Suppl):26S-30S.
- Avis NE, Stellato R, Crawford S, Johannes C, Longcope C. Is there an association between menopause status and sexual functioning? *Menopause* 2000;7:297-309.
- Laumann EO, Nicolosi A, Glasser DB, et al. Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *Int J Impot Res* 2005;17:39-57.
- Leiblum SR. Self-reported sexual complaints of US women across the lifespan. Presented at: European Federation of Sexology; May 14, 2004; Brighton, England.
- Zumoff B, Strain GW, Miller LK, et al. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. *J Clin Endocrinol Metab* 1995;80:1429-30.
- Judd HL, Judd GE, Lucas WE, et al. Endocrine function of the postmenopausal ovary: concentration of androgens and estrogens in ovarian and peripheral vein blood. *J Clin Endocrinol Metab* 1974;39:1020-24.
- McCoy NL, Davidson JM. A longitudinal study of the effects of menopause on sexuality. *Maturitas* 1985;7:203-10.
- Gracia CR, Sammel MD, Freeman EW, et al. Predictors of decreased libido in women during the late reproductive years. *Menopause* 2004;11:144-50.

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