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Review

The role of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women

Jill M. Krapf[a], James A. Simon[b,*]

[a] The George Washington University, 2150 Pennsylvania Ave, NW #6A429, Washington, DC 20037, United States
[b] George Washington University, Women's Health & Research Consultants, 1850M Street, NW, Suite 450, Washington, DC 20036, United States

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ABSTRACT

At least 16 million women over the age of 50 currently experience low sexual desire, with approximately 4 million women exhibiting hypoactive sexual desire disorder (HSDD). Although early research established that testosterone therapy improves sexual desire in postmenopausal women, safer and more efficacious administration routes were explored. Large randomized, double-blinded placebo-controlled studies demonstrate that transdermal testosterone improves sexual function and activity in postmenopausal women with HSDD. Large multi-center Phase III trials further confirm the positive effects of the testosterone patch in the treatment of HSDD. More recent studies are exploring the utility of testosterone gels. Based upon data from two recent clinical relevance studies, physicians can be reassured that postmenopausal women with HSDD report a meaningful benefit with testosterone therapy, and further, women will only continue therapy if they experience a meaningful benefit. Although most trials combined testosterone with estrogen/progesterone therapy, the recent APHRODITE trial examined testosterone alone, showing increased sexual desire with mild adverse events. Concerns regarding the long-term safety profile of transdermal testosterone must be addressed before the FDA will approve a testosterone product for women. Although some fear an increased risk of breast cancer with exogenous testosterone administration, recent studies support the idea that androgens can play a role in suppressing the proliferative effects of estrogen and progesterone. Long-term safety data is now being collected and analyzed and Phase III trials focusing on long-term risks are underway. In the meantime, transdermal testosterone appears to be a safe and effective therapy for postmenopausal women with HSDD [Swanson S, DeRogatis L, Snabes M, Simes S, Zborowski J. Treatment of HSDD in surgically menopausal women: a newly initiated Phase III, randomized, double-blind, placebo-controlled, multi-center study of the safety and efficacy of LibiGel. Presented at the Annual Meeting of the International Society for the Study of Women's Sexual Health, February 22–25, Orlando, FL; 2007].

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* Corresponding author. Tel.: +1 202 293 1000; fax: +1 202 463 6150.
E-mail addresses: jkrapf@gwu.edu (J.M. Krapf), jsimon@jamesasimonmd.com (J.A. Simon).

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1. Introduction

The medical field has long accepted the importance of male sexuality, but sexual dysfunction in women and treatment options to address these concerns have met with great controversy. It is estimated that at least 16 million women over the age of 50 currently experience low sexual desire and approximately four million women report associated distress. Aging and menopause has been linked with low libido, with 52% of naturally menopausal women and 39% of surgically menopausal women reporting reduced sexual desire [1]. When low desire leads to distress, it is termed hypoactive sexual desire disorder (HSDD). The definition of this disorder includes three basic criteria for diagnosis: desire for sexual activity, marked distress due to lack of sexual activity, and ruling out psychological, general medical or substance-related causes [2]. The prevalence of HSDD has been estimated between 8% and 26%, highest among surgically menopausal women [3].

The decline of androgen levels with ovarian failure and following oophorectomy has sparked the hypothesis that decreased testosterone is related to diminished desire. To support this theory, data has clearly shown that exogenous testosterone has a positive effect on sexual function in postmenopausal women. Fueled by contradictory guidelines and position statements, concerns over indications and long-term safety of testosterone therapy have spurred literary debates and highlighted the need for continued research.

This article will review the role of testosterone in sexual function, the emerging research examining the effects of transdermal testosterone on postmenopausal women with low sexual desire and HSDD, and the recent data exploring the clinical relevance of testosterone treatment outcomes. Data examining testosterone therapy without concurrent estrogen and the risk of breast cancer with testosterone administration will also be discussed.

2. Physiology of testosterone and sexual dysfunction

In women, androgens are derived from three sources: the adrenal glands, the ovaries, and peripheral conversion. About 99% of circulating testosterone is bound to sex hormone-binding globulin (SHBG). Pregnancy and estrogen therapy can increase SHBG production resulting in lower levels of free testosterone; whereas insulin and androgen therapy, obesity and menopause decrease levels of SHBG, resulting in slightly increased concentrations of free testosterone. Decreases of testosterone noted in postmenopausal women occur very gradually and are more likely a result of age, resulting in declining ovarian and adrenal function, rather than postmenopausal status [3,4]. A recent cross-sectional study of women aged 18–75 years found that total and free testosterone levels significantly decrease with age, starting in the early reproductive years. In contrast to natural menopause, women who undergo bilateral oopherectomy experience a dramatic decline in testosterone production, with levels decreasing as much as 50% [5].

The link between androgen levels and sexual dysfunction has been clouded by the inability to measure total and free testosterone in women accurately and precisely using currently available assays. Two of the larger more recent studies have shown no association between sexual dysfunction and serum testosterone levels [6,7]. Due to these concerns, the North American Menopause Society cautions that testosterone levels should not be used to diagnose testosterone insufficiency or to determine the efficacy of treatment, but only to monitor for supraphysiologic levels before and during testosterone therapy [4].

3. Testosterone therapy for low sexual desire and HSDD

3.1. Initial research with exogenous testosterone

In 1983, Dow et al. conducted one of the first randomized controlled trials of exogenous estrogen in postmenopausal women. Testosterone implant therapy (100 mg) was added to estradiol implant therapy (50 mg) in 40 postmenopausal women with decreased sexual interest. No significant differences were found between the two groups [8]. Sherwin et al. conducted a prospective crossover study examining the effect of intramuscular testosterone on sexual function in 53 surgically postmenopausal women. Participants were randomized to testosterone alone (200 mg testosterone enanthate), estrogen alone (10 mg estradiol valerate), testosterone plus estrogen (7.5 mg estradiol dienanthate and 1.0 estradiol benzoiate plus 140 mg testosterone enanthate), placebo, or control. Testosterone significantly increased intensity of sexual desire, arousal and fantasy compared with estrogen alone or placebo [9]. Until recently, this was one of the only studies incorporating a testosterone alone arm, with all other research combining testosterone with either estrogen or estrogen–progesterone therapy.

Two single-blind trials followed, comparing the efficacy of testosterone implants (100 mg) combined with 40 mg estradiol versus estradiol alone in naturally and surgically postmenopausal women with sexual complaints. Significant improvements in libido and sexual pleasure were noted in testosterone-treated women after 6 weeks, with effects persisting throughout the 24-week trial [10]. Davis et al. conducted a similar study in which 50 mg of subcutaneous testosterone was added to estradiol implants (50 mg) in postmenopausal women. Women receiving testosterone showed significant improvements in sexual activity, satisfaction, pleasure and frequency of orgasm compared with women receiving estrogen alone [11].

A double-blind trial in 1998 examined the efficacy of oral testosterone therapy in postmenopausal women already using estrogen therapy. Twenty women were randomized to two conditions: oral esterified estrogens (1.25 mg) or esterified estrogens plus oral methyltestosterone (2.5 mg). At 8 weeks, women receiving testosterone therapy reported significant improvements in sexual desire and satisfaction compared with the estrogen alone group [12]. Floter conducted a placebo-controlled, crossover trial where oral testosterone undecanoate (40 mg/day) was added to oral estradiol valerate (2 mg/day) for 50 surgically induced menopausal women, with each treatment period lasting 24 weeks. Testosterone recipients reported significantly greater interest in and enjoyment of sexual activity compared with women receiving estrogen alone. Free testosterone levels in this study reached 231% of the upper limit value, pushing levels into the supraphysiologic range [13]. The largest trial incorporating oral testosterone included 218 postmenopausal women receiving baseline estrogen therapy with hypoactive sexual desire disorder. This randomized, double-blind trial had a 4-month treatment period with either 0.625 mg oral esterified estrogens combined with 1.25 mg methyltestosterone or estrogen alone. Testosterone recipients reported increased sexual desire and interest, but no improvements in their sexual function score [14]. In 2004, Samboonpan conducted a Cochrane Review meta-analysis, reconfirming that testosterone improved libido, sexual function and sexual activity (Fig. 1) [15].

3.2. Transdermal testosterone patch

Although early studies established that testosterone therapy improves sexual desire and activity in both naturally and surgically induced postmenopausal women, research to explore more efficacious administration routes continued. Transdermal deliv-

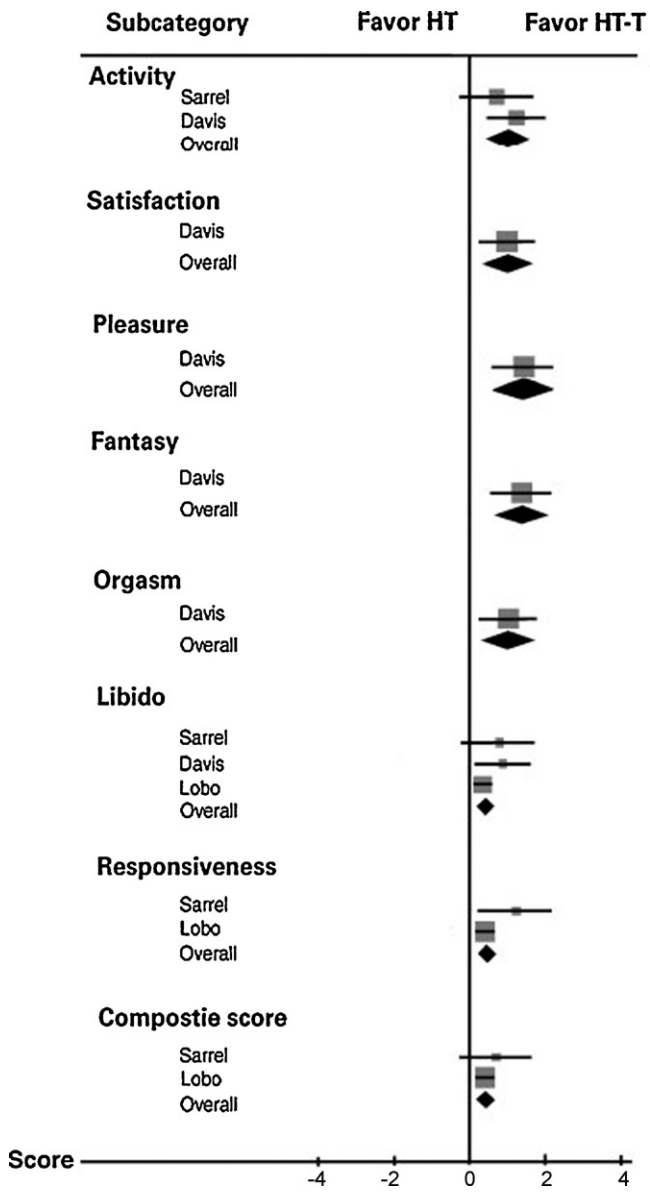

Fig. 1. Effects of testosterone on libido. Cochrane review meta-analysis of two to three randomized, controlled trials comparing hormone therapy alone to testosterone plus hormone therapy. Testosterone improved libido by 0.42 points (95% CI 0.18–0.66), sexual function by 0.41 points (95% CI 0.15–0.67) and sexual activity by 1.00 points (95% CI 0.4–1.58) [15].

ery has the advantages of avoiding first-pass hepatic metabolism and delivering consistent physiologic doses of testosterone [16].

Shifren et al. conducted the first randomized, double-blinded placebo-controlled study of a transdermal testosterone patch. This Phase II trial included surgically induced menopausal women aged 31–56 years with self-reported impaired sexual function, taking oral estrogen therapy. Women with a previously active and satisfying sex life who reported a decrease in these sexual attributes following surgery, but preferred an improvement were identified as having impaired sexual function. The 75 participants were randomly assigned to one of three 12-week treatment conditions: 150 mcg/day testosterone patch, 300 mcg/day testosterone patch, or placebo. Women receiving 300 mcg/day of testosterone reported significantly higher scores for frequency of sexual activity, sexual fantasies, masturbation and organism than those in the lower testosterone group and placebo. The higher testosterone group also showed significant improvement in positive well-being and depressed mood compared with placebo [17].

Another Phase II trial followed in 2005 that included a larger patient population, a longer treatment period, and a higher dosage group. Braunstein et al. (2005) randomized 318 surgically induced postmenopausal women with HSDD already receiving oral estrogen to a 24-week period of varying doses of the testosterone patch (150 mcg/day, 300 mcg/day, or 450 mcg/day) or placebo. Differing from Shifren et al. (2000), this study employed parallel groups instead of a crossover design. This study also used three efficacy instruments to assess female sexual function that had been validated in previous studies: the Profile of Sexual Activity Log (SAL), the Profile of Female Sexual Function (PFSF) and the Personal Distress Scale (PDS). Significant increases in sexual desire and frequency of satisfying sexual activity were found only in the 300 mcg/day group compared with placebo. Sexual desire increased 67% from baseline with the 300 mcg/day testosterone patch versus an increase of 48% with placebo. Satisfying sexual experiences increased 0.58 each week in the 300 mcg/day testosterone treatment group, which was statistically significant. No treatment effect was seen in the 150 mcg/day or, interestingly, the 450 mcg/day treatment group, which raises questions of a possible dose–response curve for testosterone. Frequency of adverse events was similar among all groups with no severe events reported. Application-site reaction was the most common complaint [18].

To further investigate the efficacy and safety of transdermal testosterone, two concurrent Phase III trials were conducted in the United States, Canada, and Australia. These large double-blind, multi-center trials were known as Investigation of Natural Testosterone In Menopausal Women Also Taking Estrogen in Surgically Menopausal Women (INTIMATE SM) 1 and 2. The INTIMATE SM 1 study included 562 surgically induced postmenopausal women with HSDD receiving estrogen therapy and assigned them to either 300 mcg/day testosterone patch or placebo for a 24-week trial period. The SAL, PFSF, and PDS were used to measure sexual function, with frequency of satisfying sexual activity serving as the primary end point. Women in the testosterone group reported an increase of 2.1 satisfying sexual episodes per 4 weeks versus 0.98 episodes per 4 weeks in the placebo group. This equates to a 74% increase from baseline in women treated with testosterone compared to a 33% increase from baseline for placebo. Desire for testosterone treated women increased 56% from baseline and personal distress improved significantly, decreasing by 65% in the testosterone group compared to the 40% decrease reported for placebo [19,16].

The INTIMATE SM 2 trial randomly assigned 532 surgically induced postmenopausal women with HSDD to either 300 mcg/day testosterone patch or placebo with either oral or transdermal estrogen. This study utilized the same instruments for assessment of female sexual function and had the same primary end points. Testosterone recipients reported an increase of 1.56 satisfying sexual episodes per 4 weeks versus 0.73 episodes per 4 weeks with placebo, an increase of 51% versus 23% from baseline for each group. Sexual desire increased 49% from baseline in the testosterone group compared to placebo. Distress decreased 68% from baseline in testosterone recipients compared to 48% from baseline in women receiving placebo [20]. Desire for increased satisfying sexual activity and distress due to lack of satisfying sexual experiences form the very definition of hypoactive sexual desire disorder.

3.3. Testosterone gels

Given the promising results of testosterone implants and patches, researchers began exploring transdermal testosterone gel as a possible alternative. In 2005, Nathorst-Boos et al. conducted a double-blind, randomized, placebo-controlled crossover study to

determine if treatment with 10 mg testosterone gel per day could improve sexuality and psychological well-being, as assessed by the "Psychological General Well Being Questionnaire," in a sample of 53 postmenopausal women with low libido already taking hormone replacement therapy. In a preliminary pharmacologic study, the group found that the 10 mg dose produced serum levels of testosterone within the normal range when applied to the outer thigh as compared to a 20 or 30 mg dose. Daily application of the testosterone gel during the 3-month trial period resulted in significant increases in arousal, excitement and fantasies, with significant improvements in anxiety and positive well-being. Side effects during treatment did not differ between the testosterone and placebo groups and no changes in lipid profile were seen [21]. El Hage et al. conducted a similarly designed study in 2007 that included only hysterectomized postmenopausal women already taking transdermal estrogen. Similarly, the authors found that the 10 mg topical testosterone dosage significantly improved sexual desire, frequency of sex, and receptivity and initiation of sex as measured by the Brief Index of Sexual Functioning for Women (BISF-W), the same questionnaire used by Shifren et al. for the transdermal testosterone patch [22,17].

4. Clinical relevance

Although data showed statistically significant improvements in sexual function measures for postmenopausal women undergoing testosterone therapy, it was not known whether these effects were clinically significant. Kingsberg et al. addressed this important query with a clinical relevance study using an anchoring technique to validate the findings of the INSTIMATE SM studies. This study included a representative sample of 132 postmenopausal women with HSDD from the INTIMATE SM studies. The sample, which formed approximately 12% of the total participant pool, was interviewed prior to unblinding, with the direct question for the anchoring analysis being "Overall. . . would you say that you experienced a meaningful benefit from the study patches?" Women were also asked how likely they would continue the patches [23].

Fifty-two percent of testosterone recipients reported experiencing an overall meaningful benefit, compared to 31% of women who received placebo, which was statistically significant. Among the women who labeled themselves as receiving a meaningful benefit, the number of satisfying sexual experiences increased to 4.4 times in 4 weeks compared to an increase of 0.5 times in 4 weeks in women reporting no meaningful benefit. The desire score was 21, changed from "seldom" to "sometimes" feeling desire, in the meaningful benefit group compared to 2.9 for placebo. The distress rating was −36.5, moving from "often" to "seldom" being distressed, in the meaningful benefit group, compared to −8.8 for placebo (Fig. 2) [23].

More than 85% of women who had a meaningful benefit stated they would continue the testosterone patch. More than 90% of women with no meaningful benefit stated they would not continue the patch (Fig. 3) [23]. As Kingsberg et al. pointed out, these findings are reassuring as patients who gain benefit from the testosterone patch will continue with therapy, whereas patients who feel that patch does not work with discontinue the medication [16].

Recently, DeRogatis et al. conducted a similar study to determine the clinical relevance of the testosterone treatment findings for postmenopausal women with HSDD. The aim of this study was to quantify the magnitude of change for the components that form the definition of HSDD, related to the perception of meaningful benefit with testosterone patch therapy. The researchers identified minimum important differences (MIDs) for sexual desire, significant sexual activity, and personal distress, comparing "treatment responders" and "nonresponders" using the direct "meaningful benefit" question from Kingberg (2007). Data indicate that increases in frequency of satisfying sexual activity greater than one episode in 4 weeks increases the sexual desire score to greater than 8.9 and decreases the personal distress score to greater than 20.0 [24]. These parameters were identified as threshold improvements that were able to delineate responders from non-responders [23,24]. A change of greater than one episode of satisfying sexual activity in a month from baseline may seem small, however, for the women sampled, this change was meaningful and this is clinically significant.

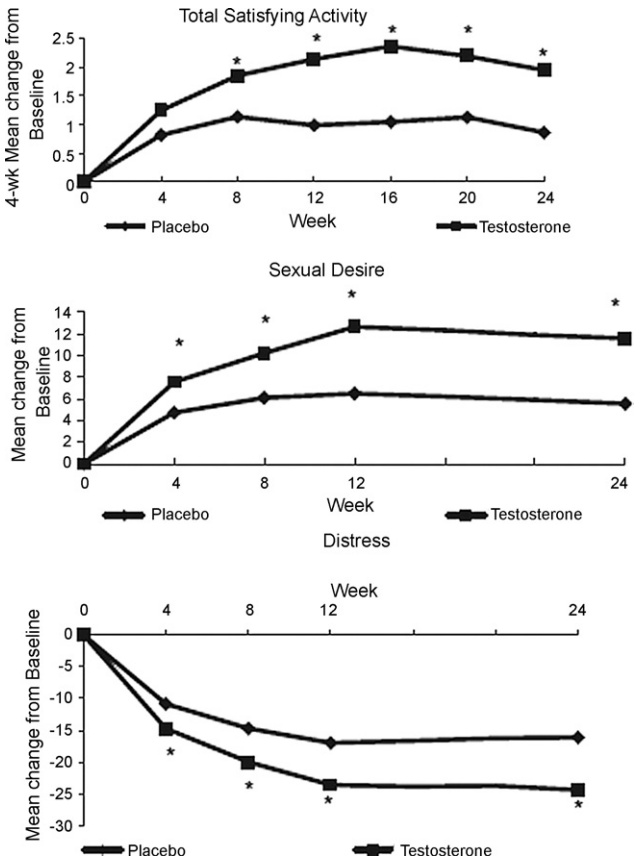

Fig. 2. Effects of testosterone on sexual activity, desire, and distress. Testosterone versus placebo effects on frequency of satisfying sexual activity, sexual desire, and personal distress over time based upon data from two Phase II trials. An asterisk indicates statistical significance ($p < 0.05$) [23].

5. Testosterone without estrogen

Until recently, Sherwin et al. was the only trial to investigate the effects of testosterone without estrogen therapy on low sexual desire in postmenopausal women [9]. Historically, studies of testosterone therapy in postmenopausal women had been limited to participants taking estrogen therapy. There were concerns that testosterone may not be effective without concurrent estrogen therapy or may have adverse effects on lipid levels, glucose, or the breast [25]. The APHRODITE study attempted to address this lack in the research.

Davis et al. conducted a double-blinded, placebo-controlled trial of 814 women with HSDD not currently taking estrogen that were randomly assigned to either a 150 mcg testosterone patch, 300 mcg testosterone patch, or placebo. The primary end point of frequency of satisfying sexual episodes in addition to assessment of female sexual dysfunction using the SAL, PFSF and PDS were measured after a 24-week trial period. Safety was assessed through week 52 and an optional extension phase was continued for an additional

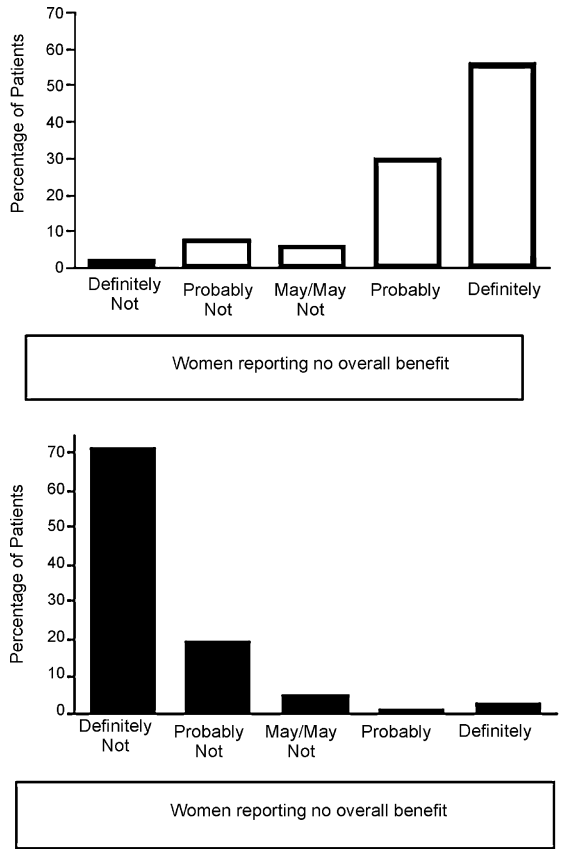

Fig. 3. Clinical relevance of testosterone effects. Responses to the question "Would you be interested in continuing treatment if this product were available?" among women who reported they did or did not experience a meaningful benefit from treatment [23].

year. Consistent with previous data, there was an increase of satisfying sexual episodes seen in the women receiving 300 mcg/day of testosterone, but not in the 150 mcg/day testosterone group. The 300 mcg/day testosterone group reported an increase of 2.1 satisfying sexual episodes per 4 weeks versus 0.7 episodes in the placebo group, equating to 78% of satisfying sexual episodes in the higher testosterone group compared to 65% for placebo. The 300 mcg/day testosterone group reported significantly higher scores for sexual desire and decreased scores for personal distress, comparable to the INTIMATE SM studies [19,20,25].

The incidence of adverse events was comparable between the testosterone and placebo groups. Participates reported application-site reaction and androgenic events as most common reasons for withdrawal from the study. The incidence of androgenic adverse events, most commonly increased hair growth, was highest in the 300 mcg/day testosterone group. Breast cancer was diagnosed with three women in the testosterone groups, with one participate later reporting the presence of symptoms before randomization and another acquiring a diagnosis of cancer 4 months into the therapy period [25]. The possibility of a causal relationship was raised.

6. Long-term safety profile and breast cancer risk

In December 2004, the Food and Drug Administration (FDA) Advisory Committee reviewed the data from the INTIMATE SM studies and other clinic trials exploring transdermal testosterone for HSDD in postmenopausal women. Although the committee accepted the efficacy of the medication, the FDA declined to approve the female testosterone patch Intrinsa (Procter and Gamble Pharmaceuticals) due to a lack of long-term safety data [26]. Most of the large clinical trials spanned a maximum of 24 weeks. Somboonporn reviewed the safety data on testosterone for postmenopausal women and concluded that therapy is associated with a reduction in HDL and triglycerides, but other health outcomes could not be assessed due to insufficient evidence [27,28]. In a 2007 review, Braunstein concluded that there are few prospective long-term data addressing the safety of testosterone administration in women, however controlled studies lasting up to 2 years and observational data in hormone therapy and female-to-male transsexual data is reassuring [29].

The recent APHRODITE study is the longest trial to date, spanning 52 weeks. Thirty-eight percent of participants opted to continue their randomized treatment for an additional year so that further safety data could be collected. The overall incidence of adverse events was similar between the study groups, with the most common reasons for withdrawal being application-site reactions and androgenic events. Although an increase in mild hair growth was seen in the 300 mcg treatment group, women in this group were not more likely to discontinue therapy. There was no significant difference between the groups in regard to lipid profiles. Of note, breast cancer was diagnosed in three women in the testosterone group, although one woman reported symptoms before randomization and another woman reported a sister with breast cancer and using estrogen for 27 years before enrolling in the study [25].

Although the FDA safety concerns focused primarily on cardiovascular risk in lieu of the Heart Estrogen Replacement Study and the Women's Health Initiative study, the possible association of exogenous androgens and breast cancer has also raised valid concerns [29,30]. Evidence that endogenous testosterone increases breast cancer risk and recurrence has led to the fear that hormone therapy regimens that increase free and total testosterone could also increase the risk of breast cancer [30]. The literature does not demonstrate such a clear picture, and data may even indicate a beneficial role of testosterone in breast protection.

In an observational, retrospective study of 508 Australian postmenopausal women using hormone replacement therapy, participants also taking testosterone reported lower rates of breast cancer than women using hormone replacement therapy alone [31]. A more recent longer prospective case–control study including women in the Nurses' Health cohort from 1978 to 2002 reported an increased breast cancer risk in participates using a combination of systemic estrogen and androgen. Data showed that each year of using estrogen plus testosterone during menopause increased the risk of breast cancer 17.2% compared with no hormonal therapy [32]. Design flaws relating to hormone type and therapy duration call for cautious interpretation of these findings [33,34]. After reviewing these observational studies with other prior studies with low sample sizes, Bitzer et al. concluded that there are "no valid randomized or observational clinical studies that provide evidence that the addition of testosterone to conventional postmenopausal hormonal therapy influences breast cancer risk [35]."

In the first prospective study to measure the effects of testosterone on breast cell proliferation, Hofling et al. (2007) randomly assigned 99 postmenopausal women receiving estradiol/norethisterone acetate either a 300 mcg testosterone or placebo patch condition. A fine needle aspiration was performed at baseline and at 6 months to determine the percentage of proliferating breast cells. Results indicated that there was more than a fivefold increase in total breast cell proliferation from baseline in the placebo group at 6 months, whereas there was no significant increase in the testosterone treatment group [36]. These findings are consistent with animal model studies, which support the idea that androgens can play a role in suppressing the proliferative effects of estrogen and progesterone [37]. Results such as these have prompted some to question if testosterone should be added to hormone replacement therapy for breast protection [33].

7. Discussion

Testosterone increases sexual desire and well-being in postmenopausal women with HSDD, which is well-supported by years of research. Although statistical significance is achieved in numerous trials, critics have questioned the clinical significance of seemingly small improvements in sexual outcome measures. It is reassuring that recent clinical relevance studies show that postmenopausal women with HSDD report a meaningful benefit with testosterone therapy. Physicians can also be reassured by the data that women who gain benefit from testosterone therapy, when given a choice, will continue taking testosterone, while those that do not will discontinue therapy. This is an important consideration in weighing risk and benefit when offering and continuing testosterone therapy for HSDD.

Because a testosterone product designed for women has yet to be approved by the FDA due to questions concerning the medication's long-term safety profile, testosterone is only available "off-label" in the United States [38,39]. General safety has been suggested by multiple studies, although safety data is limited to approximately 6 months in most trials, and as long as 4 years in a small cohort of patients (see below). The need for longer trials appears to be clear on the surface, and the response has been swift, but the high costs of such large long-term studies, and the short "intellectual property (IP)" afforded naturally occurring compounds surely complicates future development. The recent APHRODITE study analyzed safety data that spanned almost 2 years and found application-site reaction and mild hair growth as the two most common adverse events [25]. Another trial, not yet published, continued testosterone treatment for 52 weeks in 431 naturally postmenopausal women with HSDD receiving estrogen and progesterone therapy to examine efficacy and long-term safety. Data showed that testosterone is not associated with an increase incidence of adverse events or withdrawal of therapy due to adverse events [39].

Long-term safety data has also been collected and analyzed from the INTIMATE SM1 and 2 other trials. In this unpublished study, 837 participants continued testosterone therapy up to 4 years in an open-label extension period after the 24-week randomized placebo-controlled portion of the INTIMATE 1 and 2 trials. Data indicate that there is no increase over time in the occurrence or severity of adverse events or withdrawal from treatment due to adverse events [40]. To further evaluate long-term safety measures, a Phase III safety trial was presented at the 2007 Annual Meeting of the International Society for the Study of Women's Sexual Health. The objective of this randomized, double-blinded, multicenter trial is to compare the rate of cardiovascular and breast cancer events in women using testosterone gel with that in women using placebo. The trial would use a Bayesian adaptive design approach, where the use of interim analysis typically limits the number of women enrolled and time period needed to expose any possible statistical differences for these two safety parameters. The investigators expect to enroll nearly 3000 women, with an active treatment phase planned for 12 months with a 48-month follow-up period [23,41]. Continued research and long-term safety data are necessary for FDA approval of a testosterone product in women. In the meantime, transdermal testosterone appears to be a safe and effective therapy for postmenopausal women struggling with HHSD.

Competing interests

Dr. Krapf has no conflicts of interest.

Dr. Simon has served as a consultant or on the advisory boards of Allergan (Irvine, CA), The Alliance for Better Bone Health (Cincinnati, OH), Amgen Inc. (Thousand Oaks, CA), Ascend Therapeutics (Herndon, VA), Barr (Pomona, NY), Bayer (Leverkusen, Germany), BioSante (Lincolnshire, IL), Boehringer Ingelheim (Ingelheim, Germany), Corcept Therapeutics, Inc. (Menlo Park, CA), GlaxoSmithKline (Philadelphia, PA), KV Pharmaceutical Co. (St. Louis, MO), Meditrina Pharmaceuticals (Ann Arbor, MI), Merck (Whitehouse Station, NJ), Merrion Pharmaceuticals (Wilmington, NC), Nanma/Tripharma/Trinity (Glen Arm, MD), Novo Nordisk (Bagsvrerd, Denmark), Novogyne (East Hanover, NJ), Pear Tree Pharmaceuticals (Cambridge, MA), QuatRx Pharmaceuticals (Ann Arbor, MI), Roche (Basel, Switzerland), Schering-Plough (Kenilworth, NJ), Sciele (Atlanta, GA), Solvay (Marietta, GA), Warner Chilcott (Rockaway, NJ), and Wyeth (Madison, NJ). He has received grant/research support from BioSante, Boehringer Ingelheim (Ingelheim, Germany), FemmePharma (Wayne, PA), GlaxoSmithKline, Nanma/Tripharma/Trinity, Novartis (Basel, Switzerland), and Proctor and Gamble (Cincinnati, OH). He has also served on the speakers bureaus of Ascend, Barr, Bayer, GlaxoSmithKline, KV Pharmaceutical Co., Merck, Novartis, Novogyne, Sciele, Warner Chilcott, and Wyeth.

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