ORIGINAL ARTICLE

The Current Outlook for Testosterone in the Management of Hypoactive Sexual Desire Disorder in Postmenopausal Women

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ABSTRACT

Introduction. Hypoactive sexual desire disorder (HSDD) is a common clinical problem in women, especially those who have experienced surgical menopause. Because androgen levels decline with age and drop dramatically following bilateral oophorectomy, it has been hypothesized that reduced levels of testosterone are related to diminished desire.
Aim. As presented at a continuing medical education satellite symposium during the 2008 annual meeting of the International Society for the Study of Women's Sexual Health, to review the current state of knowledge about the physiologic effects of testosterone in postmenopausal women, the effects of transdermal testosterone delivery in surgically menopausal women with HSDD, and ongoing studies of a transdermal testosterone gel.
Methods. A review of the pertinent literature, including recent presentations.
Main Outcome Measures. Results from the Women's International Study of Health and Sexuality; and studies utilizing the Brief Index of Sexual Functioning for Women, the Psychological General Well-Being Index, and validated instruments that assess female sexual function: the Sexual Activity Log©, the Profile of Female Sexual Function©, and the Personal Distress Scale©.
Results. Surgically menopausal women receiving testosterone experience significant increases in total satisfying sexual activity vs. women receiving placebo, significant improvement in all domains of sexual function, and decreases in personal distress, with a favorable safety profile.
Conclusions. Testosterone deficiency may be considered among the underlying causes of HSDD. Currently, testosterone is available to women in the United States only via off-label prescribing or by unregulated compounding of testosterone preparations. New safety trials will examine the long-term safety of testosterone gel in surgically menopausal women with HSDD who are at high risk of cardiovascular disease or breast cancer. **Kingsberg SA, Simon JA, and Goldstein I. The current outlook for testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. J Sex Med 2008;5(suppl 4):182–193.**

Key Words. Menopause; Hypoactive Sexual Desire Disorder; Testosterone

Introduction

Female sexual dysfunctions (FSD) involve a number of physiologic and psychological components: diminished sexual desire, decreased sexual arousal, persistent difficulty in achieving an orgasm, and difficult or painful sexual intercourse. Nearly half of older women (ages 57–85) in the United States have at least one sexual problem, according to the National Social Life, Health, and Aging Project, a comprehensive survey conducted by the University of Chicago and published in August 2007 [1]. The most commonly reported sexual problem among older women is lack of desire [1].

Lack of desire that is persistent and causes personal distress or interpersonal distress is referred to as hypoactive sexual desire disorder (HSDD) [2].

HSDD may affect all women, particularly those who have experienced surgical menopause. Because androgen levels decline with age and drop dramatically following bilateral oophorectomy, it has been hypothesized that decreased testosterone is related to diminished desire. Phase III clinical trials of a testosterone patch have shown it effective in improving HSDD in surgically menopausal women receiving concomitant estrogen therapy [3,4]. Frequency of satisfying sexual activity, sexual desire, and distress were significantly improved, and these improvements were clinically meaningful according to women's own reports of the benefits they received from testosterone treatment [5].

This supplement reviews the physiologic effects of testosterone in postmenopausal women, the importance of psychological variables in female sexuality and desire, the research examining the effects of a transdermal testosterone patch (TTP) in surgically menopausal women with HSDD, and ongoing studies of a transdermal testosterone gel to obtain long-term safety and efficacy data.

Physiology of Testosterone in Women

The ovaries and adrenal glands produce about 50% of circulating testosterone, and the remaining 50% comes from peripheral conversion of precursors derived from the ovary and the adrenal gland. Most circulating testosterone produced is bound to sex hormone-binding globulin (SHBG) and albumin, leaving only 1% to 2% free and physiologically active [6]. Thus, when SHBG production increases, the level of free testosterone decreases, and vice-versa. Conditions that increase SHBG production include pregnancy, hyperthyroidism, and oral estrogen therapy. Although testosterone and estrogen bind to the same binding site on SHBG, the binding affinity for testosterone is higher than that for estrogen, providing another mechanism for the lower levels of free testosterone that accompany estrogen-induced increases in SHBG. Alternatively, production of SHBG decreases with insulin and androgen therapy, obesity, and menopause. During the time of the menopause transition, when estrogen production in the ovaries declines, levels of SHBG may also decline, resulting in stable or even slightly increased concentrations of free testosterone [7].

Decline in total testosterone production is a consequence of aging rather than a function of natural menopause [7–9]. After menopause, women generally have lower testosterone levels than premenopausal women, but this decline in testosterone happens very gradually, likely as a result of declining ovarian and adrenal function with increasing age [10]. Further, the postmenopausal ovary is believed to continue producing testosterone after menopause, albeit at a reduced level [11]. In a recent study, the greatest decline in testosterone was seen in the early reproductive years, followed by a plateau in midlife and then a small increase [12]. In contrast, women who undergo surgical menopause by having both ovaries removed (bilateral oophorectomy) experience a dramatic and permanent decrease in testosterone production that is as much as 50% lower than that of naturally postmenopausal women [11,12].

The Connection between Testosterone and Sexual Desire

Testosterone production is significant because it appears to play a role in maintaining women's sexual health. In some studies, low testosterone levels in postmenopausal women are associated with loss of sexual desire and sexual pleasure, feelings of diminished physical well-being, and persistent fatigue [13–17]. Low sexual desire is a common sexual problem: In the United States results from the Women's International Study of Health and Sexuality, the proportion of women classified as having low sexual desire ranged from 29% of naturally postmenopausal women age 50–70 years to 36% of surgically menopausal women age 20–49 years [18,19]. Although estrogen therapy alone may enhance sexual functioning for some women, others may need testosterone therapy as well to improve their sexual desire. Oral estrogen therapy also may exacerbate low sexual desire by increasing SHBG levels, which in turn causes already low levels of circulating testosterone to decline even further [20].

It cannot be assumed that testosterone deficiency is the conclusive or only cause of HSDD. Certain medical conditions and medications, central nervous system (CNS) function, as well as psychological and social factors, may cause diminished sexual desire. (Table 1). A complete history is necessary in order to determine the factors causing HSDD and the most appropriate treatment to use.

Deconstructing Desire

Understanding desire—its components and its role in female sexual response—is key to determining whether testosterone therapy is appropriate for

Table 1 Potential contributors to decreased sexual function in postmenopausal women. Adapted with permission from North American Menopause Society [7].

Psychosocial issues
Previous attitudes toward sex
Social customs and religious beliefs regarding sex
Poor partner relationship
Feelings toward partner
Length of relationship
Partner's decreased capacity for sexual activity
Partner's loss of interest in sex
No available partner
Life stressors from work, family, relationships
Negative body image
Psychological disorders
Depression
Anxiety
Other psychiatric illness
Medical conditions
Menopause (lower levels of endogenous estrogen, testosterone)
Vaginal atrophy
Vasomotor symptoms
Age-related decline in sexual drive
Fatigue
Incontinence
Chronic illness, including cardiovascular disease, diabetes mellitus, arthritis, renal failure
Cancer, particulary gynecologic or breast cancer
Pharmacologic agents
Psychotropics: selective serotonin-reuptake inhibitors, tricyclic antidepressants, benzodiazepines, barbiturates, anxiolytics, sedatives
Cardiovascular: beta-blockers, clonidine, methyldopa, spironolactone (which has antiandrogenic properties)
Hormones: gonadotropin-releasing hormone agonists and antagonists, corticosteroids, antiandrogens
Recreational drugs: alcohol, marijuana, cocaine, heroin, methadone

a patient who presents with HSDD, or a different treatment approach is necessary. One theoretical model of the female sexual response developed by Basson [21] (Figure 1) proposes that desire is not necessarily the first initiating component of sexual response for women, as designated by the traditional linear cycle of female sexual response put forward by Masters and Johnson, and Kaplan [22,23]. The linear cycle implies that desire initiates arousal, which is followed by orgasm, and finally resolution. According to Basson, sexual response is not linear and for many women, desire comes *after* arousal. Some women begin from a point of sexual neutrality. Arousal may come from a conscious decision or as a result of seduction or suggestion from her partner. This is important to understand when consulting a patient who has come to believe that she is no longer sexual because her initial drive is gone. Sexual neutrality or being receptive to, rather than initiating, sexual activity is a variation of female sexual function and more likely representative of women with low sexual interest, based on Sand and Fisher [24]. If such a woman experiences adequate emotional intimacy with her partner, she may seek or be receptive to sexual stimuli. Receptivity to sexual stimuli allows her to move from sexual neutrality to arousal. If the mind continues to process the stimuli on to further arousal, sexual desire will encourage the woman to move forward to sexual satisfaction and orgasm. This positive outcome fosters intimacy and reinforces sexual motivation. The fact is that women experience desire in different ways. In fact, Sand and Fisher recently surveyed a sample of female nurses about which sexual response model they felt best represented their own sexual experience. One-third selected the Masters and Johnson linear model of sexual response, which is composed of four phases (excitement or arousal, plateau, orgasm, and resolution); one-third selected the Kaplan model, which adds the concept of desire to the Masters and Johnson linear model and condenses the response into three phases (desire, arousal, and orgasm); and one-third selected Basson's nonlinear model. Based on validated outcome scales, women who selected the Basson model were more likely to have female sexual dysfunction and low sexual desire [24].

Desire is deconstructed by Levine into three separate but related components: drive, expectations, and motivation [25]. The first component, drive, is also known as spontaneous sexual interest. Drive is the biological dimension of desire, and its intensity varies from one person to the next. Drive declines naturally with age; however, certain medical conditions and medications may also cause drive to decline and should be taken into account in a patient's history. The second component of desire includes expectations, beliefs, and values. These comprise the social dimension of desire: the influences that create interest in being

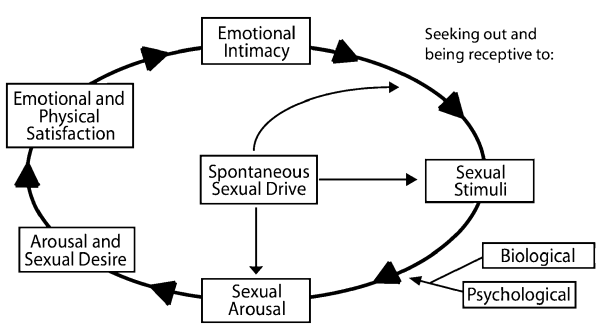

Figure 1 Female sexual response cycle. Adapted with permission from Basson [21].

sexual. A person's beliefs and values shape the sexual nature of that person. The third component of desire is motivation, which is the psychological dimension of desire. The factors that create a person's willingness to have a sexual experience are what motivates that person to do so. For example, a woman's sexual drive may be very high, but if she is having relational problems with her partner, she is not going to want to be sexual. The motivation is not there for her. In contrast, a woman with low sexual drive who has an excellent relationship with her partner wants to be sexual because her relationship motivates her to do so.

Understanding the complexities of desire enables health care providers to evaluate HSDD from every aspect, to uncover the cause or causes of it, and, consequently, how to treat it. Testosterone deficiency may be considered among the underlying causes of HSDD.

Transdermal Testosterone Therapy for HSDD

Treatment with testosterone and estrogen combined has been shown to improve sexual desire in surgically menopausal women, and is more effective than estrogen alone [26–29]. Routes of testosterone administration in early studies included oral [29], intramuscular injection [27], and subcutaneous implants [30], all of which resulted in increases in sexual desire in postmenopausal women. However, transdermal delivery of testosterone may prove advantageous over these routes, because it avoids first-pass hepatic metabolism and delivers consistent physiologic doses of testosterone.

Shifren and colleagues [31] conducted the first randomized, double-blind, placebo-controlled trial of a transdermal testosterone patch (TTP), published in 2000. This Phase II trial included 75 women aged 31–56 years with surgically induced menopause who had been using oral estrogen therapy for at least 8 weeks. Impaired sexual functioning was deemed present in women who answered positively to the following three questions:

- At any time before surgery would you have characterized your sex life as active and satisfying?
- Since your surgery has your sex life become less active or less satisfying?
- Would you prefer your sex life to be more active or more satisfying than it is now?

Women received 150 μg or 300 μg/day TTP or placebo with concomitant oral estrogen therapy for 12 weeks. At study end, only those in the 300-μg group experienced significant improvements in sexual function over placebo according to the Brief Index of Sexual Functioning for Women [32], with increased scores on measures of sexual thought, desire, frequency of activity, and pleasure-orgasm. The Psychological General Well-Being Index [33] showed significant improvement in positive well-being and depressed mood in the 300-μg group compared with placebo. Treatment with TTP was well-tolerated in all groups.

The mean serum concentrations of free and bioavailable testosterone, which remained at low or low-normal values during treatment with placebo, increased to mid-normal values during treatment with testosterone 150 μg/day and to high-normal values with testosterone 300 μg/day. Mean serum concentrations of total testosterone and dihydrotestosterone also increased and exceeded their respective normal ranges during treatment with testosterone 300 μg/day. These supraphysiologic elevations in serum total testosterone and dihydrotestosterone at the 300 μg/day dose resulted from the concomitant oral estrogen therapy, which, as previously discussed, raises serum concentrations of SHBG and reduces clearance of androgens. Despite these elevations, the hirsutism and acne scores did not change significantly during treatment; however, the mean facial-depilation rate increased during treatment with the 300 μg/day dose of testosterone.

Braunstein et al. [34] followed with another Phase II investigation that had a larger patient population, extended the treatment period to 24 weeks, and added a third dosage, comparing the effects of TTP at 150, 300, and 450 μg/day in 318 surgically menopausal women aged 24–70 with HSDD. Women also were taking oral estrogen therapy and were maintained on their current dose throughout the study. Whereas the Shifren study had a crossover design, this study used parallel groups. Expanding on the questions used by Shifren and colleagues [31], the investigators asked women the following series of questions as part of the recruitment process:

- Before your ovaries were removed, would you say that in general your sex life was good and satisfying?
- Since your ovaries were removed, do you feel you have experienced a meaningful loss in your level of desire for sex?

Table 2 Validated instruments to assess female sexual function: SAL [35], PFSF [36,37], and PDS [38].

SAL	PFSF	PDS
Weekly diary to record the number of intercourse and non-intercourse sexual events, number of orgasms, and satisfying sexual activity experienced; not limited to only intercourse as a sexual activity.	A 37-item self-administered questionnaire that measures seven domains of sexual function: desire, pleasure, arousal, responsiveness, self-image, orgasm, and reduced concerns. Designed specifically for use in postmenopausal women with low sexual desire.	A 7-item, self-administered questionnaire to assess the level of distress associated with a woman's lack of interest in sex.

SAL = Sexual Activity Log; PFSF = Profile of Female Sexual Function; PDS = Personal Distress Scale.

- Since your ovaries were removed, do you feel you have experienced a significant decrease in your sexual activity?
- Are you concerned about or bothered by your current level of desire for or interest in sex?
- Would you like to see an increase in your level of interest in or desire for sex and sexual activity?

Affirmative answers to these questions in the absence of other conditions that can cause low sexual desire enabled the investigators to enroll participants whose onset of HSDD did indeed follow oophorectomy.

The study also incorporated the use of three efficacy instruments designed and validated specifically to assess female sexual functioning: the Sexual Activity Log© (SAL) [35], the Profile of Female Sexual Function© (PFSF) [36,37], and the Personal Distress Scale© (PDS) [38], all of which are described in Table 2. The primary efficacy outcome measures were changes in sexual desire and frequency of satisfying sexual activity.

Only the 300-μg/day group had significantly increased sexual desire and frequency of satisfying sexual activity compared with placebo. Specifically, sexual desire increased 67% from baseline with TTP compared with 48% with placebo, and a statistically significant increase from baseline of 0.58 satisfying sexual experiences each week was noted in this group. No treatment effect was seen in the 150-μg/day group, and the 450-μg/day group showed no statistical difference from the 300-μg/day group. Although all treatment groups experienced decreased distress, there was no statistically significant difference from that of the placebo group. Adverse events were similar in frequency among all groups, with application site reaction being the most common. No severe events occurred.

With this study, Braunstein et al. established that the 150-μg/day dose is not effective in improving HSDD, and the 450-μg/day dose is no more effective than the 300-μg/day dose, suggesting that the 300-μg dose may be at the top of the dose-response curve. The study also confirmed that TTP is safe for at least 24 weeks.

Because the SAL, PFSF, and PDS measure sexual functioning based on women's personal, individual responses, the investigators were able to gauge aspects of sexuality that are truly meaningful to the women participating in the study. Although an increase of just over two satisfying sexual episodes in a month may not appear to be a great benefit, for women living with HSDD, this seemingly small increase can prove substantial.

Phase III Trials Define the Effectiveness of TTP for HSDD

Two concurrent Phase III trials of TTP provided further evidence of the effectiveness of TTP in improving HSDD in surgically menopausal women. The Investigation of Natural Testosterone In Menopausal Women Also Taking Estrogen in Surgically Menopausal Women (INTIMATE SM) 1 and 2 studies were conducted in the United States, Canada, and Australia to further examine the efficacy and safety of TTP 300 μg/day in treating HSDD in women with surgically induced menopause [3,4]. The INTIMATE SM 1 study [4] included 562 women, and the INTIMATE SM 2 study [3] involved 532 women with HSDD. The remaining characteristics of both studies were identical: a pretreatment baseline period of 8 weeks followed by randomized, double-blind, placebo-controlled treatment for 24 weeks consisting of 300 μg/day TTP or placebo.

A major component of both studies was the use of the SAL, PFSF, and PDS to measure sexual function. The primary end point of both studies was the change in the frequency of total satisfying sexual activity as determined by participants' SAL. In both studies, women treated with TTP had a significantly higher frequency of total satisfying sexual activity compared with those receiving

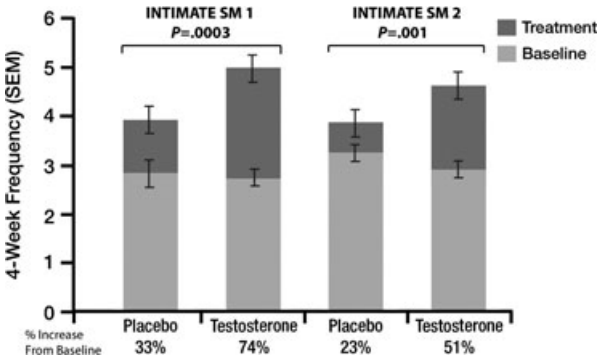

Figure 2 Increased total satisfying sexual activity at 24 weeks, measured by means of the Sexual Activity Log© (SAL). INTIMATE SM = Investigation of Natural Testosterone in Menopausal Women Also Taking Estrogen in Surgically Menopausal Women; SEM = standard error of the mean. Adapted with permission from Kingsberg S. Testosterone treatment for hypoactive sexual desire disorder in postmenopausal women. *J Sex Med.* 2007;4(Suppl 3):227–234.

placebo (Figure 2). At baseline, women in both studies reported having satisfying sexual experiences approximately three times per month. At study end, TTP increased the number of satisfying sexual episodes to about five times per month. As Figure 2 shows, the change seen from baseline with TTP was double that seen with placebo, with increases of 74% vs. 33% in INTIMATE SM 1 and 51% vs. 23% in INTIMATE SM 2.

In both studies, women using TTP also showed significant improvement over those using placebo on the PFSF in all seven domains of sexual function (desire, pleasure, arousal, responsiveness, self-image, orgasm, and reduced concerns). Improvement in desire for women using TTP in both studies was of similar magnitude and statistically significant, with increases of 56% and 49% from baseline in INTIMATE SM 1 and SM 2, respectively (Figure 3A). This improvement is particularly clinically relevant, because desire is an essential component of the diagnosis of HSDD. Improvement in many of the other domains was nearly double with TTP compared with placebo.

Personal distress, another critical component of HSDD, and the secondary end point in both INTIMATE SM 1 and INTIMATE SM 2, also improved significantly with TTP compared with placebo in both studies (Figure 3B). In women using TTP, scores for personal distress on the PDS decreased by 65% in INTIMATE SM 1 and by 68% in INTIMATE SM 2, compared with 40% and 48%, respectively, in women receiving placebo. As with the domain of desire on the PFSF, a decrease in distress is extremely clinically relevant, because distress is necessary for a diagnosis of HSDD. The extent of distress reported by study participants signifies the impact of HSDD in their lives.

A placebo response is typical in patient-centered studies, regardless of the treatment being analyzed [39–43], and not unexpected with any treatment that acts on a complex process such as sexual desire. As have other studies of sexual functioning [29,31,34,44], the INTIMATE SM 1 and INTIMATE SM 2 studies demonstrated strong placebo effects. Improvements reported in women who received placebo may have been influenced by a number of factors, including the women's desire to improve their sex life, as evidenced by participation in the studies; their active role in seeking help; regular contact with health care providers; weekly activity diary collection acting as an incentive to increase sexual activity; the constant, visible presence of the transdermal patch; and increased communication with their partners about

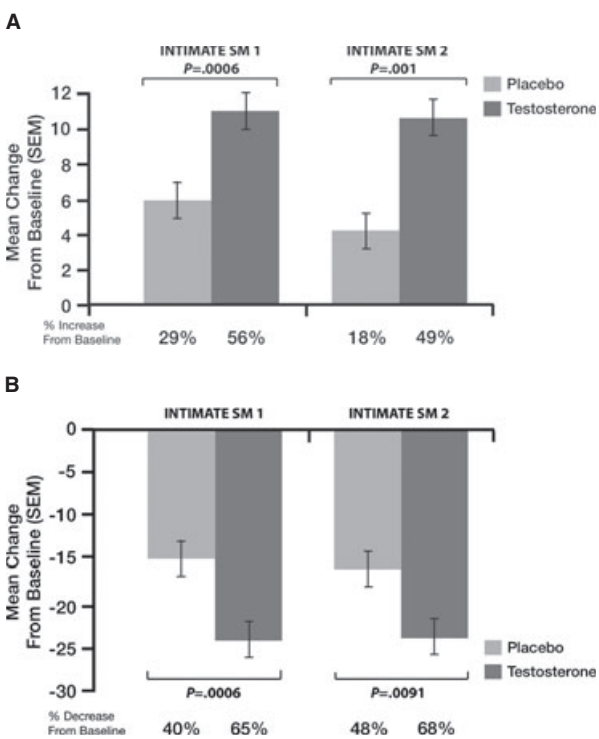

Figure 3 Increased desire at 24 weeks, measured by means of (A) the Profile of Female Sexual Function© and (B) decreased distress at 24 weeks, measured on the Personal Distress Scale©. INTIMATE SM = Investigation of Natural Testosterone in Menopausal Women Also Taking Estrogen in Surgically Menopausal Women; SEM = standard error of the mean. Adapted with permission from Kingsberg S. Testosterone treatment for hypoactive sexual desire disorder in postmenopausal women. *J Sex Med.* 2007;4(Suppl 3):227–234.

wanting better sexual experiences. The psychological impact of these factors likely contributed to increased sexual activity; nevertheless, the improvements did not reach the significance of those seen in women using TTP.

In both studies, adverse events were similar with TTP and placebo, with the exception of unwanted hair growth, which was higher in women treated with TTP in INTIMATE SM 2 (9% TTP vs. 5.3% placebo, 5.7% TTP vs. 6.5% placebo in SM 1). The most common adverse event among all participants in both studies regardless of treatment was application site reaction, occurring in about 30% to 40% of participants. Acne, alopecia, and voice deepening were slightly more common with TTP in INTIMATE SM 2 compared with placebo, but not in INTIMATE SM 1. Overall, the incidence of these events was low in both studies and considered mild and reversible. The incidence of serious adverse events or study withdrawal due to adverse events was low in all groups in both studies.

Anchoring Technique Validates Clinical Relevance of INTIMATE SM Results

The primary end point of the INTIMATE SM 1 and INTIMATE SM 2 studies may not seem particularly impressive: an increase in satisfying sexual activity from 3 to 5 times per month in women treated with TTP is not a great change. However, this increase, as well as the treatment effects of TTP seen in the areas of increased desire and decreased distress, speaks to clinical relevance in a number of other ways. First, all of the end points in these Phase III studies were constructed from HSDD patients' statements about aspects of their sexual functioning that were important to them. Designing end points in this manner creates end points that are clinically relevant to the study participants. Second, the decrease in personal distress indicates that TTP had a direct impact on participants' feelings about their HSDD and their quality of life. Third, improvement seen in every PFSF domain with TTP indicates that the improvement in sexual function is consistent and reaches across all domains.

Beyond this evidence of clinical relevance of the findings in the INTIMATE SM 1 and INTIMATE SM 2 studies, a separate study was conducted to explore the clinical relevance of the effects of TTP using the anchoring technique [5]. The anchoring technique is one of the most direct, well-established, and readily understood methods of examining clinical relevance. Simply explained, it is a patient-based tool that ties a score from a new scale or instrument to something that is already known to have clinical meaning. Questions concerning treatment benefit are used to link, or "anchor," study participants' own perceptions or report of meaningful benefit to the study outcome measures. Study participants are directly asked whether they experienced a meaningful benefit; then these participants' scores on the study end points are examined. This shows which changes in the study end points are associated with participants' perceptions that they experienced meaningful benefit from the study treatment.

A representative sample of 132 women (about 12%) from both INTIMATE SM studies was interviewed after the 24-week treatment period, but prior to unblinding and entry into the open label phase of the trials. Of the 132 women, 64 had received TTP and 68 had received placebo. The interviews began with open-ended questions to assess women's general experiences before and during the clinical trial, followed by questions about specific benefits that women may have experienced during the trial. Women then were asked the following direct question for the anchoring analysis: "Overall, considering everything we talked about today, would you say that you experienced a meaningful benefit from the study patches?" Finally, women were asked how likely they would be to continue using the patches if they were available on the market by prescription.

When women were separated according to the overall meaningful benefit that they did or did not experience, a rather large difference was clear in the primary end point: for women who reported having a meaningful benefit, the number of satisfying sexual experiences increased to 4.4 times per month vs. 0.5 times per month in women who reported no meaningful benefit (Table 3). These results are where the clinical relevance is real for women with HSDD, and are critical in gaining a better understanding of the INTIMATE SM 1 and INTIMATE SM 2 outcomes. Going back to Figure 2 and reviewing the seemingly modest change in satisfying sexual activity between treatment responders and non-responders, the difference nevertheless had a truly substantial impact on women's sexual lives and quality of life when their personal perceptions of what constitutes a meaningful benefit were considered. Significant and clinically relevant differences also were seen in the scores for desire and distress in women who had

Table 3 Clinical relevance study results: mean change from baseline in satisfying sexual activity, desire, and distress [5].

	Reported meaningful benefit overall	Reported no meaningful benefit overall
Satisfying sexual activity per 4 weeks	4.4	0.5
Desire	21.0*	2.9
Distress	–36.5**	–8.8

*Corresponds to moving from feeling sexual desire seldom to feeling sexual desire sometimes.
**Corresponds to moving from often distressed to seldom distressed.

meaningful benefit compared with those who did not, as shown in Table 3.

When women and investigators were unblinded, a meaningful treatment benefit was reported by more women receiving TTP (52%) than those receiving placebo (31%). This difference was statistically significant. The fact that one third of women receiving placebo reported meaningful benefit is interesting but not unusual. As previously noted, other clinical trials of sexual dysfunction have reported similar placebo effects [29,31,34,44], and trials in a number of other therapeutic areas, including depression, urinary incontinence, and irritable bowel syndrome, have shown placebo response rates in the same general range [39–43].

The true treatment effect of TTP was further revealed when women were asked whether they would continue using TTP if it was available. More than 85% of women who had a meaningful benefit said they would continue with the patch. In contrast, more than 90% of women who had no meaningful benefit said they would not continue using the patch if it was available. Providers can be reassured by these data: women who find that TTP works for them will continue to use it, and those who find no benefit will not. These data are also important in determining the risk-to-benefit analysis of transdermal testosterone, and can be used to estimate the benefit received by women who would likely be exposed to continued TTP therapy if it were commercially available.

The INTIMATE SM 1 and INTIMATE SM 2 studies demonstrated that TTP is effective in treating HSDD in surgically menopausal women over 24 weeks and is well tolerated. The clinical relevance study confirms these findings. Significantly more women receiving TTP benefited from treatment and would continue it, which reflects the true success of TTP in managing HSDD.

Limited Long-Term Safety Data on Testosterone in HSDD

Although testosterone and other androgens have been used to treat postmenopausal women for more than 50 years, there are only limited long-term safety data available, especially regarding the effects of exogenous androgens on cardiovascular and breast cancer risks. No long-term prospective studies have been sufficiently powered to examine the cardiovascular risk of administering exogenous testosterone to women, and the ability of randomized, double-blind, placebo-controlled trials to detect an increase in events among testosterone-treated groups of women is severely limited by the short duration of treatment and relatively small numbers of women involved in the studies [45].

Some epidemiologic studies have shown an association between higher endogenous androgen levels and an increased risk of breast cancer in postmenopausal women [46]. Most studies that have controlled for the confounding effects of estradiol levels and other variables have not shown a significant increase in risk [47]. In a large retrospective study, lower rates of breast cancer were observed among postmenopausal women who used testosterone in addition to other hormonal replacement therapy vs. those taking hormones without testosterone [48]. However, prospective case control comparisons recently found an increase in breast cancer risk with androgen supplementation [49,50].

Before the U.S. Food and Drug Administration (FDA) will approve a testosterone product for women, more long-term safety data are required. This decision came in December 2004, after an FDA Advisory Committee review of data from the INTIMATE SM studies and other clinical trials of TTP in postmenopausal women with HSDD [51]. The efficacy of TTP was accepted; however, long-term safety data were deemed inadequate and further study was mandated. Consequently, the New Drug Application for TTP was withdrawn in the United States. It subsequently was approved by the European Union, and TTP is currently marketed in several European countries.

Assessing the Long-Term Safety of Testosterone in HSDD

To address the long-term safety issues of testosterone raised by the FDA, as well as provide further efficacy data, two separate Phase III efficacy studies and one safety study focusing on cardiovas-

cular and breast cancer risk are underway. The product being evaluated for use in women with HSDD is a testosterone gel that is absorbed transdermally when applied to the skin once daily. Results of a recent Phase II randomized, double-blind, placebo-controlled study of this novel product have shown it effective in managing HSDD in surgically menopausal women [52]. The Phase III efficacy studies are similar in design to the INTIMATE SM studies, with an 8-week screening period followed by a 24-week active treatment phase using 300 μg/daily of testosterone gel or placebo in 500 women, with approximately 250 women in each treatment group.

The Phase III safety trial will examine long-term safety of the testosterone gel particularly as it pertains to cardiovascular and breast cancer risk in postmenopausal women with HSDD [53]. This trial is unique in that it incorporates an adaptive design model, in which the number of women enrolled depends on the event rate and accrual rate. This allows for a smaller and more efficient study process because the study population consists of women who are at higher risk for a cardiovascular or breast cancer event. The trial is enrolling women who are older than 50 years, either naturally or surgically menopausal, either using or not using estrogen and/or progestins, and have at least one cardiovascular risk factor. With this adaptive study design, a difference between testosterone and placebo is more likely to occur and in a shorter period of time. Enrollment is expected to reach nearly 3,000 women.

The two primary objectives are to compare the rate of a first adjudicated, predefined cardiovascular event in women using testosterone gel with that in women using placebo, and to compare the rate of a first adjudicated, predefined breast cancer event in women using testosterone gel with that in women using placebo. The primary safety outcome measures are the combined incidence of predefined cardiovascular events, including cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction. Secondary safety outcome measures include breast carcinoma in situ, atypical breast hyperplasia, and breast density as a surrogate for breast cancer risk.

The active treatment phase of this randomized, double-blind, placebo-controlled, multicenter, adaptive design safety study is much longer than that in previous studies of TTP, planned for 12 months of drug exposure with 48 months of follow-up. The investigators believe this duration of treatment and follow-up in approximately 3,000 women is appropriate to demonstrate whether the testosterone gel is safe in women at high risk of a cardiovascular or breast cancer event.

Conclusion

Currently, testosterone is available to women only by way of off-label prescribing of products that are licensed for other uses or by unregulated compounding of testosterone preparations. Off-label prescribing of products licensed for use in men may lead to higher than normal androgen levels and may produce significant side effects in women. Such products have not been tested rigorously in women and there are no reliable safety and efficacy data for them. Studies are currently underway to assess the long-term safety of transdermal testosterone gel as well as its efficacy in managing HSDD that may facilitate future approval of a testosterone product specifically for women.

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Conflict of Interest: Irwin Goldstein, MD, has been a consultant for Alagin Research, Boehringer Ingelheim, Johnson & Johnson, Medtronic, and Pfizer Inc, and is a member of the speakers' bureaus for Auxilium, Bayer HealthCare, Coloplast, Eli Lilly & Company, and Pfizer Inc. Dr. Goldstein has received financial support from Pfizer Inc, Eli Lilly & Company, Auxilium, and Coloplast.

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James A. Simon, MD, CCD, FACOG, has been a consultant for Abbott Laboratories; Ascend; Barr Pharmaceuticals, Inc.; Bayer HealthCare; BioSante Pharmaceuticals; Depomed; Duramed Pharmaceuticals, Inc.; Esprit Pharma; GlaxoSmithKline; Johnson & Johnson; KV Pharma; Meditrina; Merck & Co., Inc.; Nanma/Tripharma; Noven; Organon; Pfizer Inc; Procter & Gamble; QuatRx; Roche; Solvay; TAP; Trinity Marketing; Vivus; Warner Chilcott; and Wyeth. Dr. Simon has received grants and research support from Amgen, Inc.; Barr Pharmaceuticals, Inc.; Bayer HealthCare; Besins; BioSante Pharmaceuticals; Boehringer Ingelheim; Duramed Pharmaceuticals, Inc.; EndoCeutics; GlaxoSmithKline; Ortho-McNeil, Inc.; Nanma/Tripharma; Novartis; Pfizer Inc; Procter & Gamble; Trinity Marketing; Vivus; and Wyeth. Dr. Simon has also served on the speakers' bureaus for Abbott Laboratories; Ascend; Aventis; Bayer HealthCare; Duramed Pharmaceuticals,

Inc.; Esprit Pharma; GlaxoSmithKline; Merck & Co., Inc.; Novogyne; Ortho; Pfizer Inc; Roche; Solvay; Warner Chilcott; and Wyeth.

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