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Testosterone Patch Increases Sexual Activity and Desire in Surgically Menopausal Women with Hypoactive Sexual Desire Disorder

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Context: Hypoactive sexual desire disorder (HSDD) is one of the most common sexual problems reported by women, but few studies have been conducted to evaluate treatments for this condition.

Objective: The objective of this study was to evaluate the efficacy and safety of a testosterone patch in surgically menopausal women with HSDD.

Design: The design was a randomized, double-blind, parallel-group, placebo-controlled, 24-wk study (the Intimate SM 1 study).

Setting: The study was performed at private or institutional practices.

Patients: The subjects studied were women, aged 26–70 yr, with HSDD after bilateral salpingo-oophorectomy who were receiving concomitant estrogen therapy. Placebo (n = 279) or testosterone 300 μg/d (n = 283) was administered. There were 19 patients who withdrew due to adverse events in the placebo group and 24 in the 300 μg/d testosterone group.

Intervention: Testosterone (300 μg/d) or placebo patches were applied twice weekly.

Main Outcome Measure(s): The primary end point was the change in the frequency of total satisfying sexual activity at 24 wk. Secondary end points included other sexual functioning end points and safety assessments.

Results: At 24 wk, there was an increase from baseline in the frequency of total satisfying sexual activity of 2.10 episodes/4 wk in the testosterone group, which was significantly greater than the change of 0.98 episodes/4 wk in the placebo group ($P = 0.0003$). The testosterone group also experienced statistically significant improvements in sexual desire and a decrease in distress. The overall safety profile was similar in both treatment groups.

Conclusion: In the Intimate SM 1 study, the testosterone patch improved sexual function and decreased distress in surgically menopausal women with HSDD and was well tolerated in this trial. **(*J Clin Endocrinol Metab* 90: 5226–5233, 2005)**

HYPOACTIVE SEXUAL DESIRE disorder (HSDD) is defined as a chronic or recurrent deficit in or absence of desire for sexual activity that causes personal distress (1). Investigators have noted that up to 50% of postoophorectomy patients report a decrease in sexual desire after surgery (2, 3). It is hypothesized that this decrease may be associated with lower levels of circulating androgens due to removal of the ovaries. Women who have undergone bilateral oophorectomy typically experience a drop of 50% in their circulating testosterone levels (4). Treatment with oral estrogens after surgery frequently increases SHBG levels, which may exacerbate the effects of a low testosterone level, because a greater proportion of circulating testosterone is bound to SHBG and does not enter target tissues (5).

Study findings have suggested that libido can be improved for women with HSDD through the use of postoperative estrogen and testosterone therapy, and this combination therapy has been found to be more effective than estrogen alone (6–8). Testosterone delivered by a transdermal patch may have advantages over other dosage forms, because it bypasses first-pass metabolism and can provide consistent levels of hormone over time. A 12-wk, placebo-controlled trial of a testosterone transdermal matrix patch showed that administration of 300 μg/d produced increases in sexual functioning and well-being in oophorectomized women with low libido receiving concomitant oral conjugated equine estrogens (9). We undertook this phase III study to investigate the efficacy and safety of 300 μg/d testosterone

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Abbreviations: CV, Coefficient of variation; HSDD, hypoactive sexual desire disorder; LLOQ, lower limit of quantification; PDS, Personal Distress Scale; PFSF, Profile of Female Sexual Function; SAL, Sexual Activity Log.

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administered by this patch in women with HSDD after surgically induced menopause.

Subjects and Methods

Study design and patients

This trial enrolled women at 52 centers in the United States, Canada, and Australia and consisted of a 24-wk, double-blind, placebo-controlled treatment period, followed by a 28-wk, open-label, safety follow-up period. This manuscript reports results of the placebo-controlled treatment period. Participants were required to be 20–70 yr of age, in good health, have a normal mammogram if age 40 yr or older, have a normal Pap smear, have undergone bilateral salpingo-oophorectomy and hysterectomy at least 6 months before screening, and have no physical impediment to sexual function. All women were also receiving a stable dose of estrogen therapy (oral or transdermal patch) for at least 3 months before screening and in a stable, monogamous relationship with a partner who was sexually functional, based on the assessment of the woman. The goal in requiring a functional partner was to ensure that a woman's sexual activity was not limited by impairment of the partner. No medical information was collected regarding the partner.

To be eligible to participate, a woman had to report having a satisfying sex life before oophorectomy and a meaningful loss of sexual desire and decrease in sexual activity after surgery and being bothered or concerned about this decrease in desire for sexual activity. Women were excluded if they had other conditions that could impact sexual function, including dyspareunia; major life change interfering with sexual function; a psychiatric disorder, including depression [Beck Depression Inventory II score (10) of 14 or greater]; or drug or alcohol dependency, or were taking medications known to affect sexual function, including androgens, phytoestrogens, selective serotonin reuptake inhibitors, systemic β-blockers, raloxifene, tamoxifen, and sildenafil. Women were also excluded if they had a history of breast cancer or estrogen-dependent neoplasia, significant organic disease that could affect the outcome of the study, active gall bladder disease, diabetes, history of cerebrovascular disease or thromboembolic disorders, or abnormal levels of TSH, serum creatinine, or liver enzymes.

Women were stratified by route of concomitant estrogen therapy (transdermal or oral) and were then randomly assigned in a 1:1 ratio to receive placebo or 300 μg testosterone daily for 24 wk in the form of a twice weekly patch worn on the abdomen. The placebo and testosterone patches were identical in appearance. Patients and all study personnel were blinded to treatment assignments. Study participants visited the sites at baseline and every 4 wk during the 24-wk, double-blind study period.

The treatment of human subjects was consistent with the principles outlined in the Declaration of Helsinki. All patients gave written, informed consent to participate, and the appropriate ethic committees or institutional review boards approved both the protocol and patient consent form.

Efficacy measurements

The primary efficacy end point, the change in frequency of total satisfying sexual activity over a 4-wk period evaluated at 24 wk, was assessed using a weekly diary, the sexual activity log (SAL). The SAL was completed for 8 wk before and for the 24 wk of study treatment and questioned patient physical health status, partner availability, and the frequency of sexual activity during the preceding 7 d. Women were asked to record the frequency of sexual activity, the number of orgasms, and whether the activity was satisfying. As specified in the SAL, sexual activity included sexual intercourse, masturbation (with or without the partner), giving or receiving oral sex, or any other sexual activity. This allowed patients to include whatever sexual practices in which they chose to engage, but still to count episodes of sexual activity as a common unit for comparison. All episodes of sexual activity in the last 4 wk were included when calculating the frequency of total sexual activity; only episodes that the woman considered satisfying were included when calculating the frequency of total satisfying sexual activity.

Secondary efficacy measurements included evaluation of changes in the profile of female sexual function (PFSF), a 37-item questionnaire that has been developed and validated in postmenopausal women (11, 12). The PFSF measures seven different domains of sexual function: sexual desire, sexual pleasure, sexual arousal, orgasm, sexual responsiveness, sexual concerns, and sexual self-image. Each item in every PFSF domain had six scoring levels, ranging from always (1) to never (6). In addition, a question regarding the patient's overall satisfaction with her sexuality had to be completed. The possible responses to this question were: 1 = poor, 2 = fair, 3 = good, 4 = very good, and 5 = excellent. Domain scores were computed by summing the scores for items within a domain. Each raw domain score was then transformed to a 0–100 scale using the following formula: transformed score = [(actual raw score − lowest raw domain score possible)/(highest raw domain score possible − lowest raw domain score possible)] × 100. Scores of 0, 20, 40, 60, 80, and 100 on each domain of the PFSF correspond, on the average, to the following categories of response: never, seldom, sometimes, often, very often, and always, respectively. Note that an increase in the sexual concerns score indicated a decrease in patients' concerns related to sexuality.

The level of patient distress was evaluated using the Personal Distress Scale (PDS), which consisted of seven questions concerning level of distress associated with decreased interest in sex. Each item of the PDS had six scoring options, ranging from always (score of 1) to never (score of 6). The PDS score was the sum over the scores for the items on the scale. The raw score was transformed to a 0–100 scale using the same formula shown above. Scores of 0, 20, 40, 60, 80, and 100 on the PDS correspond, on the average, to the following categories of response: never, seldom, sometimes, often, very often, and always distressed about a lack of interest in sex, respectively. A decrease in PDS score indicated a decrease in patient distress. The PFSF and PDS were administered at baseline and after 4, 8, 12, and 24 wk of treatment.

Safety assessments

Adverse event reports were collected from the time of first application of study drug (either placebo or testosterone patch) until the patients exited the study. Women experiencing any clinically significant adverse event were to remain under medical supervision until the event resolved, stabilized, or was no longer serious enough to warrant follow-up. All adverse events were categorized using the Medical Dictionary for Regulatory Activities coding dictionary. The Medical Dictionary for Regulatory Activities is a registered trademark of the International Federation of Pharmaceutical Manufacturers Associations.

Any report of a reaction at the patch application site volunteered by a participant was recorded as an adverse event; in addition, the site of most recent patch application was examined at each clinic visit. Application site adverse events were rated as mild, moderate, or severe depending upon the degree of erythema, pruritis, or other symptoms.

At each clinic visit, study personnel assessed the degree of lip or chin hair using the facial portion of the Ferriman-Gallwey/Lorenzo scoring system (13). Facial acne was evaluated using the scale developed by Palatsi *et al.* (14) Women also were asked whether they had experienced any change in scalp hair or voice and positive responses were recorded as adverse events.

Blood samples were collected 8 and 4 wk before treatment and 24 wk after initiation of treatment for determination of serum chemistry, hematology, lipid profile, carbohydrate metabolism, renal and liver function, and coagulation parameters (Quintiles Laboratories, Smyrna, GA).

Hormone measurements

Blood samples were collected at baseline and after 24 wk of treatment for determination of hormone levels using validated methods (Quest Diagnostics, Inc., San Juan Capistrano, CA).

The analysis of total testosterone was performed by RIA after sample extraction and column chromatography. The lower limit of quantification (LLOQ) for the testosterone measurement was 2 ng/dl, and the interassay coefficient of variation (CV) was 12.5% or less for all quality control samples analyzed with the study samples. The percent free testosterone was determined by equilibrium dialysis using radiolabeled tracer techniques. Free testosterone concentrations were calculated by multiplying the total testosterone by the percent free testosterone.

The concentration of dihydrotestosterone was measured by RIA after sample extraction and column chromatography; tritiated dihydrotestosterone was used as an internal standard to correct for recovery. The LLOQ was 3 ng/dl (0.10 nmol/liter), and the CV was 14.2% or less.

TABLE 1. Baseline study subject characteristics

Characteristic	Placebo (n = 279)	Testosterone (n = 283)
Age (yr) (range)	48.9 ± 7.4 (26–66)	49.2 ± 7.7 (28–70)
Time since oophorectomy (yr)	8.2 ± 6.6	8.7 ± 7.0
Weight (kg)	75.9 ± 17.2	74.3 ± 16.0
Height (cm)	163.5 ± 6.5	163.8 ± 6.5
Body mass index (kg/m^2)	28.3 ± 6.1	27.6 ± 5.9
Race/ethnicity		
Caucasian	242 (87)	257 (91)
Black	27 (10)	19 (7)
Hispanic	8 (3)	7 (2)
Other	2 (<1)	
Route of administration of concomitant estrogen		
Oral	208 (75)	209 (74)
Transdermal	71 (25)	74 (26)
Length of relationship with partner (yr)	18.6 ± 10.9	19.7 ± 11.6
No. of satisfying sexual episodes over 4 wk	2.9 ± 3.13	2.8 ± 2.57
Score on sexual desire domain of PFSF	20.7 ± 13.72	19.9 ± 12.96
Score on PDS	62.4 ± 25.35	64.7 ± 24.92

Data represent mean ± SD or number of subjects (percentage). Differences between groups were not statistically significant. Percentages are based upon the number of patients for whom data were available.

Androstenedione measurements were performed by RIA after sample extraction for which tritiated androstenedione was used as an internal standard. For the androstenedione measurements, the LLOQ was 3 ng/dl (0.10 nmol/liter), and the CV was 11.2% or less.

The concentrations of SHBG were determined using a sandwich immunoassay. The LLOQ was 2 nmol/liter, and the interassay CV was 8.1% or less for all quality control samples.

The analyses of total estradiol and estrone were performed by RIA after sample extraction and column chromatography. For the total estradiol assay, the LLOQ was 2 pg/ml (7.34 pmol/liter), and the CV was 12.5% or less. The corresponding values for the estrone assay were 10 pg/ml (37 pmol/liter) and 9.6% or less.

Statistical methods

Assuming a two-sided test, a minimum of 230 patients/arm were estimated to be necessary to provide approximately 90% power to detect a difference between treatment groups of 0.34 satisfying sexual activities/wk. Analyses were performed using an intent to treat approach, with all patients who received at least one application of study medication included in the analyses. A last observation carried forward approach was used to account for patients who did not complete the study. The sample size was increased to 250 patients/arm, because it was assumed that 5–10% of the patients would not contribute data for inclusion in the primary efficacy analysis. All hypothesis tests were two-sided, and treatment differences were assessed at the 0.05 significance level. Analyses were performed using SAS 8.2 software (SAS Institute, Inc., Cary, NC).

The primary efficacy end point was the change from baseline in the 4-wk frequency of total satisfying episodes during wk 21–24. Treatment groups were compared using an analysis of covariance model, adjusting for route of administration of concomitant estrogen therapy, baseline rate of activity, age, and pooled center. Model assumptions were as-

TABLE 2. Four-week frequency of total sexual activity, sexual desire, and distress at week 24

	Placebo [mean (SE)]	Testosterone [mean (SE)]	Treatment difference [95% CI]	P^a
SAL[b]				
Total satisfying activity				
Baseline	2.94 (0.19)	2.82 (0.15)	−0.12 [−0.60, 0.36]	0.615
Value at wk 24	3.93 (0.27)	4.92 (0.30)	0.99 [0.20, 1.79]	0.015
Change from baseline	0.98 (0.19)	2.10 (0.25)	1.11 [0.5, 1.73]	0.0003
Total no. of orgasms				
Baseline	2.65 (0.17)	2.73 (0.15)	0.09 [−0.36, 0.54]	0.701
Value at wk 24	3.61 (0.26)	4.92 (0.34)	1.31 [0.47, 2.15]	0.0023
Change from baseline	0.97 (0.20)	2.19 (0.27)	1.22 [0.56, 1.87]	0.0002
Total activity				
Baseline	4.94 (0.28)	4.98 (0.24)	0.04 [−0.69, 0.78]	0.906
Value at wk 24	5.39 (0.33)	6.27 (0.33)	0.88 [−0.04, 1.81]	0.0602
Change from baseline	0.45 (0.19)	1.29 (0.23)	0.84 [0.25, 1.43]	0.0036
PFSF				
Sexual desire[c]				
Baseline	20.82 (0.84)	19.79 (0.78)	−1.04 [−3.29, 1.22]	0.367
Value at wk 24	26.76 (1.15)	30.85 (1.22)	4.09 [0.79, 7.38]	0.015
Change from baseline	5.94 (1.02)	11.06 (1.07)	5.12 [2.20, 8.04]	0.0006
PDS[d]				
Baseline	62.57 (1.56)	64.78 (1.52)	2.21 [−2.08, 6.49]	0.312
Value at wk 24	47.50 (1.78)	42.01 (1.81)	−5.49 [−10.47, −0.51]	0.031
Change from baseline	−15.07 (1.49)	−22.77 (1.70)	−7.70 [−12.14, −3.26]	0.0006

[a] *P* value for baseline and values at wk 24 based on *t* test. *P* value for change from baseline based upon ANCOVA model, adjusting for route of administration of concomitant estrogen therapy, baseline rate of activity, age, and pooled center.
[b] For SAL, n = 273 placebo; n = 276 testosterone.
[c] For PFSF sexual desire, n = 269 placebo; n = 269 testosterone.
[d] For PDS, n = 266 placebo; n = 268 testosterone.

sessed qualitatively by visual inspection of the residuals. Similar methods were used to analyze the secondary efficacy end points. Correlations between changes from baseline in hormone levels and efficacy assessments were evaluated using Spearman correlation coefficients.

The number of adverse events and the percentage of patients reporting adverse events through wk 24 were summarized by treatment group. Laboratory test findings, vital signs, and body weights were summarized by treatment group using descriptive statistics. Lip and chin facial hair scores, facial depilation frequency, and facial acne scores were summarized using frequency tables. Changes in lipids by treatment group were summarized using descriptive statistics.

Results

Patient characteristics and disposition

Baseline characteristics were similar for the treatment groups (Table 1). Baseline PFSF scores for sexual desire corresponded to the seldom interested in sex category, whereas baseline PDS scores were reflective of patients who were often distressed by their lack of desire.

Of 562 women randomized, 230 of 279 (82%) women in the placebo group and 221 of 283 (78%) of women in the testosterone group completed the 24-wk, double-blind study period. The reasons for withdrawal included adverse events [placebo, 19 patients (6.8%); testosterone, 24 patients (8.5%)], protocol violation [placebo, three patients (1.1%); testosterone, three patients (1.1%)], voluntary withdrawal [placebo, 12 patients (4.3%); testosterone, 26 patients (9.2%)], and investigator recommendation [placebo, five patients (1.8%); testosterone, one patient (0.4%)]. Examination of the reasons given for voluntary withdrawals provided no evidence that the difference between groups in the number of voluntary withdrawals was related to any treatment effect. Eighteen women [placebo, 10 patients (3.6%); testosterone, eight patients (2.8%)] were lost to follow-up.

Efficacy measures

At 24 wk, the increase in the 4-wk frequency of total satisfying sexual activity was significantly greater in the testosterone group compared with the placebo group ($P = 0.0003$; Table 2). A statistically significant increase in the change in frequency of total satisfying sexual activity in the testosterone group compared with placebo was observed in the 4-wk period beginning at wk 5 (*i.e.* wk 5–8), with a consistent effect maintained from wk 12 on (Fig. 1). Testosterone patch treatment also resulted in statistically significant increases compared with placebo in frequency of total sexual episodes and orgasm (Table 2).

At the 24-wk point, the mean change from baseline in the sexual desire score was significantly greater in the testosterone group compared with the placebo group ($P = 0.0006$; Table 2). A statistically significant increase in changes in desire in the testosterone group compared with placebo ($P < 0.05$) was observed at wk 4 and all other time points except wk 8 ($P = 0.057$; Fig. 1).

The decrease in personal distress scores in the testosterone group at 24 wk was significantly greater than the decrease in the placebo group ($P = 0.0006$; Table 2). A significant decrease in personal distress in the testosterone group compared with placebo was observed at wk 4 and at all subsequent time points throughout the study (Fig. 1).

Testosterone-treated women also experienced significantly more favorable changes compared with placebo-treated women in all other domains of the PFSF (Fig. 2).

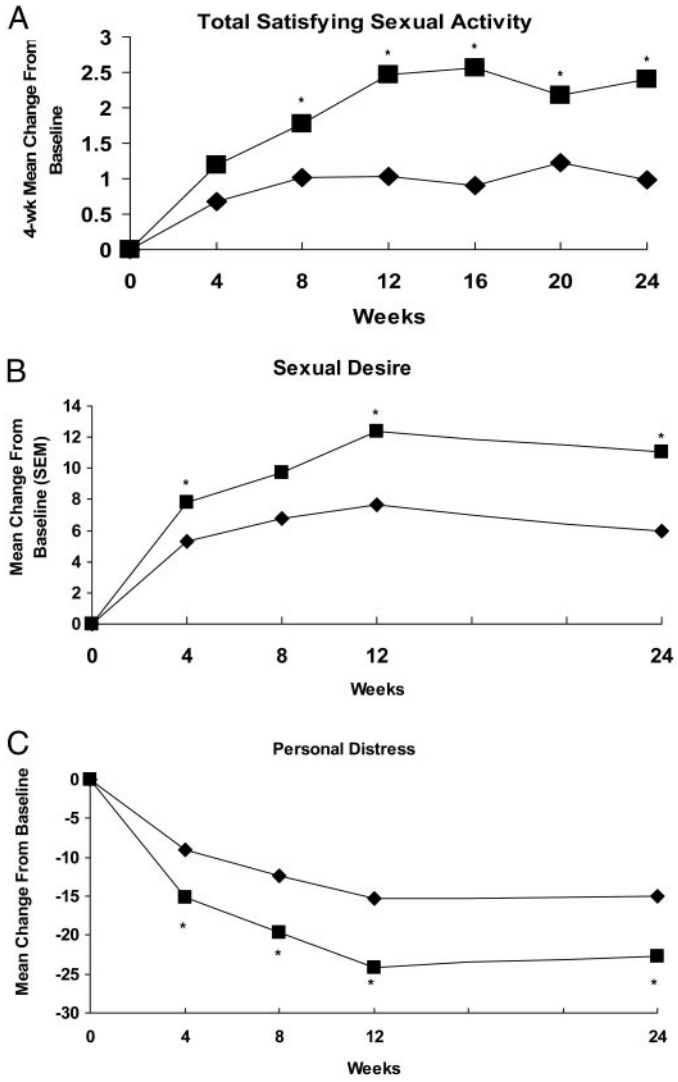

FIG. 1. Changes in 4-wk frequency of total satisfying activity, sexual desire score, and PDS in the testosterone and placebo groups over 24 wk. ■, Testosterone; ♦, placebo. *, $P \leq 0.05$ *vs.* placebo.

Safety

The overall adverse event profiles were similar in the two treatment groups (Table 3). The majority of adverse events were mild and classified by the investigator as doubtfully related to testosterone treatment. A total of 14 patients [placebo, seven patients (2.5%); testosterone, seven patients (2.5%)] reported serious adverse events during the trial. All but two of the seven testosterone patients had events that were classified by the investigator as doubtfully related to study drug (a transient ischemic attack in one patient; diaphoresis, increased heart rate, nausea, and other symptoms in a second patient). These two patients had resolution of the events while remaining on testosterone treatment. The incidence of application site reactions, the most commonly reported adverse event, was comparable in the testosterone

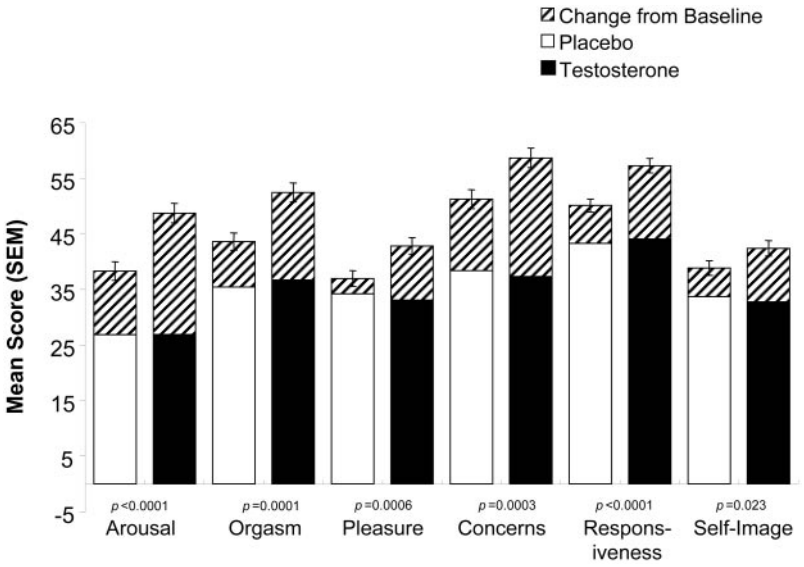

FIG. 2. PFSF domain scores: values at baseline and wk 24 in the testosterone and placebo groups. *P* values are for comparison of changes from baseline in testosterone *vs.* placebo groups. Note that the higher score for the sexual concerns domain reflects a decrease in patient concern.

and placebo groups. Most of these skin reactions were mild; 22 women [placebo, 13 patients (4.7%); testosterone, nine patients (3.2%)] discontinued treatment for this reason. The adverse events reported most commonly and by a higher percentage of patients receiving testosterone patch were headaches, upper respiratory tract infections, and acne. However, the difference between the treatment groups in the percentage of patients reporting these events was small. A higher percentage of patients reported migraine headache in the testosterone group (12 patients, 4.2%) than in the placebo group (four patients, 1.4%). Eight of the 12 patients in the testosterone group who reported migraines had a history of migraines before entering the study.

The risk of a patient experiencing at least one type of androgenic event (acne, alopecia, unwanted hair growth, or voice deepening) during the 24-wk treatment period was lower in the testosterone group compared with the placebo group (12.7% *vs.* 15.8%, respectively). Most of these events were considered mild by the study investigators, and very few patients discontinued treatment [testosterone, three patients (1.1%); placebo, one patient (0.4%)]. Changes in lip and chin facial hair scores and facial acne scores, as assessed by the investigators, were similar in the testosterone and placebo groups after 24 wk of treatment (Table 4).

Serum lipid/lipoprotein profile, carbohydrate metabolism parameters, coagulation tests, renal and liver function tests, and serum chemistry and hematology parameters were similar in both treatment groups at 24 wk, and no clinically relevant changes were observed during treatment. No meaningful changes between groups in vital signs or physical examination findings were noted.

Serum hormone levels

The median serum concentrations of free and total testosterone were similar in both treatment groups at baseline and were increased in the testosterone-treated group after 24 wk of treatment; no change in SHBG levels was observed with testosterone treatment (Table 5). There were no appreciable changes from baseline observed in serum estradiol (free and total) or estrone in either treatment group.

TABLE 3. Summary of adverse events

Adverse event	Placebo (n = 279) [n (%)]	Testosterone (n = 283) [n (%)]
Patients with any adverse event	222 (79.6)	220 (77.7)
Patients with any serious adverse event	7 (2.5)	7 (2.5)
Patients who withdrew from study due to adverse events	19 (6.8)	24 (8.5)
Most common adverse events reported at higher incidence in testosterone group		
Upper respiratory tract infection (NOS)	26 (9.3)	28 (9.9)
Headaches (NEC)	21 (7.5)	28 (9.9)
Androgenic adverse events		
Acne	17 (6.1)	17 (6.0)
Unwanted hair growth	18 (6.5)	16 (5.7)
Alopecia	9 (3.2)	9 (3.2)
Voice deepening	8 (2.9)	7 (2.5)
Application site reaction	109 (39.1)	88 (31.1)

Differences between groups are not statistically significant. NOS, Not otherwise specified; NEC, not elsewhere classified.

TABLE 4. Objective assessments of facial hair and acne

Change from baseline score	Placebo (n = 279) [n (%)]	Testosterone (n = 283) [n (%)]
Chin hair[a]		
≤0	250 (96)	253 (96)
1–2	11 (4)	11 (4)
Upper lip hair[a]		
≤0	245 (94)	249 (94)
1–2	16 (6)	15 (6)
Acne[b]		
≤0	256 (98)	257 (97)
1–2	5 (2)	7 (3)

Differences between groups are not statistically significant. Percentages are calculated based on number of patients with assessments (placebo, 261; testosterone, 264).

[a] Ferriman-Gallwey/Lorenzo scale (Ref. 13).

[b] Palatsi scale (Ref. 14).

TABLE 5. Serum hormone levels in the placebo and testosterone groups at baseline and after 24 wk

Hormone [reference range][a]	Treatment group	N	Baseline	N	Wk 24	P^b
Free testosterone [0.9–7.3 pg/ml]	Placebo	279	0.8 [0.4, 1.7]	218	0.7 [0.3, 1.5]	<0.01
	300 μg/d	280	0.8 [0.3, 1.5]	218	4 [1.2, 8.5]	
Total testosterone [12–50 ng/dl]	Placebo	279	17 [8, 28]	219	16 [7, 28]	<0.01
	300 μg/d	282	16 [8, 29]	219	70 [33, 139]	
SHBG [13–98 nmol/liter]	Placebo	279	79 [32, 174]	218	100 [36, 188]	<0.01
	300 μg/d	282	75.5 [31, 181]	220	77.5 [33, 172.5]	
Total estradiol [12–101 pg/ml; follicular phase]	Placebo	278	29.5 [10, 110]	212	32 [10, 114]	0.49
	300 μg/d	281	29 [10, 84]	209	31 [12, 99]	
Estrone [15–150 pg/ml; early follicular phase]	Placebo	279	87 [25, 363]	212	83 [24, 457]	0.73
	300 μg/d	281	79 [28, 332]	209	80 [30, 316]	
Total dihydrotestosterone [7–31 ng/dl]	Placebo	272	7 [0[c], 14]	155	7 [0, 12]	<0.01
	300 μg/d	271	7 [0[c], 14]	143	19 [9, 36]	
Androstenedione [50–250 ng/dl]	Placebo	276	58 [32, 108]	157	52 [21, 87]	0.96
	300 μg/d	275	60 [31, 103]	148	50.5 [29, 83]	

Values are medians [10th, 90th percentile ranges]. For free testosterone, multiply by 3.467 to convert pg/ml to pmol/liter; for total testosterone, multiply by 0.0347 to convert ng/dl to nmol/liter; for estradiol, multiply by 3.671 to convert pg/ml to pmol/liter; for estrone, multiply by 3.70 to convert pg/ml to pmol/liter; for dihydrotestosterone, multiply by 0.0344 to convert ng/dl to nmol/liter; for androstenedione, multiply by 0.0349 to convert ng/dl to nmol/liter.

[a] Reference ranges generated at Quest Diagnostics using data from premenopausal women.

[b] Comparison between treatment groups of change from baseline, Wilcoxon rank sum.

[c] Values lower than the lower limit of quantitation (4 ng/dl) were assigned a value of 0.

Relationships between hormone levels and efficacy and safety

Statistically significant correlations were observed between changes in most efficacy end points of the SAL, PFSF, and PDS and changes in testosterone serum concentrations (total, free, and bioavailable testosterone) after 24 wk of treatment (Table 6). No other correlations between efficacy end points and estrogen-related serum concentrations (*i.e.* free and total estradiol, estrone, or SHBG) were statistically significant, except for a correlation between sexual arousal and SHBG. Similar correlations were observed when efficacy end points were compared with actual hormone concentrations, rather than the changes in hormone concentrations.

Discussion

HSDD is one of the four common forms of female sexual dysfunction defined in the fourth edition of the Diagnostic and Statistical Manual of Mental Health Disorders and is characterized by chronic or recurrent deficit in or absence of desire for sexual activity that causes personal distress (1). In this study in surgically menopausal women with HSDD who were receiving concomitant estrogen therapy, the testosterone patch increased multiple aspects of sexual function, including sexual desire score and the frequency of satisfying sexual activity, and decreased distress.

TABLE 6. Correlations between changes from baseline in efficacy parameters and serum hormone levels at wk 24 for the 300-μg/d testosterone treatment group

	Total testosterone	Free testosterone	Bioavailable testosterone
Frequency of total satisfying sexual activity	0.14	0.17	0.17
Sexual desire score	0.21	0.20	0.20
PDS	−0.20	−0.17	−0.22

Data shown are Spearman correlation coefficients, where values closer to 1.0 indicate a more positive correlation (a proportional relationship) and values closer to −1 indicate a more negative correlation (an inversely proportional relationship). For all values, $P < 0.05$.

Female sexual function and associated distress were measured in our study using three patient-based instruments (the PFSF, PDS, and SAL) previously developed specifically to evaluate sexual function in surgically and naturally menopausal women with low libido. Of the aspects of sexuality captured by these measures, changes in sexual desire and distress are of particular interest, because both are defining properties of HSDD. The testosterone patch treatment produced significant favorable changes not only in both of these parameters but also in the frequency of total satisfying sexual activity. Satisfying sexual activity was a composite end point, including a variety of sexual activities, including sexual intercourse, masturbation, and oral sex as well as other sexual activities.

All PFSF, PDS, and SAL end points demonstrated statistically significant changes from baseline in the testosterone group compared with placebo after 24 wk of treatment. The magnitude and consistency of this response suggest that the testosterone patch produced a clinically meaningful change in overall sexual functioning, as measured across many aspects of sexual function and activity in this study. Statistically significant increases in some end points were evident within 4 wk of the start of treatment, and these increases were maintained throughout the treatment period.

The placebo response in this study is consistent with that in other reports related to sexual functioning (9, 15). All women enrolled in our study stated at baseline that they desired an improvement in their sex lives, and participating in the study may have increased dialogue regarding sexual satisfaction between the study subjects and their partners. We observed statistically significant changes with testosterone treatment even compared with the response in the placebo group.

The testosterone patches used in the study demonstrated a favorable safety profile in this population of women with low sexual desire. Adverse events, including androgenic adverse events, occurred with similar frequency in the placebo- and testosterone-treated groups. We saw no clinically important effects on vital signs, clinical chemistry, or hematology. About 30% of women in our study experienced application site reactions; however, most of these reactions were mild, and less than 5% of each patient group discontinued study participation due to these events. The incidence of application site reaction or discontinuation due to application site reactions observed in this study appears similar to those observed in some other studies with patches (16, 17).

Serum concentrations of free and total testosterone were similar between the treatment groups at baseline, and women receiving transdermal testosterone had increases in these concentrations at the end of 24 wk of treatment. No appreciable changes in the serum concentrations of estradiol or estrone occurred after treatment with transdermal testosterone. It should be noted that even though patients were selected on the basis of clinical symptoms of HSDD rather than on the basis of testosterone levels, the baseline testosterone levels in these oophorectomized women were low. These findings suggest that measurement of testosterone at baseline is not necessary in oophorectomized women with HSDD who are being considered for testosterone treatment.

The majority of women included in this study were Caucasian; therefore, fewer data are available regarding the effects of testosterone transdermal therapy on patients of other racial backgrounds. Only surgically postmenopausal women were enrolled in this clinical trial, and all were receiving concomitant estrogen therapy, so other studies will be needed to evaluate this therapy in naturally menopausal women or in women without concomitant estrogen therapy. This study also evaluated only short-term use (24 wk). Given concerns with long-term safety of estrogen and progestin therapy raised by the Women's Health Initiative study (18), it will be important to obtain additional data to assess the longer-term safety of testosterone.

Conclusions

In this large, randomized, placebo-controlled trial, the transdermal testosterone patch was demonstrated to be an effective therapy for the treatment of HSDD in surgically menopausal women receiving concomitant estrogen therapy. Treatment was well tolerated, and no serious safety concerns were identified during 24 wk of therapy.

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Erratum

In the article "Expression and Functional Analysis of Pituitary Tumor Transforming Growth Factor-1 in Uterine Leiomyomas" by S.-J. Tsai, S.-J. Lin, Y.-M. Cheng, H.-M. Chen, and L.-Y. C. Wing (*The Journal of Clinical Endocrinolgy & Metabolism* **90:**3715–3723, 2005), the title is incorrect. The correct title should read as follows: "Expression and Functional Analysis of Pituitary Tumor Transforming Gene-1 in Uterine Leiomyomas." *The authors regret the error*.

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