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Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial

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ABSTRACT

Objective: Evaluation of the use of testosterone therapy for hypoactive sexual desire disorder (HSDD) after oophorectomy has mostly involved women treated with oral estrogen preparations. We investigated the efficacy and safety of a testosterone patch in surgically menopausal women receiving concurrent transdermal estrogen.

Design: Women with HSDD after oophorectomy, for whom this was a concern, who were using transdermal estrogen, were recruited to a 24-week, randomized, double-blind, placebo-controlled trial in Europe and Australia. Patients were randomly allocated to placebo (n = 40) or testosterone 300 μg/day (n = 37) treatment. Primary endpoints were changes in sexual desire measured by the sexual desire domain of the Profile of Female Sexual Function and the frequency of satisfying sexual activity at 24 weeks.

Results: Sixty-one women (79%) completed the trial. All subjects who received at least one application of study medication were included in analysis. The testosterone-treated group experienced a significantly greater change from baseline in the domain sexual desire score compared with placebo (change from baseline, 16.43 versus 5.98; $P = 0.02$). The domain scores for arousal, orgasm, decreased sexual concerns, responsiveness, and self-image as well as decreased distress were also significantly greater with testosterone therapy than placebo. The frequency of satisfactory sexual events increased but was not statistically different between treatment groups ($P = 0.06$) Adverse events occurred with similar frequency in both groups, and no serious risks of therapy were observed.

Conclusion: In this study, transdermal testosterone therapy via a skin patch improved sexual desire and other sexual function domains. It was well tolerated in these oophorectomized women with HSDD receiving concomitant transdermal estrogen.

Key Words: Surgically menopausal women – Sexual desire – Testosterone – Hypoactive sexual desire disorder – Oophorectomy – Female sexual dysfunction.

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Female hypoactive sexual desire disorder (HSDD) encompasses the deficiency or absence of desire for sexual activity that causes marked distress or interpersonal difficulty.[1] After bilateral oophorectomy, 30% to 50% of women report diminished sexual desire, a rate almost twice that of women undergoing hysterectomy alone.[2,3] Loss of ovarian testosterone production may contribute to the development of HSDD after oophorectomy.[4] The common practice of prescribing oral estrogen therapy post oophorectomy may exacerbate HSDD, as oral estrogen increases plasma levels of sex hormone binding globulin (SHBG) and thus reduces the free fraction of testosterone, which is biologically active. In contrast, transdermal estrogen therapy does not increase SHBG.[5]

Several studies indicate that the addition of testosterone to estrogen therapy improves sexual well-being in postmenopausal women.[6-9] Two randomized, placebo-controlled trials have shown that testosterone patches delivering 300 μg/day administered to women with HSDD significantly increase sexual function[9,10] and well-being.[9] The first of these studies involved only surgically postmenopausal women who were receiving moderate to high doses of oral conjugated equine estrogens.[9] More recently, Buster et al[10] reported efficacy of the 300-μg/day testosterone patch in oophorectomized women, recruited from North America and Australia, treated with a variety of oral and nonoral estrogen preparations. No study to date, however, has specifically examined the efficacy and safety of the testosterone patch in women receiving transdermal estrogen. Furthermore, evaluation of this testosterone patch has been limited to studies either exclusively or predominantly of women recruited in North America. This study was designed to evaluate the efficacy and safety of a testosterone patch in oophorectomized women with HSDD recruited in Europe and Australia who were receiving concomitant transdermal estrogen treatment.

METHODS

Study participants

Women were eligible to participate if they were aged 20 to 70 years and had undergone bilateral salpingo-oophorectomy and hysterectomy at least 1 year before enrollment. All had been receiving a stable dose of transdermal estradiol therapy for at least 12 weeks, had a serum free testosterone concentration less than 3.5 pg/mL (12.1 pmol/L), and had been in a stable, monogamous sexual relationship for at least 1 year with a partner. The partner was expected to be present for at least 50% of each month during the pretreatment and efficacy periods. Patients were determined to have onset of low sexual desire after oophorectomy with associated distress based on positive responses to all the following questions:

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?

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?

Participants were also required to have a body mass index between 18 and 30 kg/m^2 and, if 40 years or older, no evidence of malignancy on screening mammogram. Women were excluded if they had received oral, topical, or vaginal androgen therapy in the previous 3 months, or testosterone implants in the previous 7 months; if they had more than 15 moderate to severe hot flushes per week; if they had moderate or severe hirsutism (score of > 6 on the scale of Lorenzo);[11] hyperlipidemia, psychiatric illness (score of ≥ 14 on the Beck Depression Inventory-II),[12] dyspareunia, or physical limitations that interfered with normal sexual function; or if they were taking medication known to affect sexual function such as chronic glucocorticosteroids, sex steroids other than estradiol, antidepressants, or some antihypertensives.

The study was conducted in the following countries (number of clinical sites): Australia (2), the United Kingdom (5), France (2), Germany (1), The Netherlands (3), and Italy (2). Screening began on July 12, 2000, and the last observation was collected on October 9, 2001. The protocol was approved by the institutional review boards or ethics committees at all sites, and written informed consent was obtained from all participants before study entry.

Study procedures

This randomized, double-blind, placebo-controlled, parallel-group study consisted of an 8-week pretreatment period and a 24-week treatment period. Eligibility

was established at the first pretreatment visit (–8 weeks), and both the Lock-Wallace Marital Adjustment Score[13] and the Beck Depression Inventory[12] were completed at this visit. At the second pretreatment visit (–4 weeks), evaluation of hirsutism, frequency of facial depilation, acne score, frequency and severity of hot flushes, and breast tenderness were documented. At the baseline visit, participants completed the efficacy assessment questionnaires and received the study medication. During the 24-week treatment period, participants visited the study site at weeks 4, 8, 12, and 24 for efficacy and safety assessments. Blood samples for hormone and other analyses were drawn at baseline and after 12 and 24 weeks of treatment.

Treatment

Participants were stratified by dose of transdermal estradiol (50 μg/d or any other dose), which was to be maintained at a constant level throughout the 8-week pretreatment and 24-week treatment period. Within each strata and site, the method of random permuted blocks was used to randomly allocate women to either the transdermal placebo or testosterone (300 μg/day) matrix patches, which were identical in appearance. Site-specific randomization lists were generated by Procter & Gamble Pharmaceuticals' clinical supplies department. All participants, other sponsor personnel, investigators, and study personnel were blinded to treatment allocation. Study participants applied the alcohol-free, matrix patches (Watson Laboratories-Utah, Salt Lake City, UT) twice weekly (each patch was worn for approximately 3 or 4 days) to the abdomen.

Efficacy measures

All efficacy assessments were performed at baseline and after 12 and 24 weeks. Sexual activity was assessed by completion of the Sexual Activity Log (SAL)[14] at baseline (during the 8-week pretreatment phase) and weekly throughout the treatment period. The SAL is a 1-week recall diary, completed at home, that documents the number of intercourse and non-intercourse sexual activities, the number of orgasms, and the number of sexual activities that were satisfying for the woman. Other aspects of sexual function were evaluated by the Profile of Female Sexual Function (PFSF), a psychometrically validated, 30-day recall instrument for the measurement of low sexual desire and related symptoms.[15,16] The PFSF consists of seven domains measuring desire, arousal, orgasm, pleasure, sexual concerns (ie, a decrease in concerns), responsiveness, and sexual self-image, and has been developed and validated in multiple languages.[15,16] Some items are reverse-scored, so that a higher score reflects improved sexual function for all domains, including sexual concerns. Domain scores are transformed to percentage of total possible domain score so that the range for each domain score is 0 to 100. The Personal Distress Scale (PDS),[17] consisting of seven items, was developed in parallel with the PFSF domains and has been used as a separate instrument to measure distress associated with loss of desire. The Psychological General Well-Being Index (PGWB), a 22-item questionnaire, was used to measure well-being. It has six individual domains and a composite score, with a higher score indicating greater well-being.[18]

Hormone assays

All sex steroids were measured by radioimmunoassay after sample extraction using the specific tritiated sex steroid being measured as the internal standard. For each radioimmunoassay, ^{125}I -labeled steroid was used as tracer and rabbit antisteroid as antibody. Quest Diagnostics, Inc. (San Juan Capistrano, CA) performed all of the hormone assays. Hormone assay methods were validated to the extent feasible for endogenous species. Hormone values were summarized for the patients who were at least 80% compliant to wearing the patch and sample collection was limited to those within 5 days of the most recent patch application.

Safety evaluations

Safety evaluations at each visit included review of adverse events since the last visit, recording of vital signs, hirsutism assessment using the scale of Lorenzo,[11] facial depilation frequency (number of times in the past month that hair was removed from the chin or upper lip), acne score using the scale of Palatsi et al,[19] and breast tenderness (none, mild, moderate, severe). The patch application sites were examined for any dermal reaction. Blood was drawn before 1 PM of the baseline visit day (end of the 8-week pretreatment period) and after 12 and 24 weeks for serum chemistry, including coagulation factors and hormone analyses. A complete physical examination was performed at the end of 24 weeks of treatment.

Statistical analysis

Initial power calculations indicated that 80 subjects would be required in each treatment group to provide

90% power to detect differences in the primary outcomes; however, enrollment was stopped because of slow recruitment after 77 patients were randomized. All patients who received at least one application of study medication were included in the intent-to-treat analysis of the primary and secondary efficacy endpoints. All hypothesis tests were two-sided and treatment differences were assessed at the 0.05 significance level.

Demographic characteristics and baseline measures were summarized by treatment group. The primary efficacy endpoints were the sexual desire domain of the PFSF and the frequency of satisfying sexual activity from the SAL, both measured after 24 weeks of treatment. An analysis of covariance model was used to fit changes in sexual desire from baseline to the end of 24 weeks with treatment group, pooled centers, baseline values, age, and marital status as covariates. A GEE Poisson regression was used to evaluate the frequency of satisfying sexual activity during the 21st through 24th weeks of treatment as a function of treatment group, pooled centers, baseline average weekly frequency of satisfying sexual activity, age, and marital status. A log linear model was fitted and an exchangeable working correlation matrix was used to account for correlated observations within a study subject. A last-observation-carried-forward approach was used to account for missing data.

Secondary efficacy endpoints included the other PFSF and SAL domains and the PGWB composite score and individual domains at the end of 12 and 24 weeks of treatment. These parameters were analyzed using statistical methods similar to those applied to the primary endpoints.

Safety endpoints included adverse event rates, summarized by severity, causality, and relationship to treatment, and laboratory test findings summarized by time point—baseline, 12 weeks, 24 weeks, and study exit—and by change from baseline. Facial depilation and degree of facial acne scores were evaluated for change from baseline to study exit, and scores for the testosterone group and placebo group were compared using a Cochran-Mantel-Haenszel

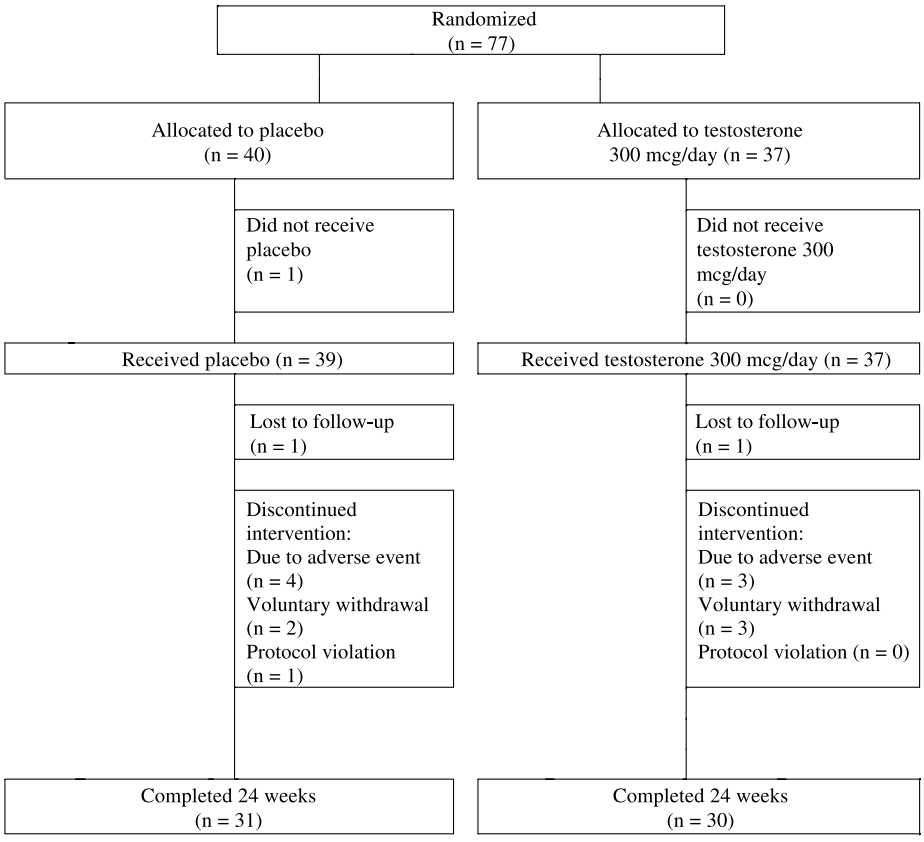

FIG. 1. Patient disposition.

test. A *t* test was used to investigate significant changes compared with placebo in total hirsutism scores at each visit and study exit. For each testosterone patch, comparison of the worst irritation assessment and modal value between the placebo and active patches was performed using a Cochran-Mantel-Haenszel test. An interim safety analysis of adverse events, acne and hirsutism assessments, and laboratory parameters was conducted at 12 weeks to identify any safety concerns. Because these results were not used to modify this study, no adjustments were made to the nominal *P* values to account for these analyses. Statistical significance was defined for all analyses as $P < 0.05$.

RESULTS

Patients

Of 77 patients randomized, 61 (79%) completed the 24-week treatment period (Fig. 1). The treatment groups were well matched for baseline parameters (Table 1) and few women (9%) had prior androgen use. Overall, 68 (89%) of the patients applied at least 80% of their scheduled patches within each 12-week interval of the 24-week study period. The proportion of patients failing to adhere to the treatment schedule was similar in both treatment groups.

Efficacy

After 24 weeks of treatment, there was a significant increase in the sexual desire domain score of the PFSF with testosterone treatment compared with placebo (adjusted mean change from baseline 16.43 ± 3.62 versus 5.98 ± 4.00, respectively, $P = 0.02$) (Fig. 2). The unadjusted mean change for the testosterone group (15.3) corresponded to a 66% increase from the mean baseline value (23.12) ($P < 0.0001$). The weekly frequency of total satisfying sexual events at baseline in the placebo and testosterone groups respectively were 0.80 (± 0.10) and 0.52 (± 0.08), and these increased by 0.28 (± 0.15) and 0.77 (± 0.15) events per week by 24 weeks, respectively. There was a 43% increase in the weekly frequency of total satisfying sexual activity at 24 weeks, as measured by the SAL for those receiving testosterone versus placebo ($P = 0.06$), with the unadjusted mean change for the testosterone group (0.77) corresponding to a 148% increase over baseline (0.52) ($P < 0.0001$) (Fig. 3). Significant differences were observed for all activity endpoints that included intercourse ($P < 0.02$). No significant differences were observed for sexual activities that did not include sexual intercourse.

After 24 weeks of treatment, testosterone patch use resulted in a significant reduction in the personal distress score compared with placebo (adjusted mean change from baseline of 22.81 versus 3.49; $P = 0.003$). Women receiving testosterone also experienced significant increases versus placebo for each of the following PFSF domains: sexual arousal ($P = 0.02$), orgasm ($P = 0.03$), sexual responsiveness ($P = 0.005$), sexual self-image ($P = 0.04$), and lessening of sexual concerns ($P = 0.003$) (Fig. 2). A positive treatment effect for testosterone was seen for the responses to the PGWB, with a significant increase in the composite score versus placebo (2.57 versus –2.82; $P = 0.04$); a borderline difference was also

TABLE 1. *Baseline characteristics of the treatment groups*

Parameter	Placebo (n = 39)	Testosterone 300 μg/day (n = 37)
Age (y)	49.3 (30-63)	51.0 (38-66)
Body mass index (kg/m^2), mean (SD)	24.4 (2.5)	24.4 (3.0)
Length of relationship (y)	21.1 (1-45)	21.1 (2-39)
Years since:		
Hysterectomy	8.0 (1-25)	8.3 (1-30)
Oophorectomy	6.6 (1-25)	6.6 (1-30)
Dose of transdermal estradiol, n (%)		
50 μg/day	23 (59%)	20 (54%)
>50 μg/day	16 (41%)	17 (46%)
Prior androgen use, n (%)		
No	33 (85%)	36 (97%)
Yes	6 (15%)	1 (3%)
Locke-Wallace Marital Adjustment score[a]	112.7 (48-148)	105.4 (58-149)
Beck Depression Inventory II score[b]	5.7 (0-13)	7.2 (0-13)
Baseline scores for PFSF domains, mean (SEM)		
Desire	19.89 (2.23)	23.13 (2.32)
Arousal	31.28 (4.01)	40.36 (4.08)
Orgasm	40.64 (4.26)	44.31 (3.52)
Sexual pleasure	30.95 (3.45)	36.60 (3.34)
Sexual concerns	56.24 (4.25)	56.40 (3.17)
Sexual responsiveness	44.84 (4.07)	45.95 (3.60)
Sexual self-image	44.27 (3.81)	42.69 (3.32)
Personal distress scale	44.47 (4.00)	44.25 (4.17)
Baseline total sexual activity (events/wk)	1.86 (0.31)	0.93 (0.13)
Baseline frequency of total satisfactory activity (events/wk)	0.80 (0.10)	0.52 (0.08)

Data shown are mean (range), unless otherwise noted. SD, standard deviation; SEM, standard error of the mean.

[a]The total score range for this test is 2 to 158 ("very unhappy" to "perfectly happy").

[b]Total scores of 0 to 13 = minimal depression/nondepressed; 14 to 19 = mild depression; 20 to 28 = moderate depression; 29 to 63 = severe depression.

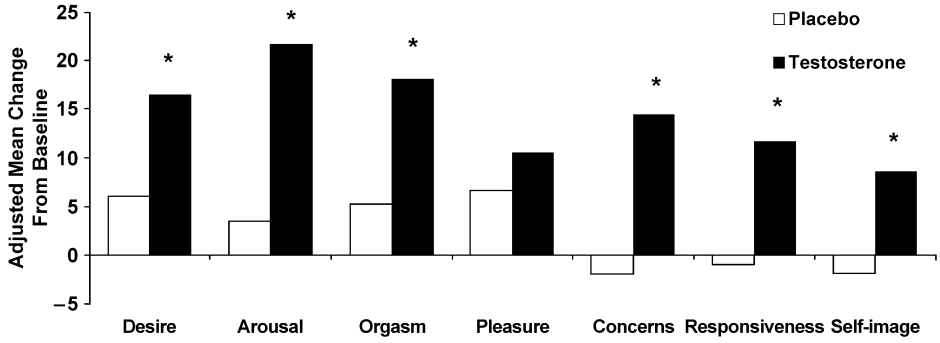

FIG. 2. Profile of Female Sexual Function domain scores: mean changes from baseline at 24 weeks by treatment group.

observed for the positive well-being domain (0.92 versus –0.33; $P = 0.05$) and the general health domain (0.32 versus –0.58; $P = 0.06$). After only 12 weeks of treatment, significant results were seen for the PDS and all PFSF domains except for sexual self-image.

Serum hormone concentrations

Median serum concentrations of free, total, and bioavailable testosterone and total dihydrotestosterone (DHT) were similar for the two groups at baseline. Values increased from baseline to Week 12 in the testosterone treatment group and did not increase further between weeks 12 and 24 (Table 2). Median serum SHBG, estradiol, and estrone concentrations were similar for both treatment groups at baseline and did not change in either group during the treatment period.

Relationship between serum hormone levels and efficacy parameters

Significant positive correlations were observed between changes in total and free testosterone and total and free DHT levels at 24 weeks and, in the frequency of total satisfying activity, sexual desire, arousal and orgasm, decline in personal distress, and positive well-being (Spearman's rank correlations 0.36 to 0.70, $P < 0.05$, see Table 3).

Safety

The overall incidence of adverse events and withdrawal due to adverse events were similar across treatment groups, as shown in Table 4. Most events were mild (59%) or moderate (37%) in severity and the majority was considered doubtfully related to the

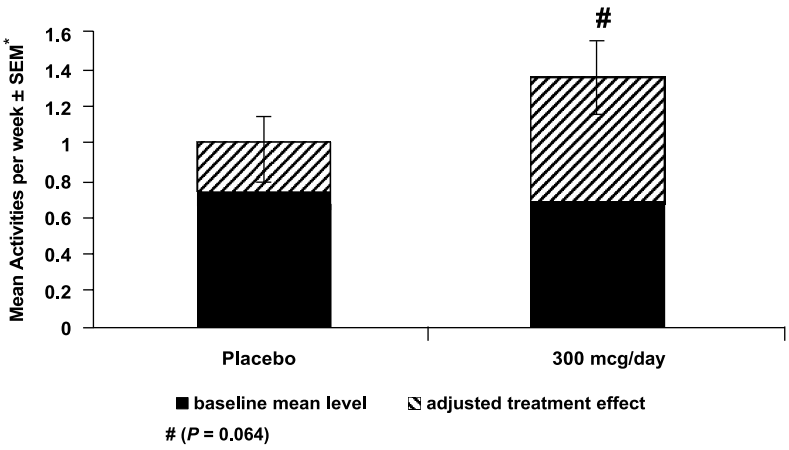

FIG. 3. Frequency of sexual activity: change from baseline at week 24 by treatment group.

TABLE 2. *Serum hormone values at baseline and during the study for placebo and testosterone treatment groups*

Hormone [reference range]	Treatment group	n	Baseline	n	Week 12	n	Week 24
Free testosterone [0.9-7.3 pg/mL]	Placebo	34	1.3 [0.9, 2.0]	30	1.1 [0.8, 1.7]	30	1.3 [0.8, 2.1]
	300 μg/day	33	1.2 [1.0, 1.5]	29	6.5 [5.0, 7.7]	23	4.8 [2.6, 6.7]
Total testosterone [12-50 ng/dL]	Placebo	34	17 [13, 23]	30	15 [12, 18]	30	17 [11, 22]
	300 μg/day	33	15 [13, 18]	29	76 [41, 97]	24	63 [38, 84.5]
Bioavailable testosterone [0.8-8.6 ng/dL]	Placebo	24	1.08 [0.76, 1.78]	23	0.93 [0.76, 1.30]	22	1.13 [0.72, 2.62]
	300 μg/day	25	1.39 [0.85, 1.64]	22	5.80 [3.29, 9.88]	15	4.79 [3.17, 8.46]
Sex hormone-binding globulin [13-98 nmol/L]	Placebo	34	54 [46, 74]	30	56 [45, 83]	30	55 [40, 78]
	300 μg/day	33	49 [40, 78]	29	48 [33, 64]	26	55 [38, 65]
Estradiol [12-101 ng/dL; follicular phase]	Placebo	34	56 [27, 75]	29	40 [27, 61]	27	47 [22, 71]
	300 μg/day	32	57 [31, 102.5]	29	49 [24, 98]	25	69 [46, 81]
Estrone [15-150 ng/dL; early follicular phase]	Placebo	34	52.5 [38, 75]	30	46.5 [31, 58]	29	42 [30, 69]
	300 μg/day	33	50 [40, 85]	29	42 [36, 63]	25	54 [41, 63]
Total dihydrotestosterone [6-31 ng/dL]	Placebo	31	8 [5, 12]	29	7 [5, 11]	25	9 [6, 14]
	300 μg/day	31	6 [4, 8]	27	19 [14, 27]	22	17.5 [13, 23]

Values are medians [25th, 75th percentile ranges].
Reference ranges for serum free, total, and bioavailable testosterone, total dihydrotestosterone, and SHBG levels were established using measurements from 161 regularly cycling, healthy women aged 18 to 49 years who were not taking any medications or hormone therapies. Estradiol and estrone reference ranges are standard values from Quest Diagnostics, Inc.

study drug. No serious adverse events and no deaths were reported during the study. Clinical assessments of acne after 24 weeks of treatment were not significantly changed from baseline (Table 4). There was a significant increase in the total hirsutism score for women treated with testosterone compared with placebo, but this difference was not significantly different from baseline, and interpretation of this difference between groups is complicated by the fact that more patients in the placebo group had an increase of three or more times per month in depilation rate. The incidence of acne and hirsutism reported as adverse events during the study was similar across both treatment groups. One study patient who received testosterone reported mild voice deepening, which reversed after study completion.

Laboratory findings, including results of liver function, hematology, carbohydrate metabolism, lipid profiles, and clotting parameters, and vital signs were essentially unchanged from baseline when evaluated after 24 weeks of study treatment. Evaluation of the skin patch site at the end of treatment showed good patch tolerability and the majority of application site reactions were classified as mild.

DISCUSSION

This study was undertaken to evaluate the efficacy of transdermal testosterone therapy in surgically

TABLE 3. *Correlations between change from baseline in efficacy parameters and hormone levels at week 24*

Subscale	Total testosterone	Free testosterone	Bioavailable testosterone	Total DHT	Free DHT
PFSF Domain Scores					
Sexual desire	0.38[a]	0.40[a]	0.46[a]	0.48[a]	0.65[a]
Sexual arousal	0.36[a]	0.40[a]	0.39	0.50[a]	0.54[a]
Orgasm	0.48[a]	0.44[a]	0.57[a]	0.49[a]	0.44[a]
Sexual pleasure	0.37[a]	0.37[a]	0.53[a]	0.28	0.43[a]
Decreased concerns	0.32	0.28	0.22	0.28	0.39
Sexual responsiveness	0.36[a]	0.32	0.29	0.45[a]	0.47[a]
Sexual self-image	0.29	0.35[a]	0.23	0.31	0.47[a]
PDS Score					
Personal distress scale	0.42[a]	0.48[a]	0.70[a]	0.51[a]	0.58[a]
Sexual Activity Log Scores					
Total sexual activities					
Number of episodes	0.59[a]	0.64[a]	0.33	0.36	0.33
Number of orgasms	0.59[a]	0.61[a]	0.29	0.33	0.44
Satisfying episodes	0.60[a]	0.61[a]	0.37	0.51[a]	0.55[a]
Psychological General Well-Being Index Score					
Positive well-being	0.57[a]	0.48[a]	0.49[a]	0.42[a]	0.46[a]

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

TABLE 4. *Summary of adverse events by treatment group and objective assessments of hirsutism and acne change from baseline to study exit*

Adverse event	Placebo (n = 39)	Testosterone 300 μg/day (n = 37)
Any adverse event	30 (77)	28 (76)
Serious adverse event	0	0
Withdrawals due to adverse event	4 (10)	3 (8)
Most common nonandrogenic adverse events:		
Application site reaction	12 (31)	6 (16)
Respiratory infection	5 (13)	0
Breast pain	1 (3)	4 (11)
Headache	6 (15)	4 (11)
Hirsutism		
Mean baseline score	2.23	1.89
Mean change from baseline	–0.42	0.33[a]
Facial depilation		
Increase of 3 times/mo	3 (8%)	1 (3%)
Acne score		
Change from baseline of 1	1 (3%)	2 (6%)
Change from baseline of 2	0	0

Data are number (%) of women unless otherwise indicated.
[a] $P < 0.05$ versus placebo; not significant versus baseline.

postmenopausal European and Australian women with HSDD using nonoral estradiol therapy. We have demonstrated that treatment with the 300-μg/day testosterone patch in this study population significantly improved sexual desire, arousal, orgasm, responsiveness, and self-image, and reduced sexual concerns and associated personal distress. Consistent with the latter there was a significant increase in the composite score for the PGWB Index with testosterone therapy versus placebo.

The frequency of total satisfactory sexual events increased with active therapy in the testosterone-treated women, but this did not achieve statistical significance. The effect sizes for change in total number of satisfactory events per month and PFSF domain scores with testosterone therapy in this study are similar to those reported by Buster et al.[10]

A strength of this study was the use of the PFSF, because its development and validation involved women of each of the countries in which our study was conducted with specific attention to the linguistic validity of the questionnaire for each language.

A limitation of this study was failure to recruit the target number of women in several of the study centers. This reflects a number of significant sociocultural differences in the conduct of research, prevalence of the use of postmenopausal hormone therapy (which was an entry criterion), and possibly attitudes toward therapy for HSSD between North America and other countries.

Not only was this study conducted entirely outside of the United States and separately from any other study, but it is also the first study of women receiving transdermal estradiol using these outcome measures and thus provides novel statistically significant data pertaining to the use of transdermal testosterone therapy for women.

Although recruitment was stopped before full accrual, potentially reducing power to pick up clinically meaningful effects, statistical significance was achieved for nearly all endpoints increasing the confidence that the effect of testosterone over placebo was real. All statistical tests were two-sided using an alpha level of 0.05. Therefore, the likelihood of rejecting the null hypothesis of no treatment difference and falsely claiming a treatment effect was controlled at 5%.

The women in our study exhibited much lower placebo response rates than those reported by Shifren et al.[9] Similarly, a low placebo response was also reported in the study of transdermal testosterone cream versus placebo conducted in Australia by Goldstat et al.[21] Whether these lower placebo responses also reflect a cultural difference between European-Australian women and women in the United States or some other difference between the study populations is not known. Furthermore, available data from combined studies of the testosterone patch used in this study suggest the route and formulation of estrogen therapy may influence treatment effect, favoring a more likely treatment effect with transdermal estradiol therapy.[22]

During the treatment period, testosterone was delivered consistently, which resulted in biologically active concentrations of free and bioavailable testosterone. A recent study by Lobo et al[23] evaluated the comparative effects of oral estrogen therapy with or without oral methyltestosterone treatment. They found that methyltestosterone did not improve the patients' Brief Index of Sexual Functioning for Women scores, but it did lower patient SHBG levels and increased bioavailable testosterone levels. In contrast, we found that use of the testosterone patch did not impact baseline SHBG levels. Although in some patients total testosterone levels in our study increased above the reference range, free and bioavailable testosterone, considered better indicators of biologically active testosterone, remained within the reference range. We observed moderate, yet statistically significant, correlations between our efficacy endpoints and testosterone levels. These were stronger however than those reported by Buster et al,[10] in

whose study 80% of the participants were using oral estrogen therapy. This most likely reflects perturbations due to the significant increase in SHBG induced by oral estrogen.

The testosterone matrix patch was well tolerated, and no clinically significant adverse events were reported. Some women experienced application site reactions; however, only 5% of the testosterone-treated and 3% of the placebo-treated patients discontinued study participation because of these events.

This study involved oophorectomized women who were required to be on concurrent estrogen transdermal therapy. Concerns have been raised regarding estrogen therapy in postmenopausal women; however, the Women's Health Initiative study has now reported that breast cancer and cardiac events were not increased in women taking estrogen only, in contrast to their findings in women receiving continuous estrogen/progestin. They also reported that the risk of stroke, although increased overall, was not increased in women under 60 years.[24] Although the effects of testosterone treatment on breast cancer are not known, the results from in vitro and in vivo studies suggest that testosterone may serve as a natural endogenous protector of the breast, and may limit the mitogenic and cancer-promoting effects of estrogen on the mammary epithelium.[25,26] Additional clinical studies are required to determine the safety and efficacy of transdermal testosterone in the absence of concomitant estrogen, whether orally or transdermally delivered.

CONCLUSIONS

In this study, use of the 300-μg/day testosterone patch increased sexual desire, improved sexual functioning, decreased distress, and improved overall well-being in surgically menopausal women aged 20 to 70 years with HSDD who were also using transdermal estrogen therapy.

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