

Safety and Efficacy 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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Background: Oophorectomy reduces serum testosterone levels. We studied the efficacy and safety of transdermal testosterone in treating hypoactive sexual desire disorder in surgically menopausal women.

Methods: A 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial was conducted in women (aged 24-70 years) who developed distressful low sexual desire after bilateral salpingo-oophorectomy and hysterectomy and who were receiving oral estrogen therapy. Women were randomized to receive placebo (n = 119) or testosterone patches in dosages of 150 µg/d (n = 107), 300 µg/d (n = 110), or 450 µg/d (n = 111) twice weekly for 24 weeks. Sexual desire and frequency of satisfying sexual activity were primary efficacy outcome measures.

Results: Of the 447 women randomized, 318 (71%) completed the trial. Compared with placebo, women receiving the 300-µg/d testosterone patch had significantly

greater increases from baseline in sexual desire (67% vs 48%; $P = .05$) and in frequency of satisfying sexual activity (79% vs 43%; $P = .049$). The 150-µg/d group showed no evidence of a treatment effect. The 450-µg/d group also was not statistically different from the 300-µg/d or placebo groups. Marginally significant linear dose-response trends were observed for total satisfying sexual activity and sexual desire at 24 weeks ($P = .06$ and $.06$, respectively). Adverse events occurred with similar frequency in both groups; no serious safety concerns were observed.

Conclusions: The 300-µg/d testosterone patch increased sexual desire and frequency of satisfying sexual activity and was well tolerated in women who developed hypoactive sexual desire disorder after surgical menopause.

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HYPOACTIVE SEXUAL DESIRE disorder, 1 of the 4 common forms of female sexual dysfunction, is characterized by chronic or recurrent deficit in or absence of desire for sexual activity, resulting in personal distress.¹

An association between surgical menopause and lack of sexual desire has been noted; 30% to 50% of women who undergo oophorectomy report decreased desire after the procedure.^{2,3} This decrease in desire may be associated with a decrease in levels of circulating androgens due to surgical removal of the ovaries. Women who have undergone bilateral oophorectomy typically experience a 50% decrease in circulating testosterone levels.⁴ Although some women may see improvements in sexual functioning with estrogen therapy alone, others may need the

addition of an androgen to achieve a satisfying level of sexual desire. Paradoxically, treatment with oral estrogens after surgery may exacerbate the effects of a testosterone deficit by increasing sex hormone-binding globulin (SHBG) levels.⁵

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Study findings have suggested that libido can be preserved for these women by use of estrogen and testosterone therapy, and that this combination is more effective than therapy with estrogen alone.⁶⁻⁸ Androgen treatments used in the past to treat loss of sexual desire include testosterone by injection,^{6,7} implanted pellets,⁹ transdermal gels and creams,^{10,11} oral methyltestosterone,¹² and dehydroepiandrosterone.¹³ A recent placebo-controlled,

crossover trial showed that administration of transdermal testosterone, 300 µg/d, for 3 months to women with low libido after oophorectomy receiving concomitant conjugated equine estrogens produced significant increases in sexual function and well-being.¹⁴ Results from that trial also indicated that the testosterone patch was well tolerated.

We undertook this study to further investigate the efficacy and safety of 3 dosage levels of testosterone administered via patch to women with hypoactive sexual desire disorder after surgically induced menopause. Unlike the previous study of the transdermal patch,¹⁴ this study used new efficacy measures specifically designed and validated for use in postmenopausal women with low sexual desire.

METHODS

STUDY SUBJECTS

We studied 447 healthy women, 24 to 70 years old, recruited between March 1 and November 30, 2000, at 39 sites in the United States. All women had undergone bilateral salpingo-oophorectomy and hysterectomy at least 1 year before entering the study and had been receiving oral estrogen at a stable dose for at least 12 weeks; the dose and type of estrogen therapy was to be maintained throughout the study. All women were also to have been in a monogamous sexual relationship for at least a year with a partner who was sexually functional. All study participants were considered to have onset of hypoactive sexual desire disorder after oophorectomy on the basis of their affirmative responses to the questions shown in the following list and the absence of other conditions that could cause low sexual desire.

- 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?

Women were excluded if they had received androgen therapy in recent months; had moderate or severe hirsutism (a score of >6 on the Lorenzo scale¹⁵), hyperlipidemia, psychiatric illness (including a score of ≥14 on the Beck Depression Inventory II¹⁶), dyspareunia, physical limitations that interfered with sexual function, or a history of breast or gynecologic cancer; or were taking medications likely to interfere with sexual function. The protocol was approved by the appropriate institutional review boards, and written informed consent was obtained from all participants.

STUDY PROTOCOL

The study used a randomized, double-blind, placebo-controlled, parallel-group design. Women were stratified on the basis of estrogen dose, and randomly assigned to the placebo or testosterone groups. To preserve the blind, each woman wore 2 patches (a 14-cm² patch and a 28-cm² patch) (Watson Laboratories—Utah, Salt Lake City) that, when combined, delivered 0, 150, 300, or 450 µg of testosterone per day. Placebo and ac-

tive patches were identical in appearance. Study participants applied the patches twice weekly to the abdomen. All participants and study personnel were blinded to treatment allocation.

SERUM HORMONE MEASUREMENTS

Samples for measurement of serum hormone levels were collected in the morning. Quest Diagnostics Inc (San Juan Capistrano, Calif) performed the hormone assays. The analysis of total testosterone was performed by radioimmunoassay after sample extraction and column chromatography; the lower limit of quantification (LLOQ) was 2 ng/dL (0.0694 nmol/L). Percentage of free testosterone and percentage of free dihydrotestosterone (DHT) were determined by equilibrium dialysis using radiolabeled tracer techniques. Free testosterone and free DHT concentrations were calculated by multiplying the total testosterone by the percentage of free testosterone and the percentage of free DHT, respectively. Bioavailable testosterone was determined by using an ammonium sulfate precipitation technique. The concentration of DHT was measured by radioimmunoassay after sample extraction and column chromatography (LLOQ of 3 ng/mL); tritiated DHT was used as an internal standard to correct for recovery. The concentrations of SHBG were determined by means of a sandwich immunoassay (LLOQ of 2.0 nmol/L). The analyses of total estradiol (LLOQ of 2.0 pg/mL [7.342 pmol/L]) and estrone (LLOQ of 1 ng/dL [36.98 pmol/L]) were performed by radioimmunoassay after sample extraction and column chromatography. During the sample analysis, the interassay percentage coefficients of variation for quality control samples were within 16% for all hormones, and the accuracy was within 8%.

In an independent study, reference ranges for serum free, total, and bioavailable testosterone and SHBG levels were established with measurements from 161 regularly cycling, healthy women 18 to 49 years of age who were not taking any medications or hormonal therapies.¹⁷ An average of serum concentrations across different phases of the menstrual cycle for each subject was used in determination of the reference ranges. Estradiol and estrone reference ranges are standard values from Quest Diagnostics Inc.

EFFICACY ASSESSMENTS

The Profile of Female Sexual Function (PFSF) is a validated, 37-item, self-administered questionnaire that measures 7 domains of sexual function (desire, pleasure, arousal, responsiveness, self-image, orgasm, and concerns) and was designed specifically for use in postmenopausal women with low sexual desire.^{18,19} Scores of 0, 20, 40, 60, 80, and 100 on each domain of the PFSF correspond, on average, to the following categories of response: "never," "seldom," "sometimes," "often," "very often," and "always," respectively. An increase in the sexual concerns score indicated a decrease in patients' concerns related to sexuality. The Sexual Activity Log, a 1-week recall diary, records the number of intercourse and nonintercourse sexual events, the number of orgasms, and the number of sexual events that were satisfying.²⁰ Changes in sexual desire and in frequency of satisfying sexual activity were primary end points. The Personal Distress Scale (PDS) is a 7-item, self-administered questionnaire designed to assess the level of distress associated with a woman's sexual function.²¹ It was developed and validated in parallel with the PFSF and queries the woman about personal feelings regarding her interest or lack of interest in sex. Scores of 0, 20, 40, 60, 80, and 100 on the PDS correspond, on average, to the following categories of response: "never," "seldom," "sometimes," "often," "very of-

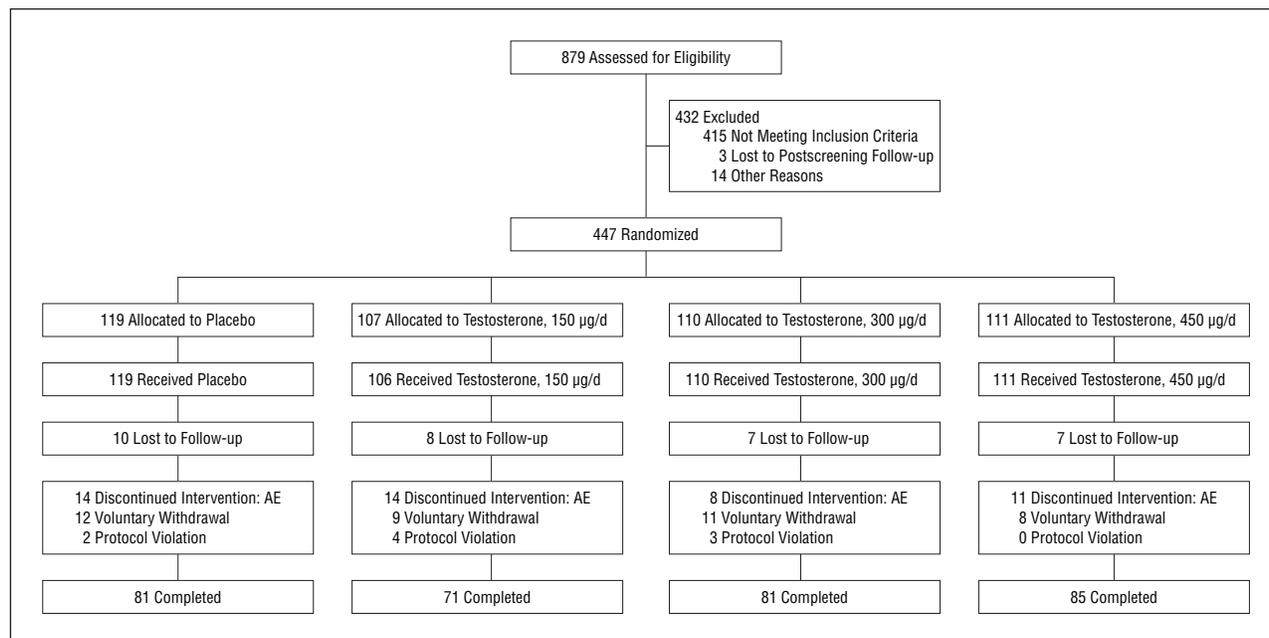


Figure 1. Disposition of patients in the study. AE indicates adverse event.

ten,” and “always” distressed about a lack of interest in sex, respectively. A decrease in PDS score indicated a decrease in patient distress.

TOLERABILITY AND SAFETY ASSESSMENTS

At each study visit, adverse event occurrence was documented and the most recent site of patch removal was examined for any sign of skin irritation. Safety assessments were also performed, including hirsutism scoring¹⁹ (to evaluate changes from baseline in hair growth on the upper lip, chin, chest, thigh, abdomen, or forearm), acne scoring²² (to evaluate change from baseline in facial acne), monthly facial depilation rate, clinical laboratory assessments, and vital signs. A complete physical examination was performed at the end of the study.

STATISTICAL ANALYSIS

Power analyses indicated that 80 patients per treatment group would provide approximately 90% power to detect a difference of 10 scale points on the PFSF sexual desire domain and a 70% increase in the weekly rate of satisfying sexual activity from the Sexual Activity Log (the primary end points). Approximately 450 women were targeted for randomization to account for potential study subject dropout, which was anticipated to be 30% at 24 weeks. Analyses were conducted on an intent-to-treat basis, using a last-observation-carried-forward approach to account for missing data.

The sexual desire domain score of the PFSF and the frequency of satisfying sexual activity from the Sexual Activity Log at the end of 24 weeks were primary end points. An analysis of covariance model was used to assess treatment group effects in changes in sexual desire from baseline to 24 weeks, adjusting for baseline values, pooled centers, age, and marital status. The effect of treatment group on frequency of satisfying sexual activity during the period 21 to 24 weeks was assessed by means of a generalized estimating equation Poisson regression analysis, adjusting for the same covariates. A log-linear model was fit and an exchangeable working correlation matrix was used to account for correlated observations within a study subject.

A gatekeeper approach was used for testing multiple primary efficacy end points. It was assumed that treatment with testosterone would have a monotonic dose response on sexual desire and frequency of satisfying sexual activity. A test for linear dose response on sexual desire was conducted by means of a 2-sided test with a significance level of .05. If a significant linear dose effect was observed, then a test for linear dose response on frequency of satisfying sexual activity was conducted by means of a 2-sided test with a significance level of .05. Linear dose response was tested by means of the linear contrast corresponding to the treatment groups. Comparisons were made between each active treatment group and placebo, but no adjustments for multiple statistical comparisons were made.

The relationships between changes in hormone concentrations and changes from baseline in efficacy assessments were evaluated by Spearman rank correlation coefficients. Changes in facial depilation and degree of facial acne for each testosterone group were compared vs placebo by a Cochran-Mantel-Haenszel test. A 2-tailed *t* test on unpaired data was used to investigate significant changes compared with placebo in total hirsutism scores at each visit.

RESULTS

PATIENT DISPOSITION AND TREATMENT GROUP CHARACTERISTICS

Of 447 women randomized, 318 (71%) completed the 24-week study period (**Figure 1**). The most common reasons for ineligibility were related to medical history or physical examination findings ($n=166$), laboratory results ($n=94$), or medication history ($n=86$). One woman assigned to the 150-µg/d treatment group was excluded from the analysis because she withdrew before receiving any study medication.

The average relationship length was 17.4 years (**Table 1**). Approximately half of the women received conjugated equine estrogens in a dosage of 0.625 mg/d or less, or an equivalent dose of other oral estrogen, and

Table 1. Baseline Characteristics of the Placebo and Testosterone Treatment Groups*

Variable	Placebo (n = 119)	Testosterone Dosage		
		150 µg/d (n = 106)	300 µg/d (n = 110)	450 µg/d (n = 111)
Age, y	48.5 (7.4)	50.4 (8.0)	49.6 (7.9)	49.0 (7.5)
Duration of relationship, y	18.1 (11.1)	17.1 (12.2)	17.2 (11.7)	17.0 (11.0)
Years since surgery				
Hysterectomy	8.7 (7.0)	10.9 (7.7)	9.7 (7.6)	9.0 (7.1)
Oophorectomy	8.1 (6.5)	9.7 (7.1)	8.9 (7.3)	8.5 (6.4)
Dosage of conjugated equine estrogens† during study, No. of patients (%)				
<0.625 mg/d	5 (4)	2 (2)	2 (2)	6 (5)
0.625 mg/d	54 (45)	47 (44)	54 (49)	57 (51)
>0.625 to <1.25 mg/d	12 (10)	13 (12)	14 (13)	13 (12)
≥1.25 mg/d	48 (40)	40 (38)	38 (35)	33 (30)
Other	0	4 (4)	2 (2)	2 (2)
Locke-Wallace Marital Adjustment Test Score‡	112.6 (23.4)	113.4 (19.0)	114.7 (18.9)	111.7 (21.7)
Beck Depression Inventory II score§	4.9 (3.5)	4.8 (3.7)	4.7 (3.8)	4.4 (3.5)

*Data are given as mean (SD) unless otherwise noted.

†Or equivalent dose of other oral estrogen.

‡Total score range for this test is 2 to 158 ("very unhappy" to "perfectly happy").

§Total scores of 0 to 13 indicate minimal depression/nondepressed; 14 to 19, mild depression; 20 to 28, moderate depression; and 29 to 63, severe depression.

half received higher doses. Seven women (2%) experienced a change in estrogen product or dose during the study. Most of the women (80%) had no previous androgen use, and the treatment groups were similar with regard to percentage of women with previous use. Overall, 342 (77%) of the women applied at least 80% of their scheduled study treatment patches. Compliance was similar across the treatment groups.

SERUM HORMONE MEASUREMENTS

Median serum concentrations of free, total, and bioavailable testosterone were similar for all treatment groups at baseline, while dose-related increases in serum concentrations were observed at 12 and 24 weeks (**Table 2**). No significant accumulation of testosterone was seen at 24 weeks compared with the levels at 12 weeks. Serum DHT concentrations were similar across the treatment groups at baseline and exhibited dose-related increases at the end of 12 and 24 weeks of treatment. Serum concentrations of free and total estradiol and estrone were similar across the treatment groups at baseline and exhibited no meaningful or consistent changes across doses after either 12 or 24 weeks.

EFFICACY END POINTS

The linear dose-response test on changes in sexual desire showed a strong statistical trend but did not reach statistical significance ($P = .06$). Women receiving testosterone in a dosage of 300 µg/d had a statistically significant increase in sexual desire score compared with placebo (adjusted mean \pm SEM of 13.7 ± 2.1 vs 8.4 ± 2.2 , respectively; $P = .05$) at 24 weeks (**Figure 2**). The mean change in the 300-µg/d group represented a 67% increase over the baseline mean score of 20.9, compared with a 48% change from baseline in the placebo group. No statistically significant difference vs placebo in desire score was observed for the

150-µg/d group ($P = .35$). Although not statistically significant, a trend toward statistical significance was seen for the 450-µg/d group compared with placebo ($P = .10$); the increase in sexual desire score in the 450-µg/d group was not statistically significantly different from the change in the 300-µg/d group ($P = .76$).

The linear dose-response test on changes in sexual activity showed a strong statistical trend but did not reach statistical significance ($P = .06$). After 24 weeks of treatment, the adjusted mean frequency of total satisfying episodes was 30% greater for the women in the 300-µg/d group than for women receiving placebo ($P = .049$) (**Figure 3**). Women treated with 300 µg of testosterone per day had a statistically significant increase from baseline of 0.58 satisfying episode per week, representing an increase of 79% from the baseline mean, compared with a 43% change from baseline in the placebo group ($P = .049$). No statistically significant differences in the number of satisfying episodes were observed for the 150-µg/d or 450-µg/d groups compared with placebo ($P = .85$ and $.19$, respectively). Women treated with testosterone at 300 µg/d also experienced statistically significant increases in the total number of sexual events and the total number of orgasms at week 24 compared with women receiving placebo ($P = .01$ and $.02$, respectively).

Comparisons of each testosterone dose with placebo for the 2 primary end points in subpopulations defined on the basis of baseline characteristics (age, estrogen dose, baseline free testosterone level, baseline total testosterone level, baseline SHBG level, baseline PDS score, length of time since bilateral oophorectomy, age at time of bilateral oophorectomy, and body mass index) supported the overall treatment effect. No consistent positive treatment effects were observed for the 150-µg/d group compared with placebo for the various subgroups. On the other hand, both the 300-µg/d and 450-µg/d dosages showed generally consistent positive treatment effects compared with placebo within the subpopulations.

Table 2. Serum Hormone Values at Baseline and During the Study for Placebo and Testosterone Treatment Groups*

Hormone (Reference Range)†	Treatment Group	Baseline		Week 12		Week 24	
		No.	Value	No.	Value	No.	Value
Free testosterone, pg/mL (0.9-7.3)	Placebo	108	0.6 (0.4-0.9)	87	0.6 (0.4-0.9)	62	0.75 (0.4-1.0)
	150 µg/d	101	0.6 (0.4-0.8)	75	2.0 (1.2-3.0)	60	2.15 (1.4-3.1)
	300 µg/d	103	0.7 (0.4-1.0)	91	3.1 (2.1-4.6)	59	3.7 (2.3-7.8)
	450 µg/d	101	0.6 (0.4-0.9)	83	4.0 (2.4-6.0)	67	5.9 (3.6-9.1)
Total testosterone, ng/dL (12-50)	Placebo	111	16 (13-22)	88	17.5 (14-21.5)	70	18 (14-22)
	150 µg/d	103	15 (11-19)	76	51.5 (40-69)	64	44.5 (31.5-66)
	300 µg/d	105	17 (12-25)	91	82 (61-102)	64	91 (67.5-130)
	450 µg/d	102	15.5 (11-21)	85	105 (74-139)	72	122.5 (78-182)
Bioavailable testosterone, ng/dL (0.8-8.6)	Placebo	101	0.74 (0.49-1.21)	69	0.79 (0.48-1.27)	57	0.73 (0.47-1.09)
	150 µg/d	97	0.74 (0.46-1.11)	63	2.84 (1.37-4.48)	53	2.02 (1.36-3.14)
	300 µg/d	99	0.80 (0.53-1.35)	77	4.19 (2.73-6.57)	50	4.33 (2.52-7.64)
	450 µg/d	97	0.87 (0.48-1.24)	71	4.52 (2.67-9.00)	55	5.32 (3.66-9.70)
Sex hormone-binding globulin, nmol/L (13-98)	Placebo	114	111.5 (81-160)	86	121 (83-172)	70	119 (90-171)
	150 µg/d	106	115 (71-150)	77	115 (80-179)	65	117 (67-166)
	300 µg/d	107	108 (78-156)	89	105 (75-146)	64	107 (71-145)
	450 µg/d	108	19.5 (73.5-163.5)	86	112.5 (77.0-158)	73	108 (67-158)
Estradiol, pg/mL (12-101; follicular phase)	Placebo	114	31.5 (17-57)	86	30 (19-61)	70	33 (19-73)
	150 µg/d	106	27.0 (16-51)	78	29 (16-47)	64	29.5 (17-45.5)
	300 µg/d	105	26 (14-43)	89	29 (18-54)	63	37 (19-53)
	450 µg/d	107	25 (17-50)	86	30 (20-51)	72	31 (17.5-55)
Estrone, ng/dL (15-50; early follicular phase)	Placebo	114	14.4 (8.1-27.6)	86	14.8 (7.2-33.1)	69	13.1 (7.1-33.3)
	150 µg/d	106	16.3 (7.2-27.6)	78	14.2 (6.9-29.2)	63	12.9 (5.3-25.8)
	300 µg/d	105	12.5 (6.9-22.5)	88	12.5 (7.8-26.8)	64	13.6 (6.2-27.2)
	450 µg/d	106	13.1 (7.1-27.4)	86	13.0 (7.5-26.0)	71	13.8 (6.4-24.5)
Free dihydrotestosterone, pg/mL (0.18-1.33)	Placebo	104	0.20 (0.10-0.20)	76	0.20 (0.10-0.20)	59	0.10 (0.10-0.20)
	150 µg/d	91	0.20 (0.10-0.20)	73	0.30 (0.20-0.40)	57	0.20 (0.20-0.40)
	300 µg/d	93	0.20 (0.10-0.30)	89	0.40 (0.30-0.70)	58	0.50 (0.30-0.70)
	450 µg/d	95	0.20 (0.10-0.20)	82	0.60 (0.40-0.80)	64	0.60 (0.50-0.80)
Total dihydrotestosterone, ng/dL (6-31)	Placebo	113	8 (5-10)	81	7 (5-11)	66	8 (5-10)
	150 µg/d	106	7 (5-9)	75	15 (11-20)	58	14 (9-17)
	300 µg/d	102	8 (5-11)	89	22 (17-29)	59	23 (18-31)
	450 µg/d	104	7 (5.5-11)	82	30 (23-35)	65	29 (21-40)

SI conversion factors: To convert total testosterone and bioavailable testosterone to nanomoles per liter, multiply by 0.0347; estradiol to picomoles per liter, multiply by 3.671; and estrone to picomoles per liter, multiply by 37.

*Values are medians with 25th to 75th percentile ranges in parentheses.

†Reference ranges generated at Quest Diagnostics Inc, San Juan Capistrano, Calif, using data from premenopausal women.

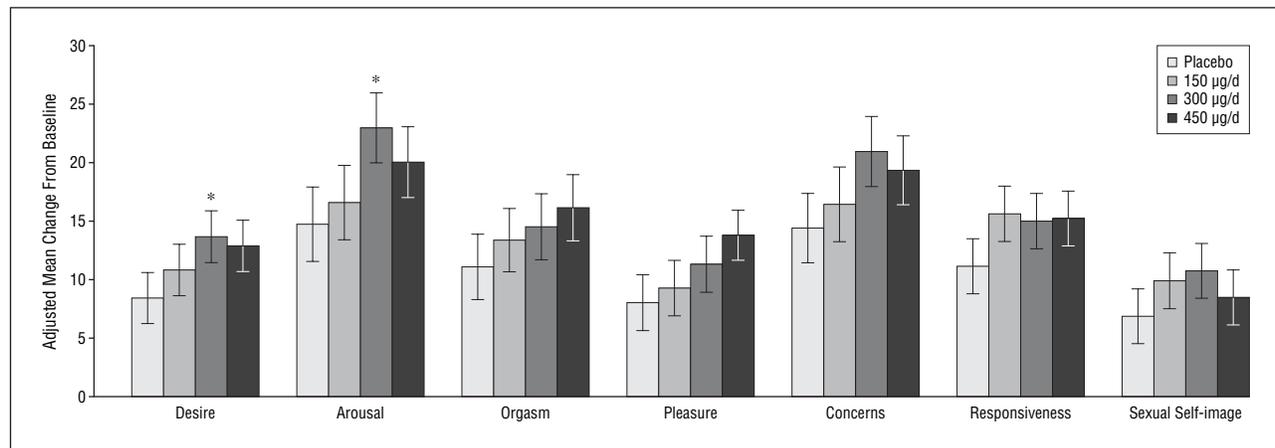


Figure 2. Profile of Female Sexual Function sexuality domain change from baseline at 24 weeks by treatment and dosage. Limit lines indicate standard error of the mean; asterisks, $P < .05$.

The women using the 300-µg/d testosterone patch showed a significant difference from placebo-treated women in the change from baseline in the sexual arousal domain score of the PFSF (adjusted mean change from

baseline of 22.8 ± 3.10 and 14.74 ± 3.16 , respectively) ($P = .04$) at 24 weeks (Figure 2). Although not statistically significant, numerical improvements were also noted in other PFSF domains with the 300-µg/d dosage (Figure 2).

At the 24-week evaluation point, a reduction in personal distress (PDS scale) was seen for all treatment groups; however, the changes were not statistically significantly different from placebo ($P = .38, .13, \text{ and } .47$ for the 150-, 300-, and 450- $\mu\text{g}/\text{d}$ groups, respectively).

Analysis of possible relationships between the efficacy measures and patient serum hormone levels showed positive correlations. Many correlations after 24 weeks between the PFSF domains (sexual desire, sexual arousal, orgasm, and sexual pleasure) and testosterone (total, free, and bioavailable) and DHT (total and free) levels were statistically significant (**Table 3**). Statistically significant correlations were also noted between Sexual Activity Log end points and the hormone measures.

TOLERABILITY AND SAFETY ASSESSMENTS

The total proportion of patients reporting any adverse event was similar across treatment groups (**Table 4**). Most events were mild (57%) or moderate (38%) and were considered by the investigator to be doubtfully related to the study drug. Forty-seven women withdrew because of adverse events (Figure 1), with an incidence that was similar across treatment groups. Ten patients reported serious adverse events; all of these events were considered to be doubtfully related to the study drug, and there was no pattern in the types of serious adverse events that suggested they were related to treatment. No patients died during the study. Treatment groups were similar in the proportion of women reporting acne, alopecia, hirsutism, and other androgenic adverse events. Changes from baseline in clinical assessments of hirsutism and acne were similar in the treatment groups at 24 weeks. No clear trends in depilation frequency were observed.

Evaluation of the skin patch site at the end of treatment showed good patch tolerability, and most application site reactions (96%) were classified as mild or moderate. The percentage of patients reporting application site reactions as adverse events was similar across the placebo- and testosterone-treated groups (Table 4), indicating that these reactions are associated with the delivery system itself and not the presence of testosterone in the system. Sixteen patients (4%) withdrew from the study because of application site reactions.

Laboratory findings (including results of liver function tests and hematology studies, carbohydrate metabolism, lipid profiles, and clotting measures) were similar between treatment groups at baseline and remained essentially unchanged when evaluated after 24 weeks of study treatment. No statistically significant changes in levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides were observed with treatment.

COMMENT

This study demonstrated that treatment with the transdermal testosterone patch at a dosage of 300 $\mu\text{g}/\text{d}$ improved sexual function in women with hypoactive sexual desire disorder after oophorectomy. Improve-

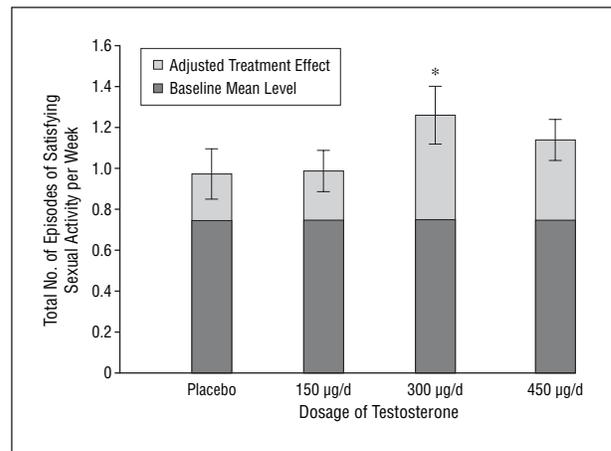


Figure 3. Frequency of sexual activity at 24 weeks of treatment. Asterisk indicates $P < .05$ vs placebo. Limit lines indicate standard error of the mean.

ments were seen consistently across a range of efficacy end points.

Female sexual dysfunction is a multidimensional problem with biological, psychological, and interpersonal components. In the National Health and Social Life Survey,²³ approximately 42% of the 1622 women interviewed complained of 1 or more sexual problems, and other studies of sexual function in postmenopausal women have produced similar results.²⁴⁻²⁶ A recent survey found that 46% of surgically menopausal women aged 20 to 49 years and 38% of surgically menopausal women aged 50 to 70 years experienced a decreased interest in sex, and that 66% of the younger women and 44% of the older women reported that they were either very or extremely bothered by their loss of desire.²⁷ One strength of our study is that sexual functioning and associated distress were measured by 3 validated instruments developed specifically to evaluate findings in menopausal women with low libido, based on interviews with the women themselves. This approach to instrument development provides reassurance that the changes being measured reflect aspects of sexuality that are meaningful to these women.

Unlike oral preparations, a transdermal delivery system allows for continuous administration of a drug while avoiding first-pass intestinal and hepatic metabolism. During the treatment period, testosterone was delivered consistently in a dose-dependent manner, which resulted in median free and bioavailable testosterone levels (measures of biologically active testosterone) for the testosterone treatment groups that fell within the reference range for young premenopausal women. The median total testosterone level was above the upper limit of the reference range. This result was not deemed to be clinically significant. Because all patients were receiving oral estrogens, the median SHBG level was also high. As a result, much of the total testosterone was bound and biologically inactive. An increase in serum DHT concentration is expected during testosterone treatment; the absence of notable changes in serum estradiol or estrone levels with testosterone treatment in this study is reassuring.

We found moderate, yet statistically significant, correlations between the changes in efficacy end points and changes in testosterone levels, which is consistent with the

Table 3. Correlations Between Change From Baseline in Efficacy Measures and Serum Hormone Levels at Week 24*

Subscale	Total Testosterone	Free Testosterone	Bioavailable Testosterone	Total DHT	Free DHT
PFSF domain scores					
Sexual desire	0.22†	0.28†	0.22†	0.20†	0.15
Sexual arousal	0.24†	0.28†	0.27†	0.20†	0.18†
Orgasm	0.18†	0.16†	0.20†	0.25†	0.16
Sexual pleasure	0.24†	0.25†	0.22†	0.22†	0.15
Sexual concerns	0.11	0.15	0.06	0.09	0.05
Sexual responsiveness	0.11	0.18†	0.03	0.10	0.08
Sexual self-image	0.11	0.13	0.06	0.12	0.01
Personal Distress Scale score	0.14	0.20†	0.14	0.18†	0.06
Sexual Activity Log scores					
No. of satisfying episodes	0.15†	0.21†	0.22†	0.18†	0.16†
No. of episodes	0.08	0.17†	0.15	0.11	0.08
No. of orgasms	0.11	0.18†	0.18†	0.15†	0.13

Abbreviations: DHT, dihydrotestosterone; PFSF, Profile of Female Sexual Function.

*Data shown are Spearman rank correlation coefficients.

† $P < .05$.**Table 4. Summary of Adverse Events During 24 Weeks for Placebo and Testosterone Treatment Groups**

Adverse Event	Placebo, No. (%) (n = 119)	Testosterone Dosage, No (%)		
		150 µg/d (n = 106)	300 µg/d (n = 110)	450 µg/d (n = 111)
Any adverse event	84 (71)	82 (77)	84 (76)	83 (75)
Serious adverse event	2 (2)	1 (1)	3 (3)	4 (4)
Withdrawals due to adverse event	14 (12)	14 (13)	8 (7)	11 (10)
Most common adverse events and androgenic events				
Application site reaction	37 (31)	36 (34)	30 (27)	38 (34)
Respiratory infection	13 (11)	18 (17)	17 (15)	16 (14)
Acne	16 (13)	10 (9)	20 (18)	14 (13)
Breast pain	17 (14)	12 (11)	12 (11)	11 (10)
Headache	9 (8)	15 (14)	10 (9)	5 (5)
Hirsutism	2 (2)	1 (1)	6 (5)	3 (3)

hypothesis that lower testosterone levels after oophorectomy contribute to the prevalence of hypoactive sexual desire disorder in this population and that increasing testosterone levels will help restore satisfactory sexual functioning.

Women in our study had a strong placebo response. Large placebo responses have been seen in previous similar studies.^{12,14,28} All women enrolled in our study stated that they desired an improvement in their sex lives, and participation in the study may have increased dialogue between the study subjects and their partners, leading to improvements in sexual satisfaction. As Shifren et al¹⁴ noted, the constant visible presence of a patch, as well as weekly activity diary collection, may also have triggered a psychological impetus to increase sexual activity. Despite the placebo response, our study did find statistically significant improvements in sexual functioning in women receiving transdermal testosterone at a dosage of 300 µg/d, compared with women receiving placebo.

The testosterone patches used in the study demonstrated a favorable safety profile in this population of surgically menopausal women with low sexual desire. The most common adverse events were application site reactions, most of which were mild or moderate and did not cause women to discontinue use. One limitation of

our study is that it cannot address the safety of this regimen when used for more than 24 weeks or in women not receiving concomitant estrogen. Additional data will need to be collected to further define the long-term safety profile, especially with regard to cardiovascular effects.

By evaluating a range of transdermal testosterone doses, this study allows appropriate dose selection for future studies. Although all 3 dosages studied were well tolerated, the 150-µg/d dosage was not effective and the 450-µg/d dosage provided no improvement in the primary efficacy end points (desire and frequency of total satisfying sexual activity) compared with the 300-µg/d dosage. One explanation for the fact that the 450-µg/d group response was not consistently better than that of the 300-µg/d group is that 300 µg/d may be at the top of the dose-response curve for this range of dosages, with the 450-µg/d dose providing no better efficacy than 300 µg/d.

CONCLUSIONS

Testosterone, 300 µg/d administered by a patch, significantly improved sexual desire and the frequency of total satisfying sexual activity in surgically menopausal women

with hypoactive sexual desire disorder. These findings were generally consistent across all sexual function instruments, end points, and time points, and highlight the important role that testosterone may play in women's sexual health. Additional studies should be undertaken to further assess the efficacy and safety of this treatment.

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