ORIGINAL ARTICLE

Testosterone for Low Libido in Postmenopausal Women Not Taking Estrogen

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ABSTRACT

BACKGROUND

The efficacy and safety of testosterone treatment for hypoactive sexual desire disorder in postmenopausal women not receiving estrogen therapy are unknown.

METHODS

We conducted a double-blind, placebo-controlled, 52-week trial in which 814 women with hypoactive sexual desire disorder were randomly assigned to receive a patch delivering 150 or 300 μg of testosterone per day or placebo. Efficacy was measured to week 24; safety was evaluated over a period of 52 weeks, with a subgroup of participants followed for an additional year. The primary end point was the change from baseline to week 24 in the 4-week frequency of satisfying sexual episodes.

RESULTS

At 24 weeks, the increase in the 4-week frequency of satisfying sexual episodes was significantly greater in the group receiving 300 μg of testosterone per day than in the placebo group (an increase of 2.1 episodes vs. 0.7, P<0.001) but not in the group receiving 150 μg per day (1.2 episodes, P=0.11). As compared with placebo, both doses of testosterone were associated with significant increases in desire (300 μg per day, P<0.001; 150 μg per day, P=0.04) and decreases in distress (300 μg per day, P<0.001; 150 μg per day, P=0.04). The rate of androgenic adverse events — primarily unwanted hair growth — was higher in the group receiving 300 μg of testosterone per day than in the placebo group (30.0% vs. 23.1%). Breast cancer was diagnosed in four women who received testosterone (as compared with none who received placebo); one of the four received the diagnosis in the first 4 months of the study period, and one, in retrospect, had symptoms before undergoing randomization.

CONCLUSIONS

In postmenopausal women not receiving estrogen therapy, treatment with a patch delivering 300 μg of testosterone per day resulted in a modest but meaningful improvement in sexual function. The long-term effects of testosterone, including effects on the breast, remain uncertain. (ClinicalTrials.gov number, NCT00131495.)

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The literature suggests that the prevalence of sexual problems among women ranges from 9 to 43%.[1-4] Among these women, hypoactive sexual desire disorder is a commonly reported, symptom-driven condition characterized by a decrease or absence of interest in sexual activity, causing distress.[5] Decreased libido is common after natural menopause[6,7] and bilateral oophorectomy.[8-10] Several studies have shown the efficacy and short-term safety of a transdermal patch delivering 300 μg of testosterone per day for the treatment of hypoactive sexual desire disorder in women who have undergone either surgically induced or natural menopause and who use concomitant estrogen.[11-16] However, the long-term use of estrogen or a combination of estrogen and progestin has been associated with risks and is not routinely recommended.[17-20] Data pertaining to the use of testosterone by postmenopausal women not receiving estrogen or estrogen plus progestin are lacking. We performed a double-blind, randomized, placebo-controlled study — A Phase III Research Study of Female Sexual Dysfunction in Women on Testosterone Patch without Estrogen (APHRODITE) — to determine the efficacy and safety of a testosterone patch (Intrinsa, Procter & Gamble Pharmaceuticals) for the treatment of hypoactive sexual desire disorder in women with natural or surgically induced menopause who were not receiving estrogen or estrogen plus progestin.

METHODS

STUDY POPULATION

Women from 65 centers in the United States, Canada, Australia, the United Kingdom, and Sweden participated in the study between July 2004 and February 2006. To participate, women with surgically induced menopause had to be 20 to 70 years of age and postmenopausal for at least 12 months; women who had undergone natural menopause had to be 40 to 70 years of age and postmenopausal for at least 2 years. Participants who were 40 years of age or older had to have had a normal screening mammogram for both breasts within the previous 12 months. All participants had to have had a normal Papanicolaou (Pap) smear within the previous 2 months, no evidence of endometrial cancer or hyperplasia, and a level of sex hormone–binding globulin above 12 nmol per liter (the lower limit of the normal range for the central laboratory). Women had to be in a stable, monogamous relationship with a sexually functional partner for at least 1 year before study entry, and partners were expected to be physically present for at least 50% of each month during the study. Women were considered to have hypoactive sexual desire disorder if they answered yes to five questions about changes in their sex life after menopause, including decreases in the levels of desire and sexual activity that concerned them; these criteria were consistent with the definition of the disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).[14,21] Exclusion criteria were the use of systemic estrogen or estrogen plus progestin during the previous 3 months; any androgen therapy during the previous 3 months (7 months for implantable testosterone); any serious medical condition, a psychiatric disorder, dyspareunia, a history of breast or gynecologic cancer, or physical limitations; and the use of nutritional supplements or medications, such as antidepressants, that were likely to affect sexual function.

Concomitant medications with the potential to affect the study medication's safety profile or interpretation of the results were not permitted during the study. Participants were restricted from starting vaginal estrogen or phytoestrogens and were encouraged to maintain their current dose and regimen of vaginal estrogen or phytoestrogens, if applicable.

All women gave written informed consent to participate, and the appropriate ethics committees approved the protocol and informed consent form. The study's sponsor, Procter & Gamble Pharmaceuticals, was involved in the design of the trial and collection of data and conducted the data analysis according to the predefined statistical analysis plan. The academic authors wrote the manuscript, had unrestricted access to the study data, and vouch for the accuracy and completeness of the reported analyses.

STUDY DESIGN

Eligibility and screening procedures, including breast and pelvic examinations, Pap smears, and collection of blood samples, were performed at the pretreatment visit (4 weeks before study entry). Women were stratified according to whether they had undergone natural or surgically induced menopause and were then randomly assigned by the method of random permuted blocks to re-

ceive placebo, 150 μg of testosterone per day, or 300 μg of testosterone per day for 52 weeks. Participants were seen at the study centers at baseline and at weeks 6, 12, 24, 36, and 52. Efficacy was measured through week 24; safety was assessed through week 52.

During the first year, women were given the option of continuing their randomized treatment for an additional year so that further safety data could be collected; the extension continued through January 2007. Women were excluded from the study extension if they had a clinically significant abnormal physical finding at the week-52 visit or if any adverse event had occurred that made continuation unsafe (as determined by the investigator or the medical monitor). Women who had commenced any other systemic hormonal therapy were also excluded from the extension. All other participants who completed the first year were invited to continue receiving their randomly assigned treatment (participants, investigators, study-center personnel, and study monitors remained unaware of the treatment assignments throughout this period). Findings from the extension phase are reported separately and in brief, since the data were from a selected subpopulation, with only 38.6% of the patients who completed week 52 participating.

TREATMENT

Each participant applied two patches — one measuring 28 cm^2 and the other 14 cm^2 — twice weekly to the abdomen. In the placebo group, both were placebo patches. In the group receiving 150 μg of testosterone per day, the smaller patch (14 cm^2) delivered approximately 150 μg of testosterone per day, and the larger one (28 cm^2) was a placebo patch. In the group receiving 300 μg of testosterone per day, the larger patch delivered approximately 300 μg of testosterone per day, and the smaller one was a placebo patch. The patches were identical in appearance for each size. All participants, investigators, and study personnel were unaware of the treatment assignments.

CLINICAL MEASUREMENTS

Efficacy Measurements

Efficacy measurements for quantifying treatment effects, previously developed among populations of menopausal women with hypoactive sexual desire disorder, included the weekly Sexual Activity Log,[22] the Profile of Female Sexual Function (with scores ranging from 0 to 100 for each domain and a score of less than 40 in the sexual-desire domain indicating low sexual desire),[23,24] and the Personal Distress Scale, which measures distress associated with low desire (with scores ranging form 0 to 100 and a score of more than 40 indicating distress).[25,26] Each of these instruments was developed by Procter & Gamble. The use of these instruments has been described elsewhere.[11,12,14-16] The Sexual Activity Log was completed weekly throughout screening and the 24-week study period. The Profile of Female Sexual Function and the distress scale were completed at baseline and at weeks 12 and 24.

Safety Assessments

Adverse events and their severity were assessed at each visit. Facial hair was assessed with the use of the Lorenzo Pictorial Rating Scale (which ranges from 0 to 4, with a higher score indicating more hair growth).[27] Adverse events included facial hair growth, assessed on the basis of the depilatory history and the investigators' observations; facial acne, scored with the use of the Palatsi scale (range, 0 to 3, with an increase in the score of 1 or more considered an adverse event)[28]; changes in voice and the amount and pattern of scalp hair, as reported on questioning of participants; and patch-site symptoms. Physical examinations, including breast and pelvic examination, were periodically performed. Pap testing, bilateral mammography for women 40 years of age or older, and transvaginal ultrasonography for women with a uterus were performed at baseline and at week 52. Women who had not undergone a hysterectomy and who gave consent for endometrial biopsy underwent this procedure at baseline and at week 52. Vital signs, weight, and any vaginal bleeding were recorded at each visit. Blood samples were collected at weeks 24 and 52 for laboratory measurements.

Hormone Measurements

Serum levels of free and total testosterone and sex hormone–binding globulin (assessed at baseline and weeks 12, 24, and 52), bioavailable testosterone (assessed at baseline and week 24), and total dihydrotestosterone, free and total estradiol, and estrone (all assessed at baseline and weeks 24 and 52) were measured by validated methods (Quest Diagnostics), as described elsewhere.[11,12,14-16]

Study Extension

For women who participated in the safety assessments extended through a second year, the assessments were made at weeks 78 and 104, and hormone levels were measured at week 104. These assessments were performed as described above.

STATISTICAL ANALYSIS

An intention-to-treat approach was used, with all women undergoing randomization who received at least one application of study medication included in the analyses. The primary efficacy end point was the change from baseline in the 4-week frequency of satisfying sexual events during weeks 21 through 24. A last-observation-carried-forward approach was used to account for women who discontinued the study; for these women, data from the final 4 consecutive weeks of the Sexual Activity Log were included in the analysis. All tests were two-sided (alpha level, 0.05).

Groups were compared with the use of a nonparametric analysis of covariance (ANCOVA) model adjusted for menopausal type (natural or surgically induced).[29] A closed test procedure was adopted, with the treatment effect of 300 μg of testosterone per day, then that of 150 μg of testosterone per day, compared with placebo to control for a type I error (alpha level, 0.05). We used 1% Winsorized means to estimate the mean treatment effect by group. An analysis of variance (ANOVA) model with factors for menopausal type and treatment group was used to analyze changes in secondary efficacy end points. Treatment effect was also assessed according to menopausal type. Post hoc ANOVA analyses were conducted to assess the interaction between the effect of treatment and baseline free testosterone levels (categorized in thirds) and menopausal type. In patients treated with testosterone, the relationship among the free testosterone level, efficacy outcomes, and incidence of androgenic adverse events during the 52-week, double-blind period was assessed with the use of Spearman's rank correlation coefficients and logistic-regression analyses. Continual accumulation of testosterone after baseline and changes from baseline in other hormonal measures were assessed by means of repeated-measures ANOVA in which the effect of linear time trend on log-transformed hormone concentrations was assessed.

RESULTS

Of 1359 women screened, 814 were randomly assigned to a study group (Fig. 1), of whom approximately 71% completed 24 weeks and 57% completed 52 weeks (151 in the placebo group, 147 in the group receiving 150 μg of testosterone per day, and 166 in the group receiving 300 μg of testosterone per day). A total of 589 participants (72%) either completed 52 weeks or had a follow-up visit at week 52 after earlier withdrawal.

Baseline characteristics were similar among the groups (Table 1). Mean scores at baseline for the 4-week frequency of satisfying sexual episodes, sexual desire (as indicated by the Profile of Female Sexual Function), and distress (as indicated by the Personal Distress Scale) were consistent with hypoactive sexual desire disorder as described in DSM-IV.[21]

EFFICACY OUTCOMES

At baseline, approximately 50% of all sexual episodes were satisfying. The increase in the 4-week frequency of satisfying sexual episodes from baseline to week 24 was significantly greater in the group receiving 300 μg of testosterone per day than in the placebo group (an increase of 2.1 episodes vs. 0.7, $P<0.001$) but was not significantly greater in the group receiving 150 μg of testosterone per day than in the placebo group (an increase of 1.2 episodes vs. 0.7, $P=0.11$) (Fig. 2). By week 24, 78% of sexual episodes were satisfying in the group receiving 300 μg of testosterone per day as compared with 65% in the placebo group. A significant increase in the frequency of satisfying sexual episodes in the group receiving the higher testosterone dose as compared with the placebo group was evident as early as the second month of treatment and continued throughout the 24-week evaluation period.

Both groups receiving testosterone had significant increases in scores for sexual desire and decreases in scores for personal distress from baseline to week 24, as compared with the placebo group (Fig. 3). At week 12 (the earliest time point for postbaseline measurements of sexual desire and distress), testosterone at the 300-μg dose but not at the 150-μg dose had a significant treatment effect as compared with placebo. This effect was observed for all domains of the

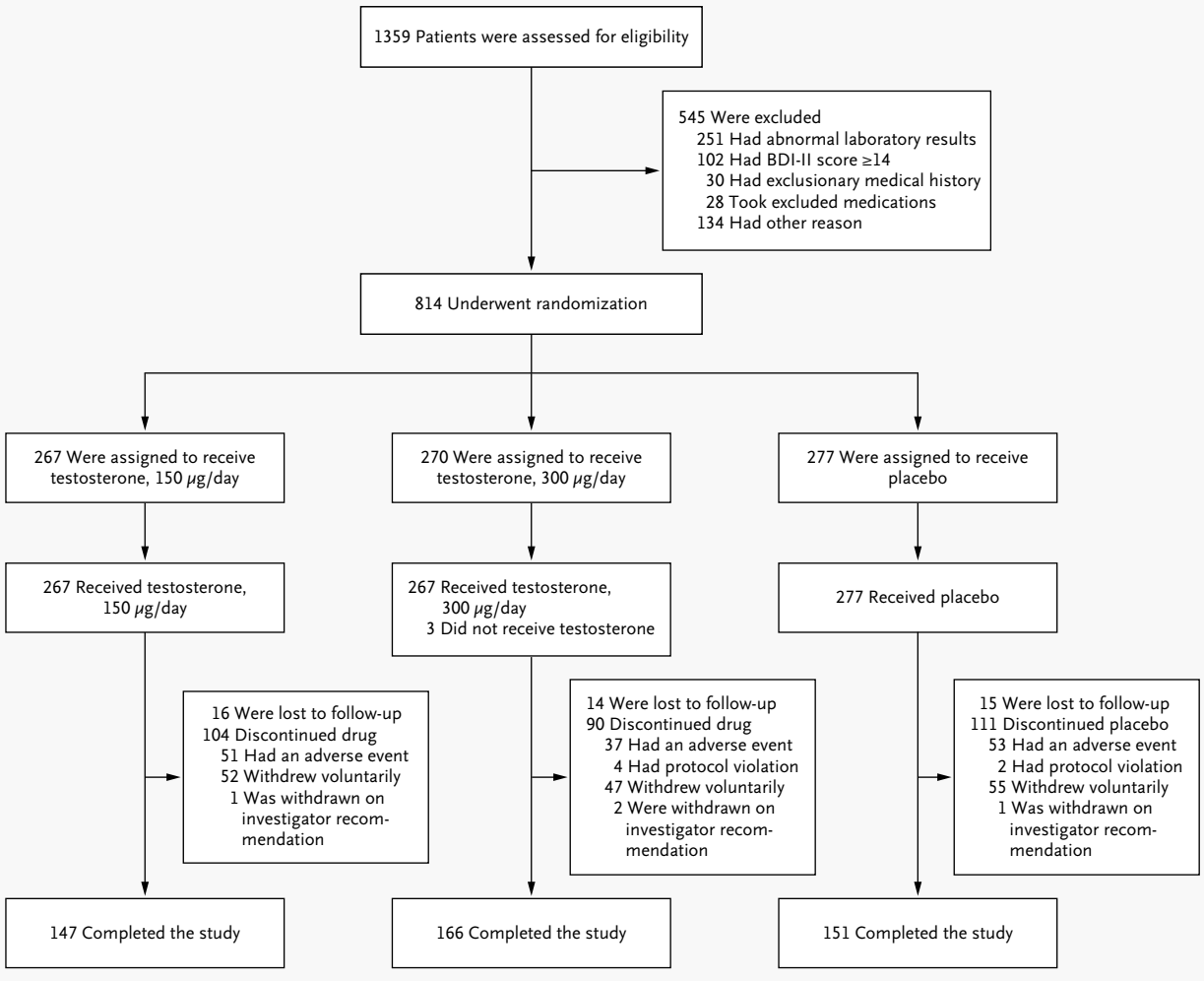

Figure 1. Enrollment and Outcomes.
BDI-II denotes Back Depression Inventory II.

Profile of Female Sexual Function and was sustained at week 24 (Fig. 3). The treatment effect was not dependent on baseline levels of free testosterone.

Treatment effects did not differ significantly between women who had undergone natural menopause and those who had undergone surgically induced menopause. Among the women who had undergone natural menopause, the 200 women who were randomly assigned to the group receiving 300 μg of testosterone per day had significant improvements in all major efficacy end points, as compared with the 203 women who were assigned to the placebo group. Among the women who had undergone surgically induced menopause, the 67 women in the group receiving 300 μg of testosterone per day did not have a significant increase from baseline in the number of sexually satisfying episodes, as compared with the 74 women in the placebo group (P=0.26) (Fig. 2), but did have significantly greater improvement in the scores for most domains of the Profile of Female Sexual Function and for personal distress (Fig. 3). It should be noted that

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Placebo (N=277)	Testosterone, 150 μg/Day (N=267)	Testosterone, 300 μg/Day (N=267)
Age — yr	54.4±5.82	54.1±5.37	54.3±6.53
Race or ethnic group — no. (%)†			
White	246 (88.8)	239 (89.5)	235 (88.0)
Black	23 (8.3)	20 (7.5)	19 (7.1)
Hispanic	5 (1.8)	4 (1.5)	6 (2.2)
Other	3 (1.1)	4 (1.5)	7 (2.6)
Menopause type — no. (%)			
Natural	203 (73.3)	196 (73.4)	200 (74.9)
Surgically induced	74 (26.7)	71 (26.6)	67 (25.1)
Hysterectomy — no. (%)			
No	158 (57.0)	150 (56.2)	145 (54.3)
Yes	119 (43.0)	117 (43.8)	122 (45.7)
Body-mass index	27.4±5.36	26.8±5.83	27.3±5.05
No. of satisfying sexual episodes over 4-wk period	2.5±2.70	2.9±3.87	2.5±2.85
Score on sexual-desire domain of Profile of Female Sexual Function‡	20.2±13.42	19.5±12.51	19.6±12.36
Score on Personal Distress Scale§	66.2±25.76	64.6±25.71	65.6±25.52

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. There were no significant differences among the three groups, as assessed with the use of the chi-square test for categorical data and the Kruskal–Wallis test for continuous data.
† Race or ethnic group was reported by the study participants on the basis of predefined categories.
‡ The sexual-desire domain scores for the Profile of Female Sexual Function range from 0 to 100, with higher scores indicating greater sexual desire. Scores of 0, 20, 40, 60, 80, and 100 correspond to the following categories of response: "never," "seldom," "sometimes," "often," "very often," and "always," respectively.
§ The Personal Distress Scale scores range from 0 to 100, with lower scores indicating less distress. Scores of 0, 20, 40, 60, 80, and 100 correspond to the following categories of response: "never," "seldom," "sometimes," "often," "very often," and "always," respectively.

the study was not powered for comparisons within strata.

SAFETY AND ADVERSE EVENTS

The overall incidence of adverse events over a period of 52 weeks was similar among the study groups, and most events were mild and reported by the site investigators as not clearly related to treatment. Few serious adverse events were reported, and rates of these events were similar among the groups (Table 2).

The most common adverse events reported as the primary reasons for withdrawal were application-site reactions and androgenic events. Other reasons for withdrawal included various coincidental common health conditions. The overall incidence of androgenic adverse events was higher in the group receiving 300 μg of testosterone per day than in the other groups; the most common androgenic event was increased hair growth. Although most women in all three groups had hair growth that was classified as mild, a higher percentage of the women in the group receiving the higher dose of testosterone had hair growth that was assessed as moderate, as compared with the other two groups. At week 52 (or at the time of withdrawal from the study among women who did not complete the 52 weeks), the percentage of women who had an increase of 1 or more in the facial-hair score (based on the Lorenzo Pictorial Rating Scale) or who had an increase in the frequency of facial depilation during the previous 4-week period was higher in the group receiving 300 μg of testosterone per day than in either of the other two groups. The frequency and severity of acne, alopecia, and voice deepening

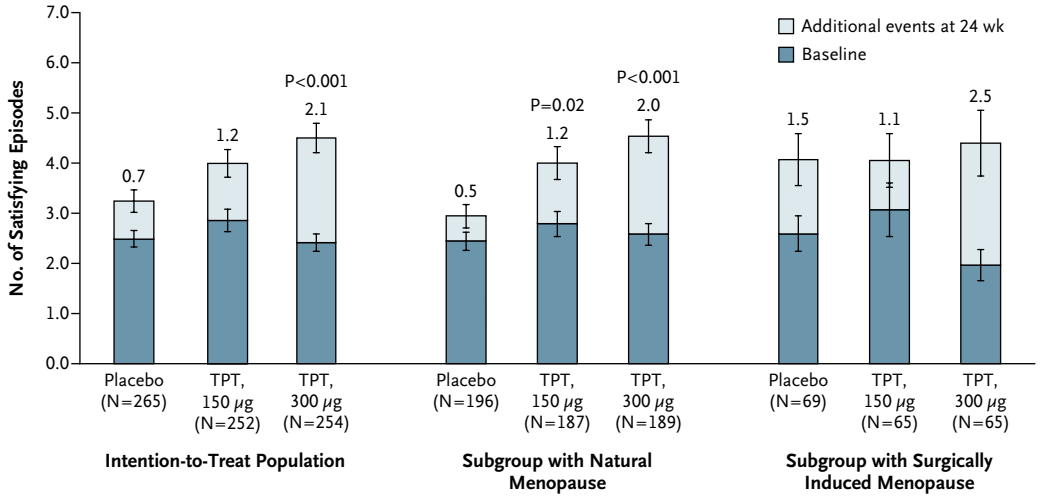

Figure 2. Four-Week Frequency of Satisfying Sexual Episodes at Week 24 as Compared with Baseline.

P values comparing testosterone patch treatment (TPT) with placebo for the change from baseline at week 24 are based on Koch's nonparametric analysis of covariance, adjusted for the type of menopause (natural or surgically induced). Values in parentheses are numbers of patients for whom baseline and post-baseline data were available. Values are 1% Winsorized means (±SE) for the number of satisfying episodes in a 4-week period.

were similar among the three groups, and most of these events were considered to be mild. Few women withdrew because of androgenic adverse events (Table 2). A higher mean free testosterone level during the study period was not a significant predictor of acne, alopecia, hair growth, or voice deepening.

Clitoral enlargement developed in one woman in the group receiving 150 μg of testosterone per day and in three women in the group receiving 300 μg per day; in all four women, clitoral enlargement was classified as mild by the site investigators. None of these women withdrew from the study, and subsequent examination revealed resolution of clitoral enlargement in the woman receiving the lower dose of testosterone and no further changes in the women receiving the higher dose.

Breast cancer was diagnosed in three women in the testosterone groups between 4 and 12 months after treatment initiation (Table 2), one of whom reported in retrospect a bloody nipple discharge before randomization.

In the group receiving 300 μg of testosterone per day, more women who had not undergone hysterectomy (10.6%) reported vaginal bleeding as compared with the other groups (placebo, 2.6%; 150 μg of testosterone per day, 2.7%). Most cases were reported as mild. The median duration of vaginal bleeding was similar among the groups (placebo group and group receiving 150 μg of testosterone per day, 2.0 days; group receiving 300 μg of testosterone per day, 1.5 days). The frequency of bleeding was not significantly higher with an increased duration of therapy. All women with vaginal bleeding underwent biopsy (13 women), transvaginal ultrasonography (10 women), or both. Two of the women receiving 300 μg of testosterone per day who underwent biopsies had proliferative endometrium. No cases of endometrial hyperplasia or carcinoma were diagnosed.

The groups did not differ significantly with respect to serum lipid or lipoprotein profiles, measures of carbohydrate metabolism, liver function, or other laboratory tests, and within each group, there were no clinically relevant changes from baseline in any of these variables (see Table 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org) or in vital signs or weight (data not shown). Levels of free, bioavailable, and total testosterone and total dihydrotestosterone showed dose-related increases with testosterone treatment (see Table 3 in the Supplementary Appendix). Changes in the frequency of satisfying sexual episodes were sig-

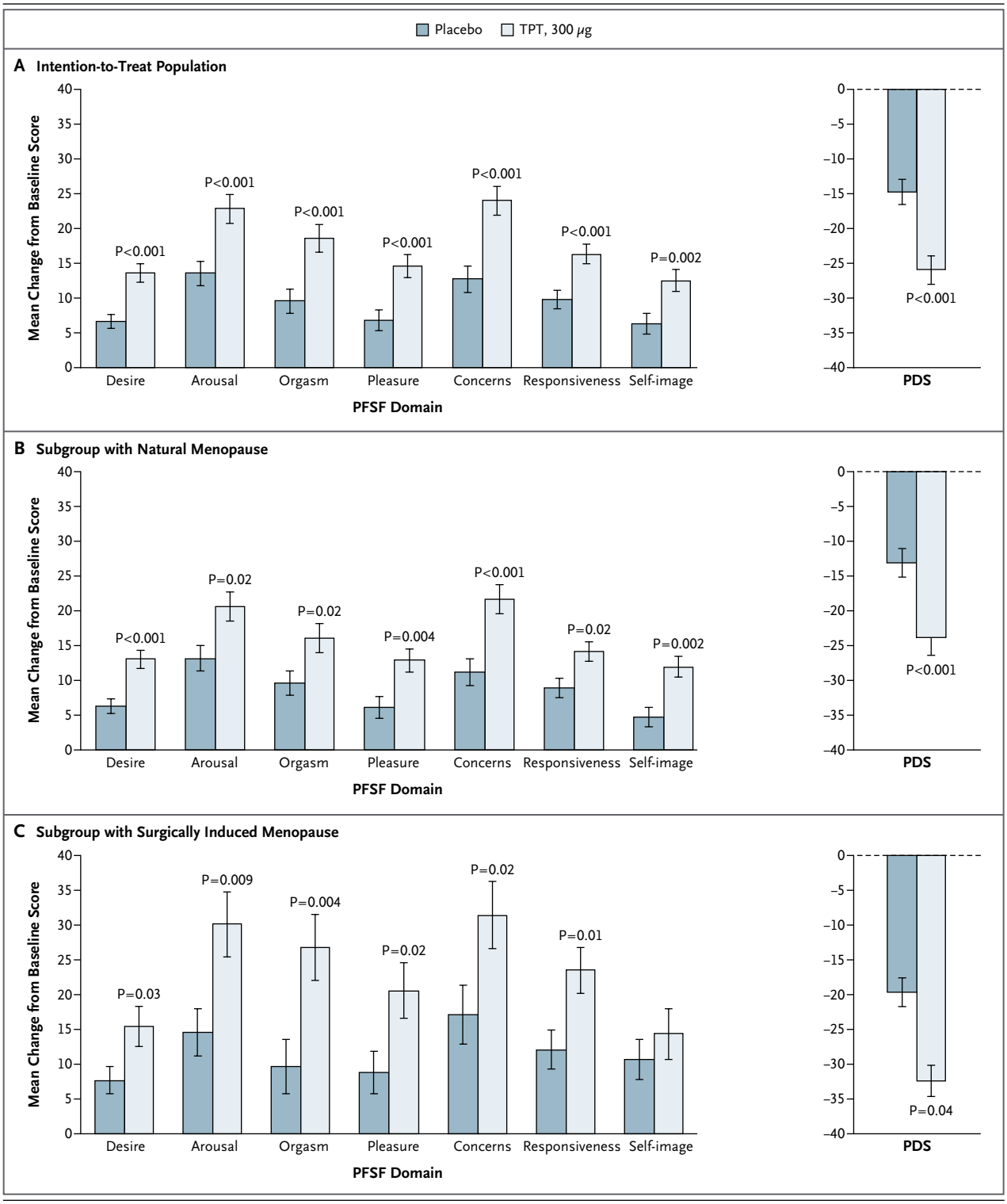

Figure 3 (facing page). Changes from Baseline in Scores for Domains of the Profile of Female Sexual Function and for the Personal Distress Scale at Week 24.

Profile of Female Sexual Function (PFSF) domain scores range from 0 to 100, with higher scores indicating increased sexual functioning or decreased concerns — that is, a positive change indicates improved sexual functioning and decreased sexual concerns. Personal Distress Scale (PDS) scores range from 0 to 100, with lower scores indicating less distress — that is, a negative change reflects a decrease in distress. P values for all comparisons shown are based on analysis of variance adjusted for type of menopause. In Panel C, no P value is given for self-image because the mean change in score was not significantly different from that for placebo. TPT denotes testosterone patch treatment.

nificantly correlated with changes in levels of serum free testosterone at week 24 (Spearman's rank correlation coefficient, 0.26; P<0.001). Median concentrations of free and bioavailable testosterone, as well as concentrations ranging from the 10th to the 90th percentile, remained within the reference ranges for premenopausal women[30] during the evaluation periods (see Table 3 in the Supplementary Appendix).

STUDY EXTENSION

Of the 464 women who completed 52 weeks of treatment, 179 agreed to continue receiving their randomly assigned treatment for an additional year; 132 completed 104 weeks of assigned therapy. The women who participated in the extension phase of the study had demographic and baseline characteristics that were similar to those of the initial study population. No clinically relevant changes were noted for vital signs, weight, or biochemical or hematologic variables through week 104. Serum androgen levels during the extension period did not vary materially from those in year 1. In one woman treated with 300 μg of testosterone per day for 104 weeks, an infiltrating ductal breast cancer was detected by mammography 3 months after study cessation; her mammogram at week 52 was reported to be normal. She had been an estrogen user for 27 years before the study began and reported having a sister who had breast cancer.

DISCUSSION

This study shows that testosterone therapy provides some benefit in the treatment of hypoactive sexual desire disorder in postmenopausal women who are not concurrent users of estrogen or estrogen plus progestin. We found significant improvements in the mean frequency of satisfying sexual episodes, which although numerically modest (an increase of 2.1 episodes per month in the group receiving 300 μg of testosterone per day as compared with 0.7 in the placebo group at 24 weeks, or a difference of 1.4 episodes) were similar to those previously shown by others to be clinically meaningful[31] and were associated with increases in sexual desire, arousal, orgasm, and pleasure and a reduction in personal distress. Efficacy was measured only for 24 weeks, since efficacy has previously been reported to reach a plateau at 24 weeks.[32]

Community-based studies indicate that many postmenopausal women continue to be sexually active despite a high level of sexual dissatisfaction,[1] engaging in sexual activity to please their partner and maintain domestic harmony.[33] Women were recruited to this study if they reported significant loss of sexual desire that was causing personal distress. A cut-off level of serum testosterone was not an inclusion criterion, since a single measurement of the serum testosterone level in women presenting with low sexual desire is not useful for diagnosing "androgen insufficiency" in women.[34]

Previous blinded studies have shown that women treated with a patch delivering 300 μg of testosterone per day were more likely to report a meaningful benefit than women receiving placebo, with more than 85% of those reporting a benefit wishing to continue treatment.[35] However, prior studies of testosterone therapy in postmenopausal women have been limited to those taking estrogen, primarily because of concern that without concurrent estrogen therapy, exogenous testosterone might be ineffective[36] or have adverse effects on lipid levels, glucose metabolism, or the breast.[37,38] Our findings are consistent with previous studies that have shown the

Table 2. Summary of Adverse Events over a 52-Week Period.

Adverse Event	Placebo (N=277)	Testosterone, 150 μg/Day (N=267)	Testosterone, 300 μg/Day (N=267)
	no. of women (%)		
All adverse events	243 (87.7)	225 (84.3)	234 (87.6)
Serious adverse event	9 (3.2)	7 (2.6)	9 (3.4)
Adverse event prompting withdrawal	53 (19.1)	51 (19.1)	37 (13.9)
Application-site reaction*	137 (49.5)	138 (51.7)	141 (52.8)
Withdrawal due to application-site reaction	19 (6.9)	19 (7.1)	12 (4.5)
Severity of reaction†			
Mild	101 (73.7)	105 (76.1)	104 (73.8)
Moderate	29 (21.2)	31 (22.5)	34 (24.1)
Severe	7 (5.1)	2 (1.4)	3 (2.1)
Androgenic event	64 (23.1)	66 (24.7)	80 (30.0)
Increased hair growth	29 (10.5)	31 (11.6)	53 (19.9)‡
Acne	14 (5.1)	15 (5.6)	16 (6.0)
Alopecia	22 (7.9)	15 (5.6)	21 (7.9)
Voice deepening	20 (7.2)	21 (7.9)	19 (7.1)
Withdrawal due to androgenic events	8 (2.9)	12 (4.5)	9 (3.4)
Severity of androgenic event†			
Mild	58 (90.6)	60 (90.9)	69 (86.3)
Moderate	5 (7.8)	5 (7.6)	10 (12.5)
Severe	1 (1.6)	1 (1.5)	1 (1.3)
Breast cancer			
Invasive ductal cancer grade II, diagnosed at 4 mo of treatment	—	1	—
Intermediate-grade ductal carcinoma in situ, diagnosed at 7 mo of treatment	—	—	1§
Estrogen-receptor–positive invasive breast cancer, diagnosed at 12 mo of treatment	—	—	1

* Skin appearance at the patch application site was evaluated at each visit. Reports of patch-site symptoms (e.g., erythema, itching, or papules) were recorded as adverse events and assessed for severity.
† The most severe adverse event is listed for women who reported more than one adverse event. Percentages are based on the number of women with the adverse event.
‡ Increased hair growth was significantly more frequent in the group receiving 300 μg of testosterone per day than in the placebo group.
§ The participant had bloody nipple discharge before study entry that she did not report until after randomization.

side-effect profile of the testosterone patch to be acceptable to women with hypoactive sexual desire disorder who had undergone surgically induced menopause and were taking estrogen (1172 women)[11-15] or who had undergone natural menopause and were taking estrogen with a progestin (549).[16] Our findings are also consistent with a recent study of transdermal testosterone in premenopausal women with low libido that showed an increase in satisfying sexual episodes with the administration of testosterone therapy as compared with placebo.[39]

Except for a higher incidence of hair growth reported by women assigned to testosterone in the present study, the incidence of androgenic adverse events was similar to that observed in prior studies of similar duration.[11-16] The increased hair growth observed during the study was not significantly related to higher serum testosterone levels. This observation may reflect heterogeneous receptor sensitivity to testosterone action in the study population. Despite the increased incidence of hair growth, women receiving 300 μg of testosterone per day were not more likely to

discontinue therapy than the women in the other groups. There was no evidence of continued accumulation of free or total testosterone concentrations over the 52-week study period or during the study extension. Concentrations of sex hormone–binding globulin, free and total estradiol, and estrone showed no clear patterns of change over time. Concentrations of free testosterone at 52 weeks in the group receiving 300 μg of testosterone per day appeared to be high relative to the reference range for premenopausal women up to 49 years of age and approximated the mean level for women 18 to 24 years of age (6.80 pg per milliliter [23.53 pmol per liter]; 10th to 90th percentile, 3.72 to 11.13 [12.87 to 38.51]).[34]

Breast cancers were detected during the primary study in three women assigned to the testosterone groups (one of whom later reported having had symptoms before randomization; cancer was diagnosed in one of the other two women after only 4 months of therapy). An additional case of breast cancer was reported in one of the testosterone groups at the completion of the study extension. The excess of cases of breast cancer in women treated with testosterone may be due to chance. However, the possibility of a causal relationship must be considered. Some epidemiologic studies have shown that endogenous and exogenous testosterone is associated with the risk of breast cancer,[38,40] but others have not. Some data suggest that the inclusion of testosterone in regimens of estrogen plus progestin may ameliorate the stimulating effects of hormones on the breast.[41,42] Long-term data from large clinical trials of testosterone use are lacking.[36,43]

The fact that vaginal bleeding was reported more frequently in the group receiving 300 μg of testosterone per day probably reflects the atrophic effect of testosterone on the endometrium,[44] and investigation did not reveal serious endometrial disease. The study extension did not reveal additional safety concerns, but these data should be interpreted with caution, since they involve a selected subgroup of the study population and follow-up was not continued beyond the second year. The study was not sufficiently large or long to assess the safety of long-term testosterone use.

In conclusion, use of the patch delivering 300 μg of testosterone per day significantly improved sexual function and decreased distress in postmenopausal women who were not receiving estrogen therapy; the increase in the frequency of satisfying sexual episodes was modest but appeared to be clinically meaningful. These findings indicate that exogenous estrogen or combined estrogen and progestin are not required for testosterone to be effective in the treatment of hypoactive sexual desire disorder. Additional data are needed to assess the long-term safety of testosterone use in women with estrogen depletion.

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APPENDIX

The following investigators participated in the APHRODITE trial: Monash Medical School, Alfred Hospital, Prahran, Australia — S. Davis; Sydney Menopause Centre, Royal Hospital for Women, Randwick, Australia — J. Eden; ReproMED Building, Dulwich, Australia — R. Norman; Betty Byrne Henderson Women's Health Research Centre, Royal Brisbane and Women's Hospital, Herston, Australia — S. O'Neill; Keogh Institute for Medical Research, Sir Charles Gairdner Hospital, Nedlands, Australia — B. Stuckey; Sydney Centre for Reproductive Health Research, Ashfield, Australia — E. Weisberg; Karolinska University Hospital, Stockholm — A. Lindén Hirschberg; Kvinnoläkarna AB, Västerås, Sweden — M. Linde; Kvinnokliniken, Danderyd, Sweden — A. Rådestad; Urogynecology Associates of Colorado, Denver — O. Aguirre; LifeSpan Research, Palo Alto, CA — D. Baldwin; Phase II Center for Women's Health, Salt Lake City — P. Bearnson; Cedars–Sinai Medical Center, Los Angeles — G. Braunstein; Tennessee Women's Care, Nashville — P. Bressman; UT Medical Group, Germantown, TN — C. Brown; Baylor College of Medicine, Houston — J. Buster; Radiant Research–Birmingham, Birmingham, AL — G. Conner; Johns Hopkins Center for Sexual Health and Medicine, Lutherville, MD — L. Derogatis; Women's

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