

Safety and Efficacy of a Testosterone Metered-Dose Transdermal Spray for Treating Decreased Sexual Satisfaction in Premenopausal Women

A Randomized Trial

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Background: It is not known whether premenopausal women who report low sexual satisfaction and have low circulating testosterone levels will benefit from testosterone therapy.

Objective: To evaluate the effects of exogenous testosterone in premenopausal women reporting diminished sexual function.

Design: Randomized, double-blind, placebo-controlled, dose-ranging trial.

Setting: 6 Australian medical centers.

Patients: 261 women age 35 to 46 years who reported a decrease in satisfying sexual activity relative to their younger years and had a morning serum free testosterone level less than 3.8 pmol/L (<1.1 pg/mL).

Intervention: 3 different doses of testosterone administered by a metered-dose transdermal spray for 16 weeks or placebo.

Measurements: The primary outcome was the mean number of self-reported satisfactory sexual events (SSEs) over 28 days at week 16. The frequency of SSEs, total number of sexual events (every 4 weeks), scores from the modified Sabbatsberg Sexual Self-Rating Scale and the Psychological General Well-Being Index, and safety variables were also measured.

Results: The number of SSEs increased during the treatment period in the active treatment groups and the placebo group. The mean number of SSEs over 28 days at week 16 was statistically significantly greater for women treated with the intermediate dose of testosterone therapy (one 90- μ L spray) than for women treated with placebo. The least-squares mean was 2.48 versus 1.70 SSEs,

respectively (event rate ratio, 1.49 [95% CI, 1.01 to 2.18]; $P = 0.04$). The frequency of SSEs in women treated with low and high doses of testosterone did not differ from that in women who took placebo. The rate ratios based on the least-squares mean rates of SSEs during weeks 4 to 16 for each treatment group showed statistically significant or borderline significant increases in all testosterone groups compared with the placebo group. The rate ratios for the one 56- μ L spray, one 90- μ L spray, and two 90- μ L sprays treatment groups were 1.34 (CI, 0.97 to 1.85; $P = 0.081$), 1.48 (CI, 1.07 to 2.06; $P = 0.018$), and 1.38 (CI, 1.00 to 1.92; $P = 0.052$), respectively. At week 16, 95% of women treated with the one 90- μ L dose had a free testosterone level less than the upper limit of the reference range for women. The most frequently reported adverse event was hypertrichosis, which was dose-related and mostly confined to the application site. No clinically relevant changes in blood test values, serum biochemical variables, or vital signs occurred.

Limitation: The study duration was short, and the placebo effect was strong.

Conclusion: A daily 90- μ L dose of transdermal testosterone improves self-reported sexual satisfaction for premenopausal women with reduced libido and low serum-free testosterone levels by a mean of 0.8 SSE per month. The rate of SSEs with higher and lower testosterone doses did not differ from that with placebo.

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Testosterone levels in women decline with age from the midreproductive years (1, 2) and do not change during menopause (2, 3). Testosterone therapy seems to improve sexual well-being in postmenopausal women (4–9), but few comparable data are available for premenopausal women. Women with low testosterone levels after menopause probably had low levels before menopause (3), and sexual well-being before menopause is a strong predictor of postmenopausal sexual well-being (10). These findings suggest that testosterone therapy may benefit women presenting with low libido in their late reproductive years.

Premenopausal women often report decreased sexual interest, arousal, and pleasure (11, 12), yet they have few treatment options. In a randomized, placebo-controlled, crossover trial, testosterone administered as a transdermal cream improved sexual function and well-being in premenopausal women with low libido and low testosterone

levels (13). However, the study enrolled few patients, efficacy was based on a 30-day recall rather than a daily event diary, and the women took only 1 dose of testosterone.

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Audio summary

Context

Testosterone levels in women gradually decline with age, and supplemental testosterone may improve sexual satisfaction in postmenopausal women.

Contribution

Sexually active women age 35 to 45 years with low serum free testosterone levels and low sexuality scores were randomly assigned to placebo or 3 doses of transdermal testosterone for 16 weeks. Sexually satisfying encounters increased in all 4 groups. Compared with placebo, the number increased by 0.8 per month with the intermediate dose ($P = 0.04$) but not with the other doses.

Caution

The study was too brief to measure adverse events reliably.

Implication

We need more evidence before prescribing testosterone supplementation to premenopausal women in clinical practice.

—The Editors

We sought to determine the efficacy and safety of several doses of testosterone, administered transdermally by a metered-dose spray system, in increasing self-reported sexual satisfaction among premenopausal women who had decreased sexual satisfaction.

METHODS**Participants**

We recruited potential participants by using radio and published press advertisements, and we screened them by telephone for suitability. Enrollment was from September 2003 to May 2004. The inclusion criteria were age 35 to 45 years, premenopausal status (regular menstrual cycles and follicle-stimulating hormone level <40 IU/L), body mass index (BMI) between 18 and 32 kg/m^2 , sexual activity (≥ 1 sexual event per 28 days, alone or with a partner) but with a low sexuality score (Sabbatsberg Sexual Self-Rating Scale [14] score <42), no evidence of severe clinical depression on the Beck Depression Inventory (score <28) (15), and early-morning serum free testosterone levels of 3.8 pmol/L or less ($\leq 1.1 \text{ pg/mL}$). In addition, each woman had to have experienced a decrease in satisfactory sexual activity of sufficient concern to seek medical advice or treatment and answer “yes” to each of the following questions: In previous years did you find sexual activity satisfying? Has there been a decline in your satisfaction with sexual activity? Would you like to use a hormonal treatment that may improve the level of satisfying sexual activity? All volunteers had general good health on history and

physical examination and had had a Papanicolaou smear within the past year. Volunteers had to have had 3 satisfactory sexual events (SSEs) at most over 28 days at baseline (week 0) and, if in an established relationship, their partner present at least 50% of the time.

We excluded women who were planning a pregnancy or were breastfeeding; had relationship problems, poor feelings for their partner, or dyspareunia; had received pharmacotherapy for depression within 8 weeks of screening or were taking medication known to interfere with normal sexual function (such as β -blockers and α -blockers); or had ever used androgen therapy. We also excluded women with a history of acne or hirsutism or treatment with antiandrogens for hirsutism in the previous 5 years, past cancer other than nonmelanotic skin cancer, uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg), any major chronic major illness that would impair overall health and well-being, genital bleeding of unknown cause, intake of more than 3 standard alcoholic drinks per day or addictions to any drugs or medication within the past 5 years, and use of medications known to interfere with sex steroid metabolism. The use of thyroid hormone was acceptable if the dose was expected to remain stable throughout the study.

The protocol required all participants to use a medically acceptable form of contraception, including oral contraceptive pills, and to have a negative pregnancy test result at screening.

All women gave voluntary, written informed consent and were specifically advised that the effects of the study doses of testosterone in the setting of pregnancy or breastfeeding were unknown. We stressed the necessity of contraception, and all participants received contraceptive counseling. Women who declined contraception were excluded.

We obtained study approval from the human research and ethics committee at each institution. The study met the Clinical Trial Notification requirement of the Therapeutic Goods Administration of Australia and the requirements for an Investigational New Drug Application for the U.S. Food and Drug Administration.

Design

The study was a multicenter, randomized, double-blind, placebo-controlled trial. Eligible patients were first asked to complete a 4-week diary to characterize baseline sexual function. We invited women who met the eligibility criteria for baseline sexual activity to enter the placebo-controlled treatment stage of 16 weeks followed by 4 further weeks after therapy was discontinued.

Treatments

Participants were randomly assigned to receive 1 of 3 different doses of testosterone or placebo. The formulation ($50 \mu\text{g}$ of testosterone per μL) was constant for each active dose, and the dose varied by applying different amounts of

formulation with a metered-dose spray (Acrux Limited, West Melbourne, Victoria, Australia) (16). On the basis of previous pharmacokinetic studies, the highest dose (two 90- μ L sprays) should have increased mean serum free testosterone levels to approximately the 75th percentile of the normal range for premenopausal women (17.3 pmol/L [5.0 pg/mL]). The normal range is 3.8 pmol/L (1.1 pg/mL) to 21.84 pmol/L (6.3 pg/mL). The other study groups received half (one 90- μ L spray) and one third (one 56- μ L spray) of the highest dose of testosterone or placebo. Participants randomly assigned to placebo were further randomly assigned to 1 of 3 placebo subgroups (one 90- μ L spray, two 90- μ L sprays, or one 56- μ L spray) that corresponded with the 3 active treatment groups. Because findings were similar in the 3 placebo subgroups, we combined them into 1 group in the analysis. Doses were applied topically to the abdomen once a day for 16 weeks. One multidose applicator was dispensed every 4 weeks.

Randomization

Computer-generated randomization schedules for each center were created in blocks of 12 without stratification. The study statistician (who was not otherwise involved in the conduct of the study) generated and held the randomization schedules. The randomization sequence was generated by using the Ranuni function (SAS software, SAS Institute, Cary, North Carolina). Each unique code number in the schedule referred to a randomly allocated treatment: either a specific dose of testosterone or 1 of the 3 placebo groups. At each center, the study staff sequentially assigned participants as they became eligible to the next unassigned treatment code on the list and then identified the treatment assignment corresponding to the code number. Both participants and center staff remained blinded to treatment assignment throughout the study.

Outcome Measures

The primary end point (the frequency of SSEs) was recorded in the 28-day patient diary, which was completed daily and collected at week 16. Secondary end points were the frequency of SSEs recorded in the 28-day patient diaries collected at weeks 4, 8, 12, and 20; frequency of total sexual events at weeks 4, 8, 12, 16, and 20; and mean (over each 28-day evaluation period) composite and subscale scores for the Sabbatsberg Sexual Self-Rating Scale (**Appendix Figure**, available at www.annals.org) and Psychological General Well-Being Index. The Sabbatsberg Sexual Self-Rating Scale (17) is a multiple-choice questionnaire covering 7 aspects of sexuality: sexual interest, sexual activity, satisfaction of sexual life, experience of sexual pleasure, sexual fantasy, orgasm capacity, and sexual relevancy. This scale has been validated in premenopausal women (14). The range of possible composite scores was 0 (low) to 56 (high). The Psychological General Well-Being Index (18) is a validated, 22-item multiple-choice questionnaire with subscales for anxiety, depressed mood, positive well-being, self-confidence, general health, and vitality. The range of

possible composite scores is 0 (most negative affective experience) to 110 (most positive affective experience). Patients self-administered questionnaires at screening; baseline (week 0); and weeks 8, 16, and 20. The **Appendix** (available at www.annals.org) provides details of biological measurements.

Safety Assessments

We compared the rates of adverse events in the 3 treatment groups with rates in the placebo group. We monitored specific known androgenic side effects, including hirsutism, by using the Ferriman–Gallwey scale (19) and acne by using the Palatsi scale (20), and we asked participants about voice changes at each visit after baseline. All events known to be consequences of excessive androgen use were classified as treatment-related, and all others were classified at the discretion of the site investigators. We also monitored hematologic tests and liver function.

Statistical Analysis

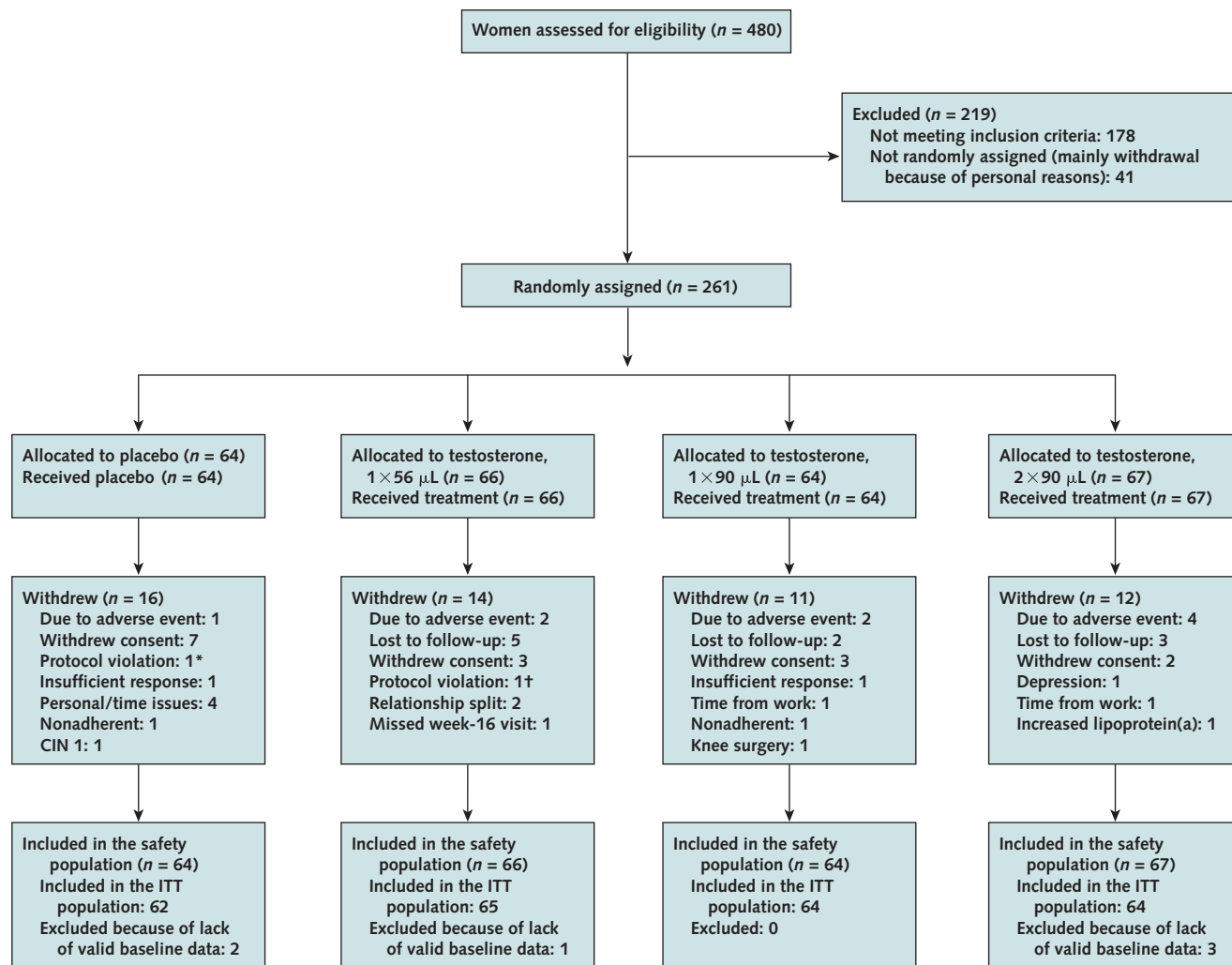
The primary outcome measure for the trial was the number of SSEs in the 4-week period from week 13 to week 16 after randomization. Satisfactory sexual events were assumed to follow a negative binomial distribution, and repeated-measures models with a log-link were used to estimate risk ratios for each active treatment group versus placebo for each month of the study. Covariates included in the models were month by treatment group, treatment center, age, and BMI. Because the relative risks were similar for each month of active treatment, we used the same method to model a summary measure, the treatment effect over weeks 0 to 16.

These models were implemented in PROC GLIMMIX SAS software, version 9.1 (SAS Institute), by using random intercept and compound symmetry error structure. We used the least-squares means statement to estimate event rates for each treatment group at each time point.

End point data were missing for approximately 20% of patients. The 4 treatment groups had similar withdrawal rates (chi-square, 1.536; $P = 0.67$). To impute missing data, we used the repeated-measures approach as implemented in PROC GLIMMIX to produce estimates under the assumption that missing data are missing at random.

We ran sensitivity analyses to assess the appropriateness of the missing-at-random assumption. We assumed zero events for participants with missing data in the active treatment group while setting the placebo SSE rate at 2 (the median number of SSEs during the study) and vice versa. A population average model provided estimates under the assumption that data were missing completely at random. The residuals from the model showed that no individual participant's results excessively influenced the estimates of treatment effect. A sensitivity analysis in which we excluded participants who reported 20 or more SSEs in 1 month produced similar estimates compared with the model that included all participants.

Figure 1. Study flow diagram.



CIN 1 = cervical intraepithelial neoplasia (mild); ITT = intention-to-treat. *Dyspareunia. †More than 3 satisfactory sexual events per month at baseline.

We explored the relationship between SSEs and testosterone by including testosterone levels at weeks 8 and 16, age, BMI, and baseline SSEs as explanatory variables in a model, with SSEs at weeks 8 and 16 as the outcome variable.

We analyzed secondary outcome variables (total sexual events, Sabbatsberg Self-Rating Scale score, and Psychological General Well-Being Index score) by using models analogous to those used for SSEs.

All adverse events were coded by using the Medical Dictionary for Regulatory Activities conventions. The Fisher exact test was used to compare treatment differences.

Role of the Funding Source

The principal investigator designed the trial and supervised its conduct in collaboration with the study's sponsor,

AcruX Limited. The investigators and sponsor collected the trial data. The manuscript was prepared and submitted for publication by the authors, who had unrestricted access to the study data and vouch for the accuracy and completeness of the reported analyses. The manuscript did not require sponsor approval before submission.

RESULTS

Of the 480 women screened at 6 study sites, 168 were ineligible, primarily because their screening free testosterone level was greater than 3.8 pmol/L (>1.1 pg/mL) (Figure 1). Two hundred sixty-one women were randomly assigned and received study medication. At baseline, the treatment groups were well balanced in terms of race, age, body weight, and BMI (Table 1); 98.9% were white. The

proportion of women using oral contraception at baseline varied across the treatment groups from 34% of the one 90- μ L group to 19% of the two 90- μ L group (Table 1).

Trial Outcomes

Primary Outcome and Other Changes in SSEs

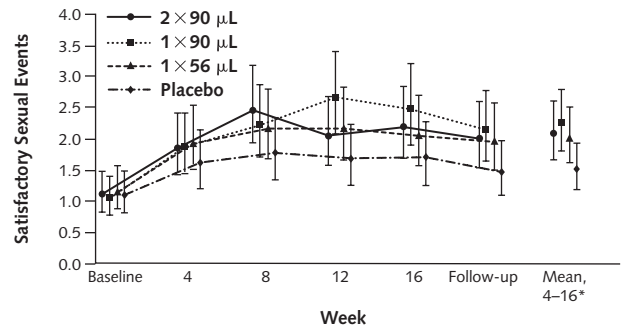
The number of SSEs during the treatment period increased in all study groups (Figure 2), with no statistically significant differences among the testosterone-treated groups. The primary end point, the least-squares mean number of SSEs at week 16, was statistically significantly greater for the one 90- μ L group versus placebo (2.48 [95% CI, 1.92 to 3.21] vs. 1.70 [CI, 1.28 to 2.28]; $P = 0.044$) (Table 2). The ratios of the number of SSEs in each treatment group versus placebo (Figure 3) show a corresponding difference in the SSE rate ratio from placebo for the one 90- μ L group at week 16 (rate ratio, 1.48 [CI, 1.01 to 2.18]; $P = 0.044$) (Figure 3) that was first apparent at week 12 (rate ratio, 1.61 [CI, 1.10 to 2.35]; $P = 0.015$). The increase in SSEs at week 16 and SSE rate ratios in the lower- and higher-dose testosterone groups did not statistically significantly differ from placebo (Table 2 and Figures 2 and 3). The average least-squares mean SSE rates versus placebo during the active treatment period reflected the results at week 16 (rate ratio, 1.34 [CI, 0.97 to 1.85] in the one 56- μ L group [$P = 0.081$], 1.48 [CI, 1.07 to 2.06] in the one 90- μ L group [$P = 0.018$], and 1.38 [CI, 1.00 to 1.92] in the two 90- μ L group [$P = 0.052$]) (Figure 3).

At week 20 (4 weeks after discontinuation of treatment), the number of SSEs for all study groups had not returned to baseline and did not differ from one another (Figure 2). The total number of self-reported sexual events did not statistically significantly increase in any group during the study (data not shown).

Secondary Outcomes

Total scores for the Sabbatsberg Self-Rating Scale, although marginally greater for the active treatment groups, did not statistically differ from placebo, and there were no clear trends in response to treatment for the subdomains or

Figure 2. Mean monthly number of satisfactory sexual events, by treatment group.



* Least-squares means from negative binomial model of mean satisfactory sexual events during treatment, adjusted for baseline satisfactory sexual event and site.

the Psychological General Well-Being Index and its subdomains (data not shown).

Serum Hormone Measurements

Mean serum concentrations of free and total testosterone were similar across treatment groups at baseline (Table 3). Baseline values for free testosterone reported are for the sensitive assay and are therefore higher than values seen at screening. All active treatment groups had a statistically significant increase in serum testosterone concentrations compared with placebo at weeks 8 and 16 ($P < 0.001$) (Figure 4). By week 20, serum testosterone concentrations had returned to baseline values ($P > 0.05$ vs. baseline). Mean increases in the one 56- μ L and one 90- μ L groups were similar to each other and smaller than those in the two 90- μ L group. At week 16, women in the one 56- μ L group (10%), one 90- μ L group (5%), and two 90- μ L group (35%) had free testosterone levels greater than 21.84 pmol/L (>6.3 pg/mL), the upper limit of the reference range. There were no substantial relationships between the number of SSEs and free testosterone levels during the study.

Table 1. Participant Characteristics at Baseline

Variable	Placebo Group	Testosterone Group		
		One 56- μ L Spray	One 90- μ L Spray	Two 90- μ L Sprays
Participants randomly assigned, <i>n</i>	64	66	64	67
Mean age (SD), <i>y</i>	40.8 (2.8)	40.6 (3.2)	39.8 (3.2)	40.0 (2.9)
Mean body mass index (SD), <i>kg/m</i> ²	23.9 (2.9)	23.9 (3.1)	23.8 (3.1)	24.2 (3.0)
Oral contraceptive use, <i>n</i> (%)	18 (2)	15 (23)	22 (34)	13 (19)
Mean total sexual events (SD), <i>n</i>	3.9 (3.2)	4.3 (2.8)	4.9 (4.7)	4.6 (3.9)
Total Beck Depression Inventory score (SD)*	5.9 (4.3)	6.9 (4.9)	5.5 (3.3)	5.2 (3.8)
Total Sabbatsberg Sexual Self-Rating score (SD)†	13.45 (6.73)	12.08 (6.04)	13.32 (6.05)	14.19 (6.71)
Total Psychological General Well-Being Index score (SD)‡	85.1 (11.7)	81.1 (11.7)	87.3 (11.1)	87.0 (8.5)

* Range, 0–63.
 † Range, 0–56.
 ‡ Range, 0–110.

Table 2. Number of Satisfactory Sexual Events at Baseline and Week 16*

Variable	Placebo Group	Testosterone Group		
		One 56- μ L Spray	One 90- μ L Spray	Two 90- μ L Sprays
Participants randomly assigned, <i>n</i>	64	66	64	67
Mean SSEs per month at baseline (SD), <i>n</i>	1.3 (1.1)	1.5 (1.2)	1.4 (1.2)	1.4 (1.2)
Least-squares mean SSEs at baseline (95% CI)*	1.11 (0.82–1.50)	1.18 (0.89–1.56)	1.05 (0.79–1.41)	1.12 (0.84–1.49)
SSEs per month at week 16, <i>n</i>				
Mean (SD)	1.79 (1.46)	2.46 (2.26)	3.36 (3.74)	2.67 (3.00)
Median (range)	1.5 (0–6)	2 (0–9)	2.5 (0–22)	2 (0–19)
Least-squares mean SSEs at week 16 (95% CI)*	1.70 (1.28–2.28)	2.06 (1.58–2.69)†	2.48 (1.92–3.21)‡	2.19 (1.70–2.84)§
Participants with change in SSEs from baseline to week 16, <i>n</i> (%)				
Decrease	22.6	16.0	17.2	18.8
No change	33.9	36.9	25.0	26.6
Increase	43.5	46.2	57.8	54.7
Change from baseline in Sabbatsberg Sexual Self-Rating Index score (SD)	5.00 (8.56)	7.91 (9.14)	6.71 (10.41)	7.83 (11.49)

* Estimates from a generalized mixed model adjusted for age, body mass index, and treatment center. SSE = satisfactory sexual event.

† *P* = 0.32 vs. placebo.

‡ *P* = 0.04 vs. placebo.

§ *P* = 0.16 vs. placebo.

Sex hormone-binding globulin concentrations were statistically significantly lower in the one 90- μ L and two 90- μ L groups compared with placebo at weeks 8 and 16 (*P* < 0.05). This effect was apparently related to an increase in sex hormone-binding globulin levels from baseline in the placebo group.

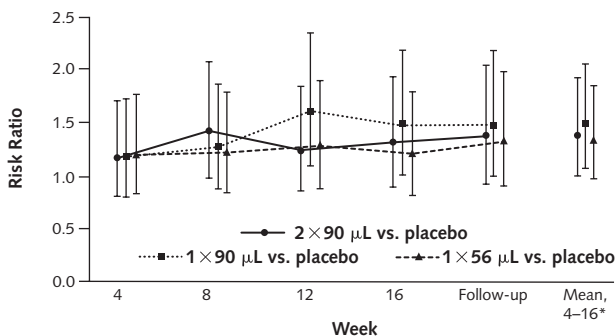
Safety

Overall, 81% to 86% of women in the active treatment groups and 70% of women in the placebo group reported adverse events (Table 4). The pattern was similar for treatment-related events (53% to 58% of women in active treatment groups and 33% in the placebo group). Most adverse events were mild (85%). Only 3.1% of women in the one 90- μ L group and 1.5% in the one 56- μ L group reported severe treatment-related adverse events.

No serious adverse events were considered to be related to the study drug. One woman receiving placebo was found to be pregnant at week 20 and subsequently delivered a healthy, full-term male infant. The most frequently reported adverse events potentially related to therapy were hypertrichosis, headache, nausea, acne, and dysmenorrhea. Eight women withdrew because of adverse events. Hypertrichosis was dose-related and occurred mostly at the application site. The median time to onset of hypertrichosis at the application site was 97 days of treatment (range, 26 days to 138 days). The incidence of acne was similar at week 16 to baseline, although severity of acne increased slightly after active treatment.

Body weight did not change statistically significantly among testosterone-treated participants versus those given placebo, and no clinically relevant changes occurred in any hematologic, biochemical, or vital sign measurements or in serum levels of lipids, homocysteine, or ultrasensitive C-reactive protein.

Figure 3. Risk ratios for monthly number of satisfactory sexual events versus placebo, by treatment group.



* Estimates from negative binomial model of mean sexual satisfactory events during treatment, adjusted for baseline sexual satisfactory events, site, age, and body mass index.

DISCUSSION

The decline in total and free testosterone levels with age provides a rationale for investigating the efficacy of testosterone therapy in older premenopausal women concerned with loss of sexual interest and sexual satisfaction. We found that administration of testosterone by transdermal spray at a dose that elevates serum free testosterone levels to the mid-to-high normal reproductive range increased the frequency of SSEs among these women. After 16 weeks of treatment, the mean number of SSEs increased by 0.8 SSE per month (relative to placebo) and treatment was well tolerated.

At baseline, participants had self-reported approximately 3.9 to 4.9 sexual events per month, of which 1.4 were satisfactory. After 16 weeks of therapy, SSEs in all

study groups (including placebo) increased. Relative to placebo, only the group that received the one 90- μ L dose of testosterone had a statistically significant increase in SSEs at week 16, although the point estimates of the number of SSEs were higher than those for placebo in the low- and high-dose testosterone groups. Likewise, the point estimates of event rates during the active treatment period were greater in each testosterone group than in the placebo group, but the differences were statistically nonsignificant for the high dose, significant for the intermediate dose, and borderline significant for the low dose.

Overall, our findings support a testosterone treatment effect. However, consistent with a randomized trial of transdermal testosterone in postmenopausal women (7), we did not

see a dose–response relationship for the effects of testosterone on sexual function. We postulate 2 possible explanations for the lack of this effect. First, there may be no further benefit beyond the intermediate dose, but this study was not sufficiently powered to test this idea. Alternatively, the increase in adverse effects with the increase in dose may interfere with any perceived benefit in women who were treated. In terms of clinical significance, the increase of 1 SSE per month experienced by the intermediate-dose group seems insignificant, and its value may in fact lie in the eye of the beholder. The mean increase in number of SSEs per month (0.8) that we observed with one 90- μ L dose of testosterone compared with placebo is similar to the number of extra successful sexual events per month (1.3) reported for vardenafil, a drug approved for the

Table 3. Serum Hormone Concentrations at Baseline, Week 16, and Week 20*

Measurement	Placebo Group	Testosterone Group		
		One 56- μ L Spray	One 90- μ L Spray	Two 90- μ L Sprays
Free testosterone				
Patients, <i>n</i>				
Baseline	59	63	64	62
Week 16	49	50	55	57
Week 20	53	56	57	58
Mean level (SD)†				
Baseline				
<i>pmol/L</i>	6.93 (3.74)	6.69 (3.74)	6.38 (2.98)	7.80 (4.20)
<i>pg/mL</i>	2.00 (1.08)	1.93 (1.08)	1.84 (0.86)	2.25 (1.21)
Week 16				
<i>pmol/L</i>	6.55 (2.88)	12.52 (9.36)	10.53 (5.58)	18.72 (11.06)
<i>pg/mL</i>	1.89 (0.83)	3.61 (2.70)	3.04 (1.61)	5.40 (3.19)
Week 20				
<i>pmol/L</i>	7.04 (6.14)	6.41 (2.98)	6.03 (2.91)	7.00 (2.94)
<i>pg/mL</i>	2.03 (1.77)	1.85 (0.86)	1.74 (0.84)	2.02 (0.85)
Total testosterone				
Patients, <i>n</i>				
Baseline	60	63	64	62
Week 16	49	50	55	57
Week 20	53	57	57	58
Mean level (SD)‡				
Baseline				
<i>nmol/L</i>	0.81 (0.34)	0.80 (1.29)	0.76 (0.30)	0.86 (0.37)
<i>ng/dL</i>	23.46 (9.71)	23.08 (8.23)	21.88 (8.77)	24.65 (10.67)
Week 16				
<i>nmol/L</i>	0.84 (0.25)	1.47 (0.87)	1.28 (0.46)	1.97 (0.88)
<i>ng/dL</i>	24.12 (7.30)	42.34 (25.17)	36.85 (13.31)	56.82 (25.41)
Week 20				
<i>nmol/L</i>	0.88 (0.96)	0.82 (0.33)	0.75 (0.24)	0.80 (0.26)
<i>ng/dL</i>	25.34 (27.52)	23.64 (9.43)	21.49 (6.79)	22.99 (7.61)
Sex hormone-binding globulin				
Patients, <i>n</i>				
Baseline	60	63	64	62
Week 16	49	51	55	57
Week 20	53	57	57	59
Mean level (SD), <i>nmol/L</i> §				
Baseline	111.80 (45.92)	133.89 (80.65)	122.91 (55.28)	106.52 (41.61)
Week 16	127.80 (52.76)	131.78 (90.40)	120.49 (54.11)	104.81 (44.13)
Week 20	120.87 (62.81)	139.58 (88.46)	121.05 (57.17)	106.27 (45.15)

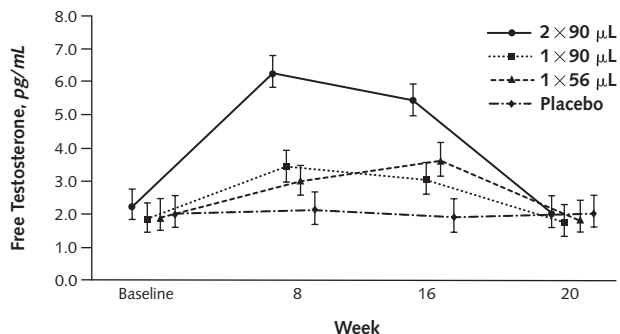
* 4 weeks after treatment discontinuation.

† Reference range, 3.81–21.84 pmol/L (1.1–6.3 pg/mL).

‡ Reference range, 0.35–1.91 nmol/L (10–55 ng/dL).

§ Reference range, 40–120 nmol/L.

Figure 4. Free testosterone levels, by month and treatment group.



The testosterone levels at baseline exceed the levels used as an inclusion criterion (<3.8 pmol/L [<1 pg/mL]) because the authors used a different, more sensitive testosterone assay than that used to screen women for eligibility.

treatment of erectile dysfunction in men (21). Physicians should inform women of the expected gain in SSEs before the women consent to try this medication.

We observed no statistically significant improvements in the total Sabbatsberg Sexual Self-Rating Scale score and its subdomains with any testosterone dose. These findings differ from the statistically significant improvement in the Sabbatsberg Sexual Self-Rating Scale score seen in crossover studies in which participants served as their own controls (5, 13). Our study had a parallel design and was underpowered to test this secondary outcome measure.

The baseline scores for the Psychological General Well-Being Index and its subdomains reflected those seen in healthy women in the community (22), in contrast to the low baseline scores in other studies in which testosterone therapy was associated with an improvement in well-being (5, 13). Thus, the decreased sexual interest in our study sample at baseline cannot be attributed to low well-being.

Our study has limitations. First, only 80% of women completed the study. The withdrawal rate was similar to rates reported in other studies of testosterone therapy for postmenopausal women (7, 9, 23). Many women cited time and personal reasons as their reasons for withdrawal. Second, women who reported hair growth at the application site may have become unblinded to group assignment. Finally, we observed a strong placebo effect on the primary outcome in this study, which persisted after cessation of therapy. This is consistent with the primary outcome being self-reported and thus being more prone than objective end points to the placebo effect (24). It also reflects the importance of a woman’s beliefs and expectations as determinants of female sexual function. The reliance on subjective reporting to evaluate female sexual function and the strong psychological component of female sexual behavior (25) present methodological challenges for research in this field.

Treatment with the testosterone spray was well tolerated for the study duration. Few application site reactions were reported, unlike in other studies (7, 9, 23), in which about 30% of participants in the testosterone patch group reported reactions. The importance of contraception for premenopausal women using prescribed hormonal thera-

Table 4. Summary of Adverse Events

Adverse Event Characteristics	Placebo Group	Testosterone Group		
		One 56-µL Spray	One 90-µL Spray	One 90-µL Spray
Total adverse events, n (%)	45 (70)	57 (86)	52 (81)	56 (83)
Withdrawals due to adverse events, n (%)	1 (1.6)*	2 (3.0)†	2 (3.1)‡	4 (6.0)§
Most common adverse events, n (%)				
Hypertrichosis	0	10 (15.2)	15 (23.4)	19 (28.4)
At application site	0	7 (17.2)	11 (17.2)	12 (17.9)
Elsewhere	0	3 (4.5)	6 (9.4)	8 (11.9)
Headache	8 (12.5)	13 (19.7)	6 (9.4)	11 (17.9)
Upper respiratory tract infection	7 (10.9)	11 (16.7)	10 (15.6)	6 (9.0)
Nasopharyngitis	6 (9.4)	4 (6.1)	8 (12.5)	8 (11.9)
Nausea	1 (1.6)	6 (9.1)	6 (9.4)	1 (1.5)
Acne	3 (4.7)	5 (7.6)	6 (9.4)	6 (9.0)
Dysmenorrhea	1 (1.6)	6 (9.1)	1 (1.6)	1 (1.5)
Application site reaction (rash, itching, eczema)	0	1 (1.5)	1 (1.6)	1 (1.5)
Other potential androgenic effects				
Voice change, n (%)	1 (1.6)	1 (1.5)	1 (1.6)	0
Mean Ferriman–Gallwey score for hair growth (SD)				
Baseline	5.94 (3.73)	6.28 (4.09)	5.63 (4.37)	5.63 (4.37)
Week 16	5.84 (4.57)	6.20 (3.83)	6.57 (5.05)	6.09 (4.43)

* 1 patient was depressed.

† 1 patient had erythema, and 1 had an increased total cholesterol level.

‡ 1 patient had an increased total cholesterol level, and 1 patient gained weight.

§ 1 patient had menorrhagia, 2 patients had hypertrichosis, and 1 had sinusitis.

pies was confirmed by the discovery of pregnancy in 1 woman at week 20.

No approved pharmacologic treatment options exist for otherwise healthy premenopausal women with substantial loss of sexual interest and satisfaction. To our knowledge, this is the first randomized, controlled trial to demonstrate that treatment with testosterone in this population results in a statistically significant improvement in sexual satisfaction. However, the improvement was equivalent to 1 SSE in 1 month and occurred in only the intermediate-dose group. Moreover, there was a substantial placebo effect. For these reasons, our findings should be considered preliminary, and they do not provide sufficiently strong evidence to support the widespread use of testosterone in premenopausal women. Clinical decisions should be based on a body of evidence. Further clinical trials of this promising but unproven therapy are warranted.

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APPENDIX: LABORATORY PROCEDURES

Screening for serum free testosterone levels was determined by using the Coat-a-Count solid-phase¹²⁵I radioimmunoassay (DPC, Los Angeles, California). The interassay coefficients of variation were 23.2%, 15.2%, and 8.8% at concentrations of 3.4, 9.7, and 33.0 pmol/L, respectively. Serum total testosterone, free testosterone, and sex hormone-binding globulin concentrations were measured at all other time points by using validated sensitive assays (Esoterix, Calabasas Hills, California). Total testosterone analysis involved chromatographic separation followed by radioimmunoassay of testosterone. Equilibrium dialysis was done to determine the percentage of unbound and free testosterone concentrations calculated from percentage of unbound and total testosterone concentrations. Sex hormone-binding globulin was measured by radioimmunometric assay.

Total cholesterol and triglycerides (using enzymatic colorimetric tests), high-density lipoprotein cholesterol and low-density lipoprotein cholesterol (using homogenous enzymatic colorimetric tests), fasting glucose (using an ultraviolet assay), ultrasensitive C-reactive protein (using a particle-enhanced immunoturbidometric assay), and other blood biochemistry measurements were done on a Hitachi 917 analyzer (Boehringer Mannheim Systems, Lampertheim, Germany). Lipoprotein(a) was determined with the Image Immunochemistry System (Beckman Coulter, Fullerton, California) by using a rate nephelometry method. Homocysteine was analyzed by using the AxSym fluorescence polarization immunoassay (Abbott Diagnostics, Abbott Park, Illinois). Thyroid-stimulating hormone and follicle-stimulating hormone were measured by using the Advia Centaur Immunoassay (Bayer Diagnostics, Tarrytown, New York). Hematology measurements were made by using an HmX hematology flow cytometer (Beckman Coulter).

Appendix Figure. Sabbatsberg Sexual Self-Rating Scale.

Sabbatsberg Sexual Self-Rating Scale

Please tick the appropriate box (only one) for each section.

Please do not respond to any question that does not currently apply to you. Just mark such questions clearly NA.
Sexual activity includes intercourse, masturbation, oral sex, and anal sex.

1. a. My sexual interest during the past month has been:
 - very great
 - great
 - moderate
 - little
 - very little or nonexistent
- b. In comparison to previous years, my sexual interest is now:
 - much greater
 - greater
 - unchanged
 - less
 - much less
2. a. My sexual activity during the last month has been:
 - very great
 - great
 - moderate
 - little
 - very little or nonexistent
- b. In comparison to previous years, my sexual activity is now:
 - much greater
 - greater
 - unchanged
 - less
 - much less
3. a. My sexual life during the last month has been:
 - very satisfying
 - satisfying
 - rather satisfying
 - less satisfying
 - not satisfying
- b. In comparison to previous years, my sexual life is now:
 - much more satisfying
 - more satisfying
 - unchanged
 - less satisfying
 - much less satisfying
4. a. Sex during the last month has given me:
 - very great pleasure
 - great pleasure
 - moderate pleasure
 - little pleasure
 - no pleasure
- b. In comparison to previous years, sex now has given me:
 - much greater pleasure
 - greater pleasure
 - the same pleasure
 - less pleasure
 - much less pleasure

Sabbatsberg Sexual Self-Rating Scale (continued)

5. a. My sexual fantasies and imagination during the last month have been:
 - very lively
 - lively
 - moderate
 - vague
 - much more vague or nonexistent
- b. In comparison to previous years, my sexual fantasies and imagination are now:
 - much more lively
 - more lively
 - unchanged
 - more vague
 - much more vague or nonexistent
6. a. My ability to reach orgasm during the last month has been:
 - very great
 - great
 - moderate
 - little
 - very little or nonexistent
- b. In comparison to previous years, my ability to reach orgasm has been:
 - much greater
 - greater
 - unchanged
 - less
 - much less or nonexistent
7. a. Sex is for me:
 - very important
 - important
 - rather important
 - of little importance
 - of no importance
- b. In comparison to previous years, the importance of sex has for me:
 - increased a lot
 - increased somewhat
 - not changed
 - decreased somewhat
 - decreased a lot

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