ORIGINAL RESEARCH—ENDOCRINOLOGY

Testosterone Improves Antidepressant-Emergent Loss of Libido in Women: Findings from a Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Introduction. Female sexual dysfunction is a side effect of selective serotonin reuptake inhibitor (SSRI)/serotonin noradrenalin reuptake inhibitor (SNRI) therapy.
Aims. The aim of this study is to investigate the efficacy of transdermal testosterone (TT) as a treatment for SSRI/SNRI-emergent loss of libido.
Methods. This was a double-blind, randomized, placebo-controlled study. Forty-four women, aged 35–55 years, on a stable dose of SSRI or SNRI with treatment-emergent loss of libido were randomly allocated to treatment with a TT patch delivering 300 mcg of testosterone/day or an identical placebo patch (Pl) for 12 weeks.
Main Outcome Measures. The primary outcome measure was the change in the Sabbatsberg Sexual Self-rating Scale (SSS) total score over 12 weeks. The 4-week frequency of Satisfactory Sexual Events (SSEs) and the Female Sexual Distress Scale-Revised (FSDS-R) were also measured.
Results. At baseline, there were no differences between the treatment groups. At week 12, the change in the SSS score did not differ between the two groups. The increase in the 4-week frequency of SSEs was significantly greater for the TT group than for the Pl group (an increase of 2.3 events vs. 0.1, $P = 0.02$). The between-group difference in the change in the FSDS-R score approached statistical significance ($P = 0.06$). The mean total serum testosterone level at 12 weeks in the TT group was 2.1 nmol/L. No women withdrew because of androgenic adverse events.
Conclusions. TT therapy resulted in a significant increase in the number of SSEs compared with Pl therapy in women with SSRI/SNRI-emergent loss of libido. The lack of improvement in the SSS total score may reflect lack of sensitivity of this instrument for the measurement of change in sexual function. This provides the first evidence that TT therapy may be a treatment option for women with SSRI/SNRI-emergent loss of libido who need to remain on their antidepressant therapy. **Fooladi E, Bell RJ, Jane F, Robinson PJ, Kulkarni J, and Davis SR. Testosterone improves antidepressant-emergent loss of libido in women: Findings from a randomized, double-blind, placebo-controlled trial. J Sex Med 2014;11:831–839.**

Key Words. Testosterone; SSRI; SNRI; Loss of Libido; Female Sexual Dysfunction

Introduction

Selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenalin reuptake inhibitors (SNRIs) are the most commonly prescribed antidepressants [1]. Female sexual dysfunction (FSD) is an established side effect of both SSRIs and SNRIs therapy, usually presenting as loss of libido, arousal difficulties, or delayed orgasm or anorgasmia [2,3]. FSD due to SSRIs/SNRIs therapy may not be a pressing issue for women during the early phase of their treatment.

However, in the long term, women stabilized on SSRIs/SNRIs are generally well, and treatment-associated FSD can emerge as a substantial problem and contributes to noncompliance [4–6].

Efficacy of testosterone therapy for the treatment of hypoactive sexual desire disorder (HSDD) in women has been demonstrated in studies including naturally and surgically menopausal women, either alone or in combination with estrogen, with or without progestin therapy [7–12]. These studies have reported an increase in the number of satisfactory sexual events (SSEs) recorded in a 4-week daily diary, as a primary outcome, and reduction in associated personal distress. There is also evidence that testosterone therapy results in a similar improvement in sexual function in premenopausal women with loss of libido [13,14]. Testosterone therapy has been associated with significantly improved well-being in studies in which the participants had low well-being at enrollment [11,14,15]. To date, trials of testosterone for HSDD in women have excluded those with clinical depression, as well as those taking antidepressants. Whether testosterone will benefit women with HSDD who are taking an antidepressant is not known.

The primary aim of this study was to examine the effects of transdermal testosterone therapy on sexual function in women at midlife, on a stable dose of an SSRI or SNRI, who were experiencing treatment-emergent low libido. The primary study outcome was the change in the total score of the Sabbatsberg Sexual Self-rating Scale (SSS). In line with previous studies of women without depression, efficacy was measured by the change in the frequency of SSEs over 4 weeks, as well as the domains of the SSS, general well-being, depression, and mood status.

Materials and Methods

Participants

Women were eligible if they were between 35 and 55 years old, on a stable dose of an SSRI (sertraline, citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine) or an SNRI (duloxetine, venlafaxine, desvenlafaxine) for at least 3 months, experiencing a significant decrease in sexual desire, since commencing antidepressant therapy, for which they wanted treatment, and had satisfying sexual activity in previous years. Women were also required to have at least one sexual event per month and be in general good health. Women over 50 years were required to have a clinically acceptable mammogram within the past 2 years. Nonhysterectomized women were required to have a clinically acceptable Papanicolaou smear within the preceding 2 years. All premenopausal women were obliged to use a medically acceptable form of contraception, including oral contraception, and to have a negative pregnancy test at screening. Women on menopausal hormone therapy were included if they had been on a stable dose for over 3 months. We excluded women taking conjugated equine estrogen (CEE) as the efficacy of the testosterone patch is impaired by concurrent CEE use [16]. This effect is not simply attributable to effects on sex hormone binding globulin (SHBG) [16].

Women were excluded if they had unsatisfactory sexual function prior to the current episode of depression; sexual dysfunction caused by another medical condition; partnership issues; a body mass index (BMI) below 18 kg/m^2 or above 40 kg/m^2; dyspareunia not relieved by use of lubricants; undiagnosed genital bleeding; severe depression (a Beck Depression Inventory-II [BDI-II] score >28 on screening [17]); an SHBG level >160 nmol/L; recent androgen therapy (testosterone implant within the previous 16 weeks, transdermal testosterone cream within the previous 8 weeks, tibolone within the previous 12 weeks, oral testosterone within the previous 4 weeks, or injected testosterone within the previous 6 weeks); antiandrogen therapy for acne or hirsutism in the preceding 5 years; moderate to severe acne, hirsutism, or androgenic alopecia; bipolar disorder or schizophrenia; major medical illness, active malignancy, or treatment for malignancy in the preceding 6 months (except for nonmelanotic skin cancer); any clinically significant skin abnormalities in the area of study drug application (abdomen); consumed more than three standard alcoholic drinks per day; and were pregnant or lactating or were unable to attend our center for the required study visits.

Women were recruited from the community via advertisements in electronic and print media and were screened for suitability via phone. The study was approved by the Monash University Human Research Ethics Committee (Clayton, Victoria, Australia), and all participants provided written, informed consent. The study was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12610001079033).

Study Design and Treatment

The study was a single-center, randomized, double-blind, placebo-controlled, parallel group

trial. It consisted of a 4-week screening period plus a 12-week treatment phase involving three study visits and one telephone contact at week 7 of the treatment. Participants attended the Monash University Women's Health Research Program in Melbourne, Australia for their study visits. At the screening visit, all participants underwent a physical examination including vital signs and breast and pelvic examination. Menopause status was determined by the menopause staging algorithm [18]. Women who met the eligibility criteria were invited to attend a baseline randomization visit. They were randomly assigned in a 1:1 ratio to receive a transdermal testosterone patch (3.94 mg per 14 cm^2 patch) delivering 300 mcg/day testosterone or an identical placebo provided by Warner Chilcott Pharmaceuticals Inc Rockaway, NJ, USA. The testosterone and placebo patches were alcohol-free matrixes that were applied topically to the abdomen twice a week for the period of 12 weeks. Women were asked to return all unused patches, and treatment compliance was checked by counting returned patches at 12 weeks or at their final visit. A participant was considered to be compliant if she used at least 75% of the study drug that would be required for the duration of her participation.

Randomization

The computer-generated randomization schedule was created in random blocks of two, four, and six with stratification by menopause status (pre or postmenopause). The randomization schedules were generated and held by P.J.R. who was not involved in the day-to-day conduct of the study. The schedules remained concealed until data analysis was complete. The study medication boxes were numbered, and participants were sequentially assigned to the next unassigned treatment code at randomization. All study participants, study staff, including outcome assessors, remained blind to the intervention until the end of the analysis.

Outcomes Measures

Primary Outcome Measure

The primary outcome measure for the trial was the change in sexual function measured by the SSS, completed at baseline and week 12. The SSS is a 21-item, multiple-choice questionnaire containing seven domains (sexual interest, sexual activity, satisfaction with sexual life, experience of sexual pleasure, sexual fantasy, orgasmic capacity, and sexual relevancy). Each item has five levels scored from 0 to 4. Possible composite scores range from 0 (low sexuality) to 84 (high sexuality). It was developed to use in premenopausal and postmenopausal women [19]. Its validity and reliability have been independently established [20].

Other Outcomes Measures

We measured the change in the frequency of SSEs, as recorded in daily diary for 4 weeks prior to randomization, and in the month prior to final visit at week 12. Distress associated with low desire was measured using the Female Sexual Distress Scale-Revised (FSDS-R), a validated 13-item questionnaire with total scores ranging from 0 to 52. A lower score indicates less distress [21]. The scale has shown a high degree of discriminative ability to distinguish between sexually dysfunctional and functional women. The Psychological General Well-Being (PGWB) index [22], a validated 22-item questionnaire, was used to measure well-being. The domains for the PGWB are anxiety, depressed mood, positive well-being, self-control, general health, and vitality, and these are simply summed to provide a total score (range from 0 to 110). A higher score signifies better well-being. The BDI-II was used to diagnose depression. It contains 21 questions, each answer being scored on a scale value of 0–3. Higher total scores indicate more severe depressive symptoms, with a score of >28 indicating severe depression. The Profile Of Mood States (POMS) [23] measures six aspects of mood including tension, depression, anger, vigor, fatigue, and confusion. It was used to measure the effects of the intervention on mood state. The total score is the sum of the tension, depression, anger, fatigue, and confusion scores minus vigor and ranges from –32 to 200 where a lower score indicates less mood disturbance. All the secondary outcomes were assessed at baseline and week 12.

Biochemical Measurements

Total testosterone and SHBG levels were determined at screening and week 12. Both were measured by the electrochemiluminescence immunoassay (Roche, Mannheim, Germany) in the Department of Biochemistry at the Alfred Hospital, Melbourne, Australia. For total testosterone, the manufacturer's premenopausal reference range (5th–95th percentile) is 0.33–1.7 nmol/L, with interassay coefficients of variation of 8.4% and 3.2% at 0.33 and 2.4 nmol/L, respectively. The assay functional sensitivity (lower limit of quantitation) is given as 0.417 nmol/L. For

SHBG, the premenopausal reference range (5th–95th percentile) is 25–122 nmol/L.

When biochemical results were reported as being below the level of detection (<0.1 nmol/L), these results were ascribed the value of the level of detection.

Safety Assessment

Safety was assessed by comparing the rates of adverse events in the two treatment groups. Androgenic side effects including the frequency of facial depilation per month, hirsutism by the Ferriman–Gallwey scale [24] (range 0–4 for each of nine body regions), acne by the Palatsi scale [25], and clitoromegaly by examination were assessed at screening and the final visit. We also monitored vital signs and concomitant medications. Urine pregnancy tests were administered to all premenopausal women at each study visit and week 7 (performed at home).

Statistical Analyses

The sample size calculation for this study was based on the change in total score of the SSS as the primary outcome. To detect a difference between groups in the change in the total score of the SSS at week 12 of 9 units with the expected standard deviation of the change in the SSS score of 12.5 [14,26], and setting α at 0.05 with a power of 80%, we needed 40 women in each group.

The analysis was done by intention-to-treat. Women were included in the analysis if they had received at least one dose of the allocated medication. To account for patients who had an early termination visit, a "last observation carried forward" approach was used where data from an early termination visit were available. Apart from the secondary outcomes of SSEs and total sexual events, modeling was performed for each primary and secondary outcome using a linear regression approach, with the outcome variable being the change between the week 12 assessment and baseline value. The independent variables were menopause status, treatment group, and baseline result. A bootstrapping approach with 5,000 repetitions was used to address the issue of outlying values [27]. A multilevel mixed-effects Poisson regression model was fitted to the number of SSEs at week 12 and baseline with a random effect for woman and an interaction between treatment group and occasion (week 12 or baseline). Adjustment was made for menopause status. All statistical tests were two sided using an alpha level of 0.05. Statistical analysis was performed using the program Stata Version 11.1 (Stata Corp, College Station, TX, USA).

All data analysis was performed in a blinded fashion, with testosterone and placebo groups being designated as either group A or group B for all parameters. The serum testosterone measurements were analyzed last to ensure that the statistician remained blinded to the treatment group.

The principal investigator, S.R.D., designed the trial and supervised its conduct. The investigators collected the study data, which were analyzed by E.F. and P.J.R. The manuscript was prepared and submitted for publication by the authors, who vouch for the accuracy and completeness of the reported analyses. Warner Chilcott Pharmaceuticals had no role in the planning or conduct of the study or the data analyses, and the manuscript did not require Warner Chilcott's approval prior to submission.

Results

Women were recruited between March 2011 and December 2012. A total of 173 women were assessed for eligibility of whom 59 declined to participate; 56 did not meet the eligibility criteria, and 14 could not be contacted (Figure 1). The most frequent reasons for ineligibility included being out of the age range, taking excluded medications, relationship or partnership issues, coexistent medical conditions, non-SSRI-related sexual dysfunction, or high BMI.

Forty-four women were randomized. Five women withdrew from the study, and three were lost to follow-up before study completion (Figure 1). Of those randomized, 20 women (90.9%) in the testosterone group and 16 women (72.7%) in the placebo group provided data for the ITT analysis. Compared with women who completed the study, women who did not complete the study had a higher mean POMS score (14 vs. 2) indicating poorer mood status.

The treatment groups were similar with regard to baseline characteristics (Table 1). Women were mainly premenopausal (77.3%) with a mean age of 47.6 years. They had been taking an SSRI/SNRI medication for a median of 3 years, primarily for depression.

Efficacy Outcomes

The change from baseline in the total SSS score did not differ between the two treatment groups at

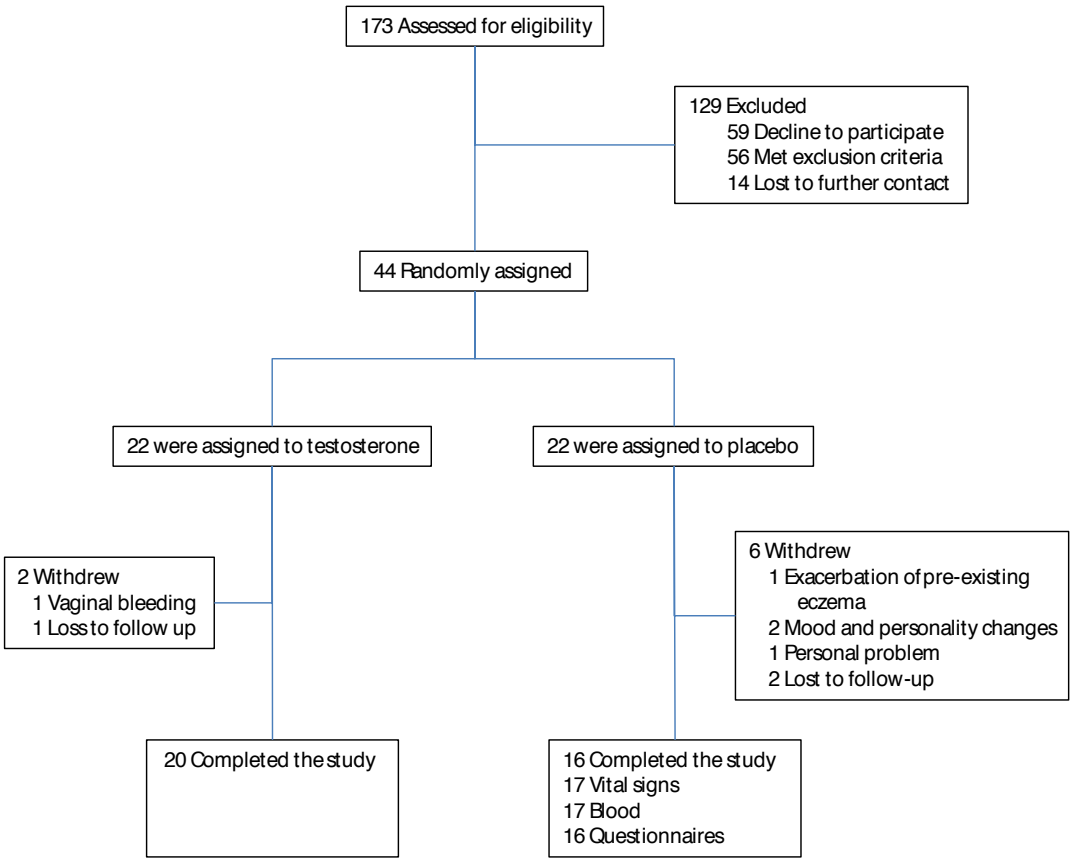

Figure 1 Participant disposition.

Table 1 Baseline characteristics of study participants by randomization group

Variable	Testosterone (n = 22) Mean ± SD	Placebo (n = 22) Mean ± SD	Total (n = 44) Mean ± SD
Age, (years)	47.3 (5.2)	48.0 (5.5)	47.6 (5.3)
Weight, (kg)	73.7 (14.8)	74.2 (12.7)	74.0 (13.6)
Body Mass Index, (kg/m^2)	26.4 (4.2)	27.6 (4.7)	27.0 (4.5)
Premenopausal (%)	17 (77.3)	17 (77.3)	34 (77.3)
Oral contraceptive user (%)	7 (31.8)	2 (9.1)	9 (20.5)
Hormone replacement therapy, n (%)	2 (9.1)	2 (9.1)	4 (9.1)
Duration of antidepressant use, (years) median (range)	2 (0, 15)	4 (0, 10)	3 (0, 15)
Relationship duration, (years) median (range)	17 (4, 38)	20 (1, 30)	19 (1, 38)
Partnership status (including married, de facto), n (%)	22 (100)	21 (95.5)	43 (97.7)
SSS total score (reference range 0–84)	25.4 (6.5)	27.2 (8.1)	26.3 (7.3)
Total number of SSEs over 28 days	2.5 (2.1)	2.8 (3.7)	2.6 (3.0)
Total number of sexual events over 28 days	4.0 (2.3)	4.4 (4.2)	4.2 (3.4)
PGWB total score (reference range 0–110)	75.8 (16.0)	71.3 (12.7)	73.5 (14.5)
FSDS-R total score (reference range 0–52)	21.0 (9.6)	19.5 (7.7)	20.7 (8.7)
BDI-II total score (reference range 0–63)	8.9 (9.7)	9.0 (6.8)	8.0 (8.3)
POMS total score (reference range −32–200)	16.7 (40.0)	15.7 (19.5)	16.2 (31.7)
Total testosterone, (nmol/L) Mean (5th, 95th percentile) (reference range for premenopausal women 0.33–1.7 nmol/L)	0.60 (0.1, 1.2)	0.44 (0.2, 1.0)	0.52 (0.1, 1.2)
SHBG, (nmol/L)	77.2 (30.8)	61.4 (38.0)	69.3 (35.1)

Values are means (and standard deviation) unless stated. To convert nmol/L to ng/dL, divide by 0.0347.
BDI-II = Beck Depression Inventory-II; FSDS-R = Female Sexual Distress Scale-Revised; PGWB = Psychological General Well-Being Index; POMS = Profile Of Mood States; SD = standard deviation; SHBG = Sex Hormone Binding Globulin; SSEs = satisfactory sexual events; SSS = Sabbatsberg Sexual Self-Rating Scale

Table 2 Comparison of baseline and week 12 of the trial outcomes for the testosterone and placebo groups

Variable	Baseline, Mean (SD)		Week 12, Mean (SD)		Beta for between-group difference in change from baseline (95% CI, P value† in bootstrap analysis)
	Testosterone (n = 22)	Placebo (n = 22)	Testosterone (n = 20)	Placebo (n = 16)	Difference between treatment groups over 12 weeks, n = 36
SSS total score	25.4 (6.5)	27.2 (8.1)	39.8 (21.2)	35.2 (10.4)	8.10 (–0.95, 18.22), P = 0.10
Sexual interest	2.7 (1)	3.1 (1.6)	5.7 (3.6)	4.4 (1.9)	1.43 (–0.35, 3.30), P = 0.12
Sexual activity	3.1 (1)	3.5 (1.6)	5.5 (3.4)	4.5 (1.6)	1.29 (–0.32, 3.07), P = 0.13
Satisfaction of sexual life	3.5 (1.8)	3.5 (1.3)	5.6 (3.5)	4.7 (2.1)	1.01 (–0.72, 2.84), P = 0.26
Experience of sexual pleasure	3.8 (1.9)	4.3 (1.8)	5.6 (3.5)	5.2 (1.9)	0.93 (–0.43, 2.32), P = 0.19
Sexual fantasy	3 (1.3)	3.4 (1.7)	5.1 (3.3)	4.9 (1.9)	0.57 (–1.04, 2.45), P = 0.52
Orgasm capacity	3.6 (2.1)	3.9 (1.7)	5.7 (3.7)	5.1 (1.7)	0.80 (–0.82, 2.65), P = 0.37
Sexual relevancy	5.7 (1.5)	5.5 (2)	6.5 (1.7)	6.1 (1.8)	0.46 (–0.74, 1.36), P = 0.38
PGWB total score	75.8 (16)	71.3 (12.8)	81.2 (13.1)	76.1 (13.6)	3.96 (–4.86, 12.47), P = 0.37
FSDS-R total score	22 (9.6)	19.5 (7.7)	16.7 (11)	20.7 (7.5)	–5.04 (–10.41, 0.10), P = 0.06
BDI-II total score	8.9 (9.7)	9.1 (6.8)	6.7 (9.9)	5.5 (5.2)	1.37 (–1.94, 5.51), P = 0.47
POMS total score	16.7 (41)	15.7 (19.5)	2.9 (26.9)	3.6 (18.5)	–0.30 (–11.07, 11.66), P = 0.96

Data in the bootstrapping analysis was performed using parametric analyses.
†P values relate to the coefficient for treatment allocation in modeling of the difference in week 12 from baseline value of each parameter. Menopause status and baseline values were also included in the model.
BDI-II = Beck Depression Inventory-II; CI = confidence interval; FSDS-R = Female Sexual Distress Scale-Revised; PGWB = Psychological General Well-being Index; POMS = Profile of Mood States; SD = standard deviation; SSS = Sabbatsberg Sexual Self Rating Scale

12 weeks after adjusting for menopause status and baseline total SSS score ($P = 0.10$) (Table 2).

The increase in the 4-week frequency of SSEs was significantly greater for the testosterone group than for the placebo group at 12 weeks (an increase of 2.3 events vs. 0.1, $P = 0.02$) (Table 3). There was no statistically significant difference between groups for the change in the 4-week frequency of total sexual events over 12 weeks ($P = 0.54$).

The difference between the testosterone and placebo groups at week 12 for the change in the FSDS-R score, corrected for baseline value and menopause status, approached significance in favor of testosterone therapy ($P = 0.06$) (Table 2). There was no significant difference between treatment groups, at 12 weeks, for the changes in the SSS domains, the PGWB, the POMS, or the BDI-II scores.

At 12 weeks, the mean serum total testosterone in the testosterone group was 2.1 nmol/L (5th–95th percentile, 0.45–5.45 nmol/L) and 0.5 nmol/L (5th–95th percentile, 0.1–1.6 nmol/L) in the placebo group.

Among participants who completed the study, the proportion of participants with at least 75% compliance with treatment was 100% in the testosterone group and 93.8% in the placebo group.

Overall, the testosterone patch was well tolerated. There was one case of application site reaction without withdrawal. One participant in the testosterone group was admitted to hospital for severe depression for 1 week, but she remained on

Table 3 Comparison of baseline and week 12 of sexual events and satisfactory sexual events for the testosterone and placebo groups

Variable	Baseline, Mean (SD)		Week 12, Mean (SD)		Change (Week 12—baseline) Mean (SD)		IRR† for between group difference in change from baseline (95% CI, P value‡ in bootstrap analysis)
	Testosterone (n = 22)	Placebo (n = 22)	Testosterone (n = 20)	Placebo (n = 15§)	Testosterone (n = 20)	Placebo (n = 15§)	Difference between treatment groups over 12 weeks, n = 35
Total number of SSEs	2.5 (2.1)	2.8 (3.7)	4.7 (4.2)	3.2 (4.4)	2.3 (3.7)	0.1 (2.7)	IRR = 1.88 (1.10, 3.20), P = 0.02
Total number of sexual events	4.1 (2.3)	4.4 (4.2)	6.2 (3.6)	5.3 (6.1)	2.2 (3.4)	1.3 (2.7)	IRR = 1.15 (0.74, 1.78), P = 0.54

Data in the bootstrapping analysis were performed using parametric analyses.
†Multilevel mixed-effects Poisson regression was used for analysis. The IRR for the interaction between group and time (baseline or week 12) is presented in the table.
‡P values relate to the coefficient for treatment allocation in modeling of the difference in week 12 from baseline value of each parameter. Menopause status and baseline values were also included in the model.
§One patient who completed the study did not return her last sexual daily diary log.
IRR = incidence–rate ratio; SD = standard deviation; SSEs = satisfactory sexual events

her antidepressant and completed the study. More women randomized to placebo discontinued the study: two reported anxiety or agitation, and one experienced an exacerbation of existing eczema (not at the application site). One perimenopausal woman in the testosterone group reported irregular vaginal bleeding and did not complete the study. The four adverse events (foot fractures, rash in the axillae, severe abdominal pain, and arthritic pain) were judged to be unrelated to the treatment. There were no androgenic adverse events. There were no clinically relevant changes for any vital sign measurements.

Discussion

In women with SSR/SNRI treatment-emergent loss of libido, although testosterone therapy was not associated with improvement in the SSS total score, our primary outcome, testosterone therapy, resulted in a significantly greater increase in the 4-week frequency of SSEs at 12 weeks compared with placebo. The effect of testosterone therapy on distress associated with low desire approached statistical significance at the 5% level. There was no treatment effect seen for general well-being, mood, or depression.

The SSS was used in this study as it has been used in past studies of testosterone in premenopausal women [13,14]. The change in the SSS total score was the basis for our study power calculation, based on outcomes from our earlier research in both premenopausal and postmenopausal women [14,26]. Failure to see a between-group difference in increase in total SSS score or any of its domains alongside a significant between-group difference in the increase in frequency of SSEs is consistent with our previous RCT of transdermal testosterone therapy in premenopausal women [13]. The lack of change in the SSS may be because of our study having been underpowered for this outcome. Alternatively, that an effect of testosterone therapy was not seen in the SSS score when this treatment was associated with a significant increase in the frequency of SSEs recorded over 4 weeks, compared with placebo therapy, might suggest that the SSS did not function as a sensitive measure of the change in sexual well-being in this study.

The magnitude of the increase in the frequency of SSEs with testosterone treatment in this study is of the same order as that reported in previous studies of testosterone treatment of premenopausal and postmenopausal women with HSDD who were not depressed and not using antidepressant therapy [8–12]. This indicates that the mechanism of action of testosterone is not impeded by concurrent SSRI/SNRI therapy. The increase in 4-week frequency of SSEs we observed over 12 weeks in the testosterone group is also in line with the time course for onset of effect seen in previous studies of both premenopausal [13] and postmenopausal women [8,9,15]. These studies have also shown that efficacy persisted, but did not increase, beyond 12 weeks [8,9] and that loss of effect was seen after cessation of therapy [13].

How testosterone enhances sexual interest and responsiveness is not known. The increase in the frequency of SSEs in our study cannot be attributed to improved mood or well-being as these outcomes did not differ between treatment groups. We have reported equivalent benefits of transdermal testosterone for women randomized to an aromatase inhibitor or placebo as well as testosterone such that the effects on sexual function do not appear to require aromatization to estradiol [28].

Treatment with testosterone resulted in increased testosterone levels, which remained within or slightly above the reference range for premenopausal women. We did not explore the relationship between individual testosterone levels and the study outcomes. We measured testosterone in this study to confirm treatment compliance and as a safety measure. The blood draws for testosterone measurement were not timed to application of the testosterone patch, and the direct immunoassay used lacks precision at the low levels measured. Therefore, an analysis of the relationship between individual testosterone levels and the study outcomes would not be meaningful. We did not estimate free testosterone [29], again because of the limitation of the total testosterone assay and because circulating levels may not be a reliable indication of intracellular action [30].

The testosterone matrix patch used in this study was well tolerated, and no clinically significant adverse events were reported. No patient withdrew from the study because of treatment-related adverse effects.

Important strengths of our study included rigorous screening of potential participants to exclude other possible causes of FSD (including schizophrenia, bipolar disorder, and persistent depression), high treatment compliance, and high study completion rate.

Although we utilized different strategies to recruit the optimal number of women, failure to

recruit the target number of women was a study limitation. Some specific issues accounted for the low recruitment. A national media announcement attracted substantial interest. However, many interested women who resided interstate were unable to attend the study center on the three occasions required. Recruitment would have been enhanced by having study sites in other cities. Work commitments and time constraints were other major reasons women gave for not participating, despite their interest in doing so. Although our study brochure was distributed to most psychiatrics and primary care physicians working in women's health in Melbourne, few women were referred from this source. This was primarily because women were taking additional non-SSRI/SNRI psychoactive medication, had recently changed their antidepressant, or had complex mental health conditions. We made a pragmatic decision to terminate recruitment prior to full accrual, potentially reducing our power to pick up other clinically meaningful effects.

In conclusion, compared with placebo, transdermal testosterone therapy significantly increased the frequency of SSEs in women with SSRI/SNRI treatment-emergent loss of libido without concurrent change in our primary outcome (the SSS), mood, general well-being, or depression. Additional studies are needed to determine if this benefit of testosterone extends to women with loss of libido related to other classes of antidepressants and whether the benefit extends to other testosterone formulations.

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Conflict of Interest: Warner Chilcott provided study medication. S.R.D. has previously been a consultant to BioSante Pharmaceuticals and Trimel Pharmaceuticals and is presently an investigator for Trimel. S.R.D. and R.J.B. have received a grant support from BioSante Pharmaceuticals and Bayer Healthcare.

Statement of Authorship

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Category 2

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