

A double-blind, randomized, placebo-controlled trial of the effect of testosterone cream on the sexual motivation of menopausal hysterectomized women with hypoactive sexual desire disorder

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ABSTRACT

Objectives To assess the safety and efficacy of 10 mg topical testosterone therapy daily (2 cm Andro-Feme[®] cream) as a treatment for low sexual desire in postmenopausal hysterectomized women who were already on transdermal estrogen.

Methods A double-blind, randomized, placebo-controlled, cross-over study (each period being of 3 months' duration) was performed in the research center of a tertiary referral women's hospital. Thirty-six menopausal healthy women were recruited who had undergone a hysterectomy, who were not depressed, were in a stable relationship and who fulfilled diagnostic criteria for low sexual desire, as measured by the Brief Index of Sexual Function for Women (BISF-W).

Main outcome measures The primary outcome measure was improvement in the sexuality score as measured by a validated tool (BISF-W); secondary measures were sub-scores of the BISF-W, effect on mood and energy, lipids and testosterone levels.

Results Testosterone cream significantly improved sexual desire, frequency of sex, receptivity and initiation as measured by the BISF-W score. It did not change mood, energy, lipids, blood pressure or weight over the study period.

Conclusions Testosterone cream significantly improved sexual scores in menopausal women with low sexual desire. It was effective, easy to use and had no side-effects over the 3-month period of active treatment. It offers a novel and acceptable method of administering testosterone to menopausal women.

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INTRODUCTION

For over 60 years, symptomatic menopausal women have been treated primarily with estrogen therapy. Progestins are added to protect the uterus from the proliferative effects of estrogen on the endometrium. However, over the last three decades, a number of clinical trials have suggested that adding testosterone to estrogen therapy may have a variety of important benefits for some menopausal women. These beneficial effects may include an improvement in sexual motivation, increased energy, improved mood, enhanced cognition, decreased abdominal fat, increased fat-free mass and increased bone mineral density¹⁻¹³.

In a study of the effects of bilateral oophorectomy, 46% of women attending a British menopause clinic identified decreased sexual desire as the greatest problem of their menopause¹. Despite the lack of any approved testosterone therapy for females in Australia, postmenopausal women complaining of low sexual desire are often treated with testosterone preparations originally designed for men, with resulting markedly supraphysiological levels of the hormone⁹. A transdermal patch designed for women (not yet available in Australia or the USA) was studied by Shifren and colleagues⁷. Of the studied doses, only the higher dose (300 µg) produced a superior improvement in frequency of sexual intercourse or masturbation, and increased scores for pleasure/orgasm than the placebo or the lower dose (150 µg). This effective dose resulted in supraphysiological total testosterone levels; although all subjects were given 0.625 mg conjugated equine estrogens and, as such, had high levels of sex hormone binding globulin, which reduced free testosterone concentrations. Three recent trials have confirmed the finding that the 300 µg testosterone patch improved sexual desire and the frequency of sexual intercourse more than placebo in surgically menopausal women¹⁴⁻¹⁶.

Our study was primarily designed to compare the effect of 10 mg daily testosterone cream (2 cm Andro-Feme[®]) on the sexual motivation of estrogen-treated menopausal women, using the BISF-W total score. Secondary outcome measures included the effect on mood, body mass index, plasma testosterone and lipids (total cholesterol, triglycerides, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol).

METHODS

Thirty-six menopausal women who had undergone a hysterectomy with or without removal of one or both ovaries were recruited via the Internet and newspaper advertisements between 1 September and 20 December, 2001. Initial screening was performed by telephone. If the inclusion and exclusion criteria (below) were satisfied, then the woman was invited to attend our research unit for a screening visit, where a full medical history and examination were performed.

Inclusion criteria

- (1) Hysterectomy,
- (2) Decreased sexual motivation (a BISF-W score less than 33.6),
- (3) In a stable relationship for at least 6 months (assessed by the sex therapist),
- (4) Thyroid stimulating hormone (TS) level between 0.220 and 3.20 mIU/l (i.e. normal thyroid function),
- (5) Postmenopausal follicle stimulating hormone (FSH) levels (> 30 U/l).

Exclusion criteria

- (1) Major illness: liver disease, kidney disease, epilepsy, diabetes, cancer, severe hypertension, coronary cardiac failure (assessed by medical practitioners),
- (2) Taking antidepressants, steroid hormones,
- (3) Severe depression (DASS score greater than or equal to 20),
- (4) Dysfunctional relationship (as determined by the sex therapist),
- (5) Use of alternative therapy products which may influence hypoactive sexual desire disorder, mood or energy (e.g. St John's Wort).

Subjects were seen by a psychologist for a comprehensive psychosexual history, to exclude depression or underlying socio-sexual problems that could be contributory to their hypoactive sexual desire disorder. The sexual questionnaire (The Brief Index of Sexual Functioning for Women; BISF-W) was filled out by the potential subject with the help of the psychologist, and a score of less than 33.6 was considered an indication of and a prerequisite for study suitability¹⁷. This was one of the inclusion criteria in the Shifren study⁷. Subjects were referred to the

pathology laboratory for a fasting morning blood sample. Of the 52 subjects assessed, 36 were suitable (72%). These were given a 2-week run-in with transdermal estrogen. This consisted of Sandrena gel (1 mg 17β-estradiol, Organon P/L), one sachet daily. If the woman was already stabilized on an estradiol patch, she was allowed to remain on it for the duration of the study. During the first period of the study, subjects were then randomized to either 1% testosterone (containing 10 mg testosterone; Andro-Feme®; Lawley Pharmaceuticals) or placebo cream, 2 cm daily applied to the non-blood collecting forearm for 12 weeks. Lawley Pharmaceuticals supplied the identically packaged active and placebo creams (the base product without the testosterone). Both products looked and smelt the same. Randomization was performed by a pharmacist using a random number generator. The same pharmacist labelled the products with a number and provided the research unit staff with active product or placebo.

All subjects continued to use transdermal estradiol throughout the trial. At the end of the first period, all subjects stopped the test cream for 4 weeks (wash-out period), then proceeded to the second period where they received the alternate cream for another 12 weeks. Thus,

the study was a double-blind, randomized, placebo-controlled, cross-over study with two treatment/placebo periods of 3 months' duration each, with a 4-week washout in the middle (Figure 1).

Subjects attended three visits during each of the two treatment periods– at weeks 0, 6 and 12 and 16, 22 and 28. At visits 0, 12, 16 and 28 weeks, the three study questionnaires were filled out by the research doctor interviewing the subject (for BISF-W), or the subject herself (for the Profile of Mood States (POMS) and the Depression, Anxiety and Stress Scale (DASS)). Our previous experience with the BISF-W was that, if we allowed the subjects to fill it in without assistance, then some women did not answer all of the questions (mostly out of embarrassment). Subjects were then examined for the presence of significant acne and excess hair (Ferriman-Gallwey hirsutism score²⁰) and their blood pressure, weight and height were recorded.

At visits 0, 6, 12, 16, 22, 28 weeks, each subject was referred to the laboratory for collection of a fasting morning blood sample. The South-Eastern Sydney Area Health Ethic Committee approved the study and all subjects gave written informed consent.

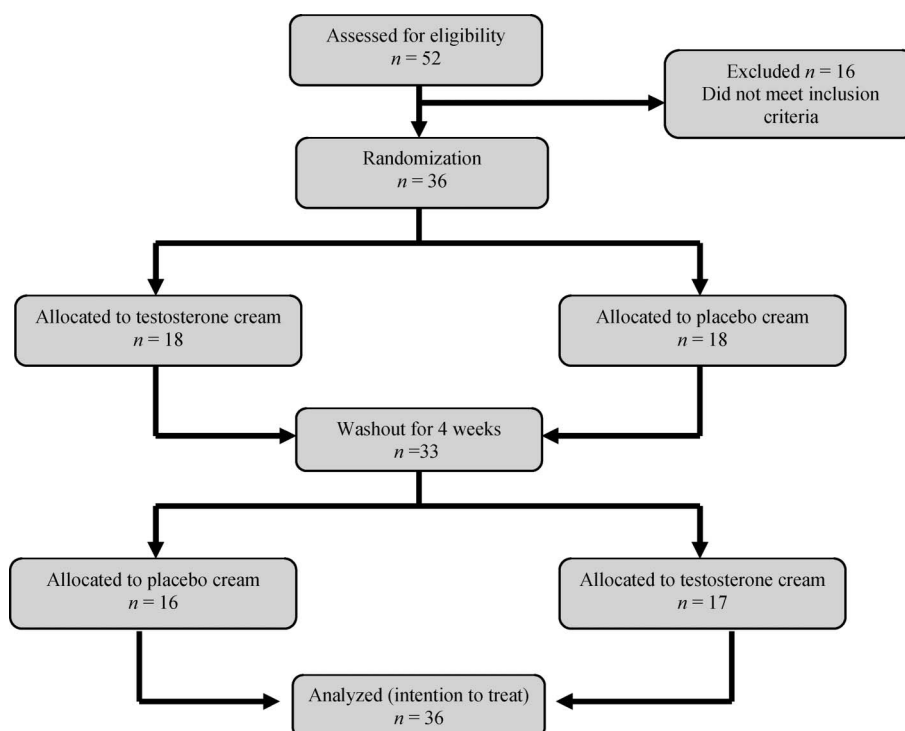


Figure 1 Diagram showing flow of participants from enrolment to analysis

Measures

The main end-point of the study was the impact of testosterone cream on the sexual motivation score. The Brief Index of Sexual Functioning for Women (BISF-W) was the chief measurement tool for this study¹⁷. The BISF-W is a 22-item multiple-choice questionnaire that has been used in previous studies of menopausal women⁷. It provides scores for sexual thoughts, arousal, frequency of sex, sexual receptivity, pleasure, satisfaction with their relationship and sexual problems. The total BISF-W score ranges from -16 (poor function) to +75 (maximal function).

The secondary study aims were the scores of the various sub-domains of the BISF-W, the effect on mood and energy, the lipid profile, the testosterone levels and the safety/side-effect profile. Mood and energy were measured using two instruments: the POMS¹⁸ and DASS¹⁹. The POMS was developed to measure six mood states: Tension-Anxiety, Depression-Dejection; Anger-Hostility; Vigor-Activity; Fatigue-Inertia and Confusion-Bewilderment. It is a validated tool for assessing psychiatric outpatients and as a clinical research tool; the higher the score, the more the mood disturbance¹⁸. The DASS is a 42-item self-report inventory¹⁹ that yields three domains - depression, anxiety and stress. It measures physical anxiety (symptoms of fear) and mental stress (nervous tension and energy); again, the higher the score, the more the psychological distress. Both questionnaires are self-administered and most subjects complete each in about 5 minutes.

Pathology tests

Mayne Health Dorevitch Pathology, Heidelberg, Victoria performed all biochemistry testing. At the screening visit, baseline blood levels of TSH, FSH, liver (LFT) and renal (UEC) function tests, in addition to estradiol, total testosterone, sex hormone binding globulin (SHBG) and serum lipids (cholesterol, triglycerides, LDL cholesterol, HDL cholesterol). These were tested again at each subsequent visit. TSH, FSH and testosterone were measured by the Bayer ADVIA Centaur automated chemiluminescence system for immunoassays. SHBG was measured by the DPC Immulite 2000 system. Estradiol was measured by the Diasorin Oestradiol-2 RIA kit. All intra- and inter-coefficients of variation were less than 10%. Free androgen index (FAI) was calculated using the formula $FAI = [\text{total testosterone (nmol/l)} \times 100] / \text{SHBG (nmol/l)}$.

Statistical analysis

An intention-to-treat analysis was performed on data from all women who completed the BISF-W at least once during the treatment. Pairwise comparisons of values for each active dose with those for placebo (with baseline values subtracted) were performed with *t* tests based on analysis of variance. On the basis of the D3 of the BISF-W, the percentage of women who reported having sexual fantasies or who were engaging in sexual intercourse were estimated for descriptive purposes. In a post hoc analysis, the composite score of the BISF-W was analyzed for subgroups of women with both ovaries removed, compared to those with at least one ovary present.

The results for the 300 µg testosterone patch arm from the Shifren study⁷ (page 684) were used to perform a power calculation. The mean BISF-W score at baseline, expressed as a percentage of the mean for normal women (i.e. score \times 100/33.6), was 52% and, after 12 weeks of treatment, it rose to 81% for the active group and 72% for the placebo-treated subjects (standard deviation, 37%). We calculated that 33 subjects would be required to demonstrate a *p* value of 0.05 at 80% power. Thirty-six subjects were recruited, expecting three or fewer to drop out.

The primary hypothesis was that the BISF-W scores of menopausal women who have taken estrogen and testosterone cream for a period of 3 months will be significantly higher at 80% power (*p* < 0.05) than the scores of women using estrogen alone. The secondary hypotheses were that testosterone improves energy levels and mood, raises total testosterone to the therapeutic range and does not adversely affect the safety parameters (serum creatinine, liver function tests and serum lipids).

RESULTS

Thirty-six women were enrolled in the study and received at least one dose of study cream. All the women were Caucasian, the average age of the women in both groups was 54 years and average body mass index was 25.4 kg/m². Three women withdrew from the study, one because of personal reasons (moved out of State); one because she perceived no change to her condition after three visits (she was on placebo), and one was lost to follow-up.

Mean total testosterone levels were not statistically different at the commencement of the study. At the end of 12 weeks, the active treatment

increased serum testosterone by an average of 1.8 nmol/l (Table 1). No such rise was seen for the placebo group. Serum estradiol and SHBG levels were similar in both groups and in all phases (Table 1). It was noted that both groups had a mean cholesterol level of 6.0 mmol/l, and the testosterone therapy had no apparent effect on any of the lipid parameters (Table 1).

The mean (\pm standard deviation) BISF-W composite scores were similar for the two groups at the commencement of the study. After 12 weeks of treatment, no effect on the BISF scores was seen in the placebo group. In contrast, the testosterone active treatment saw an increase by 8.8 points (44%, $p=0.000$). No significant differences were seen for DASS and POMS scores at commencement or after active or placebo treatment (Table 2).

Table 3 summarizes the findings in the domains found in the BISF-W scores. It can be seen that sexual desire (D1) improved significantly on active treatment. Testosterone therapy also significantly improved the frequency of sexual intercourse (D3) and sexual initiation (D4) by the female partner.

Descriptive statistics of the BISF-W were used to illustrate the prevalence of particular types of sexual behavior during treatment. Petting and foreplay increased by 30% in the group treated

with the testosterone cream. Also, the percentage of women who engaged in petting and foreplay two or three times a week increased from 6% to 25% in the group treated with the testosterone cream. Seventy-eight per cent of women were having vaginal intercourse at the commencement of the study; after 12 weeks of testosterone therapy, this had increased to 89%. The percentage of respondents who had sexual intercourse two to three times a week increased from 3% to 9% in the placebo group and from 9% to 31% in the testosterone cream group.

A post hoc analysis (t test) concerning the influence of removal of ovaries on the total BISF-W score was performed by comparing the BISF-W score of women without ovaries to those having at least one ovary. No statistically significant difference was detected when comparing the composite BISF-W score at baseline to the score after treatment in both groups (Table 4).

The BISF (total scores) baseline values of Period 1 and Period 2 have been compared to investigate any sequence effect corresponding to the cross-over trial. Table 5 shows that neither active treatment nor placebo has statistical significant carry-over effect from Period 1 to Period 2.

The testosterone cream was well tolerated, with no participants complaining of any skin or allergic reactions. Hirsutism, as measured by a

Table 1 Biochemical results, means \pm standard deviations. The reference range is given in parentheses

	Initial visit	Mid-point visit	Final visit	Last – first visit	t Score	p Value
<i>Testosterone (<2.6 nmol/l)</i>						
Treatment	2.1 \pm 1.2	4.1 \pm 1.8	3.8 \pm 2.5	1.8 \pm 2.9	2.825	0.009
Placebo	1.6 \pm 0.5	1.7 \pm 0.6	1.7 \pm 0.4	0.2 \pm 0.5		
<i>Estradiol (<100 pmol/l)</i>						
Treatment	199 \pm 205	187 \pm 153	166 \pm 232	-18 \pm 232	0.206	0.838
Placebo	239 \pm 245	189 \pm 263	172 \pm 126	-30 \pm 186		
<i>SHBG (20–118 nmol/l)</i>						
Treatment	59 \pm 27	54 \pm 21	52 \pm 21	-4 \pm 14	-0.013	0.990
Placebo	59 \pm 27	56 \pm 21	61 \pm 36	-4 \pm 9		
<i>FAI (1.0–4.5)</i>						
Treatment	4.8 \pm 3.6	9.6 \pm 5.7	8.1 \pm 5.7	3.6 \pm 5.6	1.7	0.069
Placebo	3.3 \pm 1.8	4.3 \pm 4.5	4.3 \pm 4.5	1.4 \pm 4.3		
<i>Total cholesterol (<5.5 mmol/l)</i>						
Treatment	6.0 \pm 1.0	5.9 \pm 0.8	5.9 \pm 0.9	-0.2 \pm 0.5	-1.072	0.289
Placebo	6.0 \pm 1.1	6.0 \pm 1.0	6.0 \pm 1.1	0.0 \pm 0.6		
<i>Triglycerides (0.5–2.0 mmol/l)</i>						
Treatment	1.3 \pm 0.6	1.3 \pm 0.7	1.2 \pm 0.6	0.0 \pm 0.5	0.239	0.812
Placebo	1.3 \pm 0.7	1.3 \pm 0.7	1.3 \pm 0.5	-0.0 \pm 0.4		
<i>LDL cholesterol (<3.4 mmol/l)</i>						
Treatment	3.7 \pm 0.9	3.5 \pm 0.8	3.7 \pm 0.9	-0.1 \pm 0.5	-0.871	0.388
Placebo	3.6 \pm 1.0	3.7 \pm 1.0	3.6 \pm 1.1	0.0 \pm 0.6		

SHBG, sex hormone binding globulin; FAI, free androgen index; LDL, low density lipoprotein

Table 2 Mean (\pm standard deviation) scores for the Brief Index of Sexual Function for Women (BISF-W); the Depression, Anxiety and Stress Scale (DASS) and the Profile of Mood States (POMS)

	<i>First visit</i>	<i>Last visit</i>	<i>Last – first visit</i>	<i>t Score</i>	<i>p Value</i>
<i>BISF (total score)</i>					
Treatment	19.85 \pm 10.67	28.45 \pm 11.28	8.76 \pm 7.46	3.935	0.000
Placebo	21.05 \pm 10.41	21.52 \pm 12.57	0.54 \pm 9.16		<i>t test</i>
<i>DASS (total score)</i>					
Treatment	8.21 \pm 9.74	4.34 \pm 7.43	-3.04 \pm 10.21	-0.636	0.528
Placebo	6.64 \pm 7.81	5.77 \pm 9.48	-0.91 \pm 14.40		<i>t test</i>
<i>POMS (total score)</i>					
Treatment	166.63 \pm 30.45	177.42 \pm 30.21	9.58 \pm 26.45	0.302	0.763
Placebo	171.93 \pm 31.96	178.62 \pm 33.52	7.59 \pm 23.14		<i>t test</i>

Table 3 Results for the BISF-W domains

	<i>First visit</i>	<i>Last visit</i>	<i>Last – first visit</i>	<i>t Score</i>	<i>p Value</i>
<i>BISF (total score)</i>					
Treatment	19.85 \pm 10.67	28.45 \pm 11.28	8.76 \pm 7.46	3.935	0.000
Placebo	21.05 \pm 10.41	21.52 \pm 12.57	0.54 \pm 9.16		<i>t test</i>
<i>D1 (Thoughts/desire)</i>					
Treatment	1.15 \pm 1.29	2.55 \pm 1.96	1.41 \pm 2.08	2.312	0.024
Placebo	1.51 \pm 1.41	1.73 \pm 1.95	0.18 \pm 2.17		<i>t test</i>
<i>D2 (Arousal)</i>					
Treatment	4.13 \pm 2.80	5.51 \pm 2.19	1.41 \pm 2.41	1.424	0.159
Placebo	4.17 \pm 2.41	2.61 \pm 2.80	0.48 \pm 2.84		<i>t test</i>
<i>D3 (Frequency of sex)</i>					
Treatment	1.34 \pm 1.09	2.09 \pm 1.33	0.78 \pm 1.38	2.108	0.039
Placebo	1.55 \pm 1.22	1.64 \pm 1.46	0.12 \pm 1.13		<i>t test</i>
<i>D4 (Receptivity/initiation)</i>					
Treatment	5.39 \pm 3.18	8.34 \pm 3.30	2.94 \pm 3.61	3.809	0.000
Placebo	6.24 \pm 3.59	5.97 \pm 3.31	-0.28 \pm 3.13		<i>t test</i>
<i>D5 (Pleasure/orgasm)</i>					
Treatment	2.61 \pm 2.19	3.95 \pm 2.07	1.30 \pm 2.17	1.835	0.071
Placebo	2.63 \pm 2.06	3.49 \pm 2.28	0.84 \pm 2.01		<i>t test</i>
<i>D6 (Relationship satisfaction)</i>					
Treatment	9.03 \pm 2.88	8.94 \pm 2.64	-0.13 \pm 2.61	0.881	0.382
Placebo	8.64 \pm 2.98	7.94 \pm 3.20	-0.63 \pm 2.78		<i>t test</i>
<i>D7 (Sexual problems)</i>					
Treatment	3.81 \pm 1.94	3.21 \pm 2.01	-0.66 \pm 2.21	-0.165	0.870
Placebo	3.72 \pm 2.18	3.11 \pm 1.68	-0.58 \pm 1.88		<i>t test</i>

Table 4 Effect of oophorectomy: BISF-W scores

	<i>BISF (total score)</i>			<i>t Score</i>	<i>p Value</i>
	<i>First visit</i>	<i>Last visit</i>	<i>Last – first visit</i>		
<i>Subjects with no ovaries</i>					
Treatment	19.28 \pm 9.86	30.49 \pm 11.52	11.63 \pm 6.90	2.808	0.010
Placebo	19.27 \pm 10.19	20.24 \pm 16.35	0.97 \pm 11.66		<i>t test</i>
<i>Subjects with one or two ovaries</i>					
Treatment	20.26 \pm 11.48	27.06 \pm 11.21	6.80 \pm 7.35	2.714	0.01
Placebo	22.06 \pm 10.65	22.29 \pm 10.06	0.29 \pm 7.61		<i>t test</i>
Ovaries status \times treatment effect				<i>F score = 0.919</i>	0.334

Table 5 BISF (total scores) baseline values: comparison by period

Treatment group	BISF (total score) baseline	Comparison	t Score	p Value
<i>Period 1</i>				
Treatment	19.66 ± 8.21	Period 1 (treatment) × Period 2 (placebo)	-1.410	0.169
Placebo	18.95 ± 12.22			
<i>Period 2</i>				
Treatment	20.05 ± 13.07	Period 1 (placebo) × Period 2 (treatment)	-0.253	0.802
Placebo	23.56 ± 7.35			

Ferriman-Gallwey score at each visit, did not change over the study time. No patient complained of acne during the study. Full blood count, serum creatinine and liver function did not change significantly throughout the study. No differences were seen throughout the study in blood pressure, body mass index or pulse rate.

DISCUSSION

Women's sexual desire and responsiveness are a complex entity, with multiple interrelated parameters. They are negatively affected by organic disease, psychological depression and relationship discord. They seem to be positively influenced by testosterone therapy. It is believed that estrogens are important for the physiological sexual response, in particular helping vaginal lubrication, whereas androgens are needed for sexual interest and desire²¹.

In our study, we found that treating postmenopausal, estrogen-replete women with hypoactive sexual desire disorder with testosterone cream produced a significant elevation in serum testosterone (and no effect on SHBG concentrations), which was accompanied by improvement in sexual desire, frequency of sexual intercourse and/or masturbation, and an improvement in sexual receptivity. It did not have any beneficial effects on mood or energy in our subjects, and did not change lipids, blood pressure or weight over the trial period.

We tested sexual function using the BISF-W and found a significant improvement in the overall score, as well as an improvement in sexual desire, sexual initiation by the female partner, receptivity to sex and frequency of sexual intercourse. These results are consistent with other studies of testosterone therapy given to females, especially postmenopausal women.

Testosterone implants had a positive effect on sexual desire in one study¹, no effect in another²² and approached significance in a third⁹. In contrast to the first study, the latter studies directly compared testosterone and estrogen with

estrogen-only treatment and may not have been powered to show an effect. The first study, however, gave all women estrogen implants and then gave testosterone implants only to women who had persistent low sexual desire. Another study using intramuscular testosterone showed improvement in sexual fantasy and arousal³ when given together with intramuscular estrogen, compared with intramuscular estrogen-alone and control groups. The addition of oral testosterone to oral estrogen improved sexual desire compared to estrogen alone¹¹. In a landmark study comparing two doses of testosterone patch and placebo, only the 300 µg testosterone patch had a significant effect on the BISF-W score⁷ compared with a 150 µg patch and placebo; however, the 150 µg patch only lead to a modest increase in serum testosterone (2.22 ± 0.87 nmol/l) compared to the 300 µg patch (3.54 ± 1.35 nmol/l). Three more recent studies have confirmed the efficacy of the 300 µg testosterone patch in hypoactive sexual desire disorder¹³⁻¹⁵. The product used in our study achieved a mean serum testosterone level of 3.8 ± 2.5 nmol/l. We have performed (in-house) two pharmacokinetic studies with this product²³. One experiment examined the pharmacokinetic properties of testosterone cream after a single dose exposure and a second experiment examined the pharmacokinetics of a 2 cm daily dose over 2 weeks. Steady-state blood levels of testosterone were apparent at 2 weeks. We were somewhat surprised by the lack of placebo effect seen in our study. Great care was taken with the two test products. They looked, felt and smelt the same.

In our study, 10 mg testosterone cream did not have a significant effect on mood or energy. This is in contrast to a positive effect in another study where a testosterone patch⁷ led to improvement in both these parameters. This may be due to our sample size ($n = 36$ compared to 75) not being powered to reach statistical significance. As in our study, Floter and colleagues ($n = 50$) found no significant difference on psychological well-being and self-esteem between their two groups¹¹.

One-percent testosterone cream achieved a mildly elevated blood level, with a mean value of 3.8 nmol/l (normal limit <2.6 nmol/l) after 12 weeks of treatment with 2 cm (10 mg testosterone) daily. Other delivery systems (except for the transdermal patches which are not available in Australia or the USA) can lead to even higher elevations in serum testosterone levels^{3,9,24} and therefore pose a risk for the development of symptoms of hyperandrogenism and subsequent virilization. To date, one case report with patients using intramuscular testosterone has reported the development of virilization following a minimum of 6 months of treatment²². Urman and colleagues reported nine women who developed significant clinical signs of androgen excess associated with long-term usage of injectable androgen–estrogen therapy²⁴. Eight exhibited significant hirsutism and seven had clitorimegaly; the serum testosterone levels ranged from 5.7 to 14.9 nmol/l. Sherwin and colleagues⁴ reported 10–20% of patients developed facial hirsutism following intramuscular monthly testosterone injections for a period of 4 years, with serum testosterone levels that were ten times higher than the pre-injection levels. Floter¹¹ reported the development of hirsutism or acne in 20% of patients receiving 40 mg daily oral testosterone for 6 months, with testosterone levels twice the upper limit of normal, although the time of sampling was not commented upon and these results may only represent trough levels. Using 100 mg testosterone implants, patients appear to have a 5% chance of developing hirsutism², even after one dose. One larger study reported no side-effects of androgen excess if implants (50 mg) were omitted until testosterone levels returned to normal⁹ despite treatment for 2 years. The present study probably did not run for long enough to truly examine the risks of hirsutism and virilization.

The cardiovascular risks or benefits of combined estrogen–testosterone therapy have not been adequately assessed yet in large, long-term, randomized, controlled trials. However, importantly, our study did not detect a significant change in the serum lipids over the 12-week period. Also, women are concerned about breast cancer risk on hormo-

nal therapies and, to date, the impact of combined estrogen–testosterone therapy on breast cancer risk is largely unknown and the few population studies available give conflicting results^{25,26}. The Nurses' Health Study is the largest population study to date and it found that combined estrogen–testosterone therapy was associated with a higher risk of breast cancer than estrogen-only treatment²⁵. In contrast, a smaller Australian study found that, when testosterone therapy was added to hormone replacement, the breast cancer risk appeared to be smaller than usual²⁶.

The positive effect of testosterone cream on sexuality is consistent with the effect of testosterone therapy delivered by implant, the intramuscular, the oral and the transdermal routes, as shown in other studies, with hormone levels closer to the physiological range (although still supra-physiological). The cream delivery system lends itself to dose titration (1–3 cm daily) to achieve the desired serum testosterone levels. Recently, sensitive testosterone assays have become commercially available in Australia, which might help prevent over-treatment with testosterone.

Presently in Australia, postmenopausal women with hypoactive sexual desire disorder are being treated with intramuscular or implanted testosterone. However, these treatments usually produce very high levels of testosterone and are being used out of their approved indication. Injections are painful and implants involve a minor surgical procedure. Therefore, the testosterone cream preparation that we used (Andro-Feme[®]) represents a major improvement over these existing treatments. Its long-term safety and efficacy have yet to be assessed.

Conflict of interest Associate-Professor John Eden has received payment from Lawley Pharmaceuticals as a scientific advisor.

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