

# Transdermal testosterone replacement to improve women's sexual functioning

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**Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, et al.**  
**Transdermal testosterone treatment in women with impaired sexual function after oophorectomy.** *N Engl J Med* 2000;343:682-8.

## Research question

Does transdermal testosterone replacement improve sexual functioning and general well-being among women who have had hysterectomies and bilateral oophorectomies?

## Type of article and design

Randomized, double-blind, placebo-controlled crossover trial.

## Relevance to family physicians

Prevalence of decreased libido, if defined as lack of interest in sex, is reported in a recent American study to be around 32% in women aged 18 to 59.<sup>1</sup> Low libido can be due to diverse causes that include social, cultural, psychological, and hormonal factors.<sup>2</sup> As patients' awareness and openness regarding sexual health increases, more and more of our female patients are asking for help to improve their sexual functioning. Some of these patients have experienced a decline in sexual functioning coincident with surgically induced menopause.

Testosterone and other androgens are known to play a role in women's sexual interest and arousal. Premenopausal women's ovaries are responsible for an estimated 40% of total body androgen production.<sup>3</sup> Thus, after bilateral surgical oophorectomy, serum testosterone levels drop markedly and suddenly. Many studies have explored the effect of testosterone in improving sexual interest and functioning in oophorectomized women. In contrast, after natural menopause, androgen production generally diminishes over time. In the perimenopausal period, levels can vary substantially.<sup>3</sup>

Many women who present with low libido have read about testosterone replacement in the media.

In Canada, available androgen preparations licensed for women are injectable only (testosterone enanthate and testosterone cypionate). An oral formulation, testosterone undecanoate, is licensed for men; its use for women has been described anecdotally.<sup>3</sup> A local formulation can be compounded as 2% testosterone propionate or cypionate in petrolatum jelly.<sup>4</sup> A transdermal patch, as evaluated in this study, might be more acceptable and convenient for patients than injections.

## Overview of study and outcomes

The study enrolled 75 women aged 31 to 56 years who had undergone hysterectomy and bilateral oophorectomy before natural menopause. All subjects were considered to have impaired sexual functioning when they answered yes to three questions: "At any time before surgery would you have characterized your sex life as active and satisfying?" "Since your surgery has your sex life become less active or less satisfying?" and "Would you prefer your sex life to be more active or more satisfying than it is now?" All women had serum testosterone levels lower than 1.0 nmol/L (median level for normal premenopausal women). All took conjugated equine estrogens before and throughout the study period.

Patients were included if they had been in a monogamous, heterosexual relationship for more than 1 year and excluded if they had received androgen therapy in the previous 6 months; if they had moderate-to-severe hot flashes, severe acne, hyperlipidemia, psychiatric illness, dyspareunia, or physical limitations preventing normal sexual functioning; or if they were taking glucocorticoids, antidepressants, phytoestrogens, ginseng, yohimbine, or melatonin.

After a 4-week run-in period, women were randomly assigned to three consecutive 12-week treatment periods. In random order, they used twice weekly transdermal patches delivering placebo, 150 µg/d of testosterone, or 300 µg/d of testosterone.

Outcome measures for efficacy were based on laboratory measurements of serum free testosterone, bioavailable testosterone,

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and total testosterone; sex hormone binding globulin; dehydroepiandrosterone sulfate (DHEAS); estradiol; estrone; luteinizing hormone (LH); and follicle-stimulating hormone (FSH). Sexual functioning was evaluated using the Brief Index of Sexual Functioning for Women,<sup>5</sup> and a telephone-based diary. Overall well-being was assessed with the Psychological General Well-Being Index.<sup>6</sup> Safety was evaluated with scores for hirsutism and acne; serum concentrations of lipids, glucose, and insulin; blood counts; and liver function. Tolerability of patches was also monitored throughout the study.

### Results

Sixty-five women had at least one evaluation for efficacy and were included in the intention-to-treat analysis. Six withdrew because of adverse events (one or more from each of the three treatment groups), six withdrew for personal reasons, and six were excluded due to poor compliance with the telephone-based diary.

The patches provided a dose-dependent increase in free testosterone and bioavailable testosterone to an average value in the high-normal range for premenopausal women. Total testosterone rose in a dose-dependent fashion as well, to a level exceeding the normal range. There were no significant changes in DHEAS, estrone, estradiol, LH, or FSH.

Results from the Brief Index of Sexual Functioning revealed a strong placebo response compared with baseline. Average composite score at the end of the 4-week run-in period was  $52 \pm 27\%$  of the mean value in normal women. At the end of the placebo period, score was  $72 \pm 38\%$ . With  $150 \mu\text{g}/\text{d}$  of testosterone, score was  $74 \pm 37\%$ , and for  $300 \mu\text{g}/\text{d}$ , score was  $81 \pm 37\%$ . Scores of women using the  $300\text{-}\mu\text{g}/\text{d}$  patch were slightly different from scores of women receiving placebo ( $P = .05$ ).

The large placebo response observed in this study points to the complexity of the physiology of female sexual desire. The authors speculate that participation in the trial might have facilitated communication within couples or that the visibility of the patch might have been a stimulus for increased sexual activity. The crossover design and lack of washout period might have inflated the observed placebo response.

A subanalysis of the Brief Index of Sexual Functioning was performed by breaking down the scores into various components of sexual functioning. Significant improvement was found with the  $300\text{-}\mu\text{g}/\text{d}$  patches for frequency of sexual activity ( $P = .3$ ) and pleasure-orgasm ( $P = .3$ ), but not for thoughts-desire, arousal, receptivity-initiation, or relationship satisfaction.

Interestingly, analysis of the above data revealed that, when the women were divided by age into those

younger than 48 and 48 years or older, results for younger women were similar in all treatment groups. Among the older women, there was significant improvement with both  $150\text{-}\mu\text{g}/\text{d}$  and  $300\text{-}\mu\text{g}/\text{d}$  patches compared with placebo. Both age groups had similar serum free testosterone levels.

Results from the telephone diary were fraught with compliance problems, but there appeared to be a trend toward dose-dependent improvement in frequency of sexual thoughts, desires, and activities. Composite scores on the Psychological General Well-being Index showed a significant improvement over placebo only with the  $300\text{-}\mu\text{g}/\text{d}$  patch ( $P = .4$ ). No placebo effect was observed with this index.

Treatment with transdermal testosterone appears safe. Five serious adverse events occurred during the study, but only one was thought possibly related to treatment (depression during the placebo arm.) There were no important changes in hirsutism; acne; hot flashes; cholesterol, fasting glucose, or insulin levels; blood counts; or liver-function tests during treatment. One woman withdrew due to a skin reaction to the placebo patch; one withdrew due to recurrence of a pink nipple discharge while receiving testosterone; and two withdrew due to agitation while receiving testosterone.

### Analysis of methodology

Strengths of this study include the double-blind design and the random way the women entered the three treatment arms. Although the details and outcome of the randomization process were not provided, the authors did note that analysis-of-variance models found no statistically significant effects of treatment sequence. Inclusion of a placebo group was invaluable, for without it, a treatment effect with the  $150\text{-}\mu\text{g}/\text{d}$  patch might have been assumed. Use of standardized questionnaires for sexual function and well-being gave more validity to the results of such subjective end points. Finally, while 18 participants (24%) withdrew or were withdrawn from the study, intention-to-treat analysis was used for the 65 patients for whom data were available.

Limitations of the study include the small sample size. Given the high rate of hysterectomy and oophorectomy in North America and the reported high prevalence of sexual dysfunction among women, we wonder whether a greater number of women could have been recruited. Also, the authors do not state how the patients were recruited, or in what setting. Did they present with sexual complaints or were they discovered by anticipatory history-taking? It is likely that they were patients attending specialty clinics rather than primary care offices. Finally, the treatment period was relatively short. An increase in serum total testosterone to

above normal range might make us wonder whether adverse effects would appear during the longer treatment period that would be used in practice.

### Application to clinical practice

The transdermal patch was shown in this study to be effective at a dose of 300 µg/d for increasing sexual functioning and general well-being in women with surgically induced menopause. The testosterone patch appears to be well tolerated and safe, at least in the short term.

Reviewing this study, however, raises many questions regarding treatment of sexual dysfunction in the general postmenopausal female population. Not all women who present to family physicians' offices with complaints of low libido fall within this study population. In any case, we must be careful to treat coexisting conditions, such as depression, dyspareunia, or relationships that are unstable or unhealthy, before considering testosterone replacement therapy. Women's overall state of well-being and the quality of their relationships with their partners might well be more important than testosterone levels in predicting the quality of sexual functioning.<sup>7</sup>

As yet, the testosterone patch used in this study is not available in Canada. This study does, however, prepare us for what is to come. Just as the choices in preparations of estrogen replacement therapy have multiplied, our therapeutic options for testosterone replacement in postmenopausal women will likely multiply.

### Bottom line

- Sexual response in women is complex, and low libido can be attributed to physiologic, psychological, social, or cultural factors.
- The drop in serum testosterone levels after surgically induced menopause is more dramatic than after natural menopause.
- A testosterone patch might be more acceptable to women than injectable preparations.
- A 300-µg/d testosterone patch, in conjunction with estrogen replacement, might help improve women's sexual functioning and general well-being after hysterectomy and oophorectomy. ❖

### Points saillants

- La réceptivité sexuelle chez la femme est complexe et une faible libido peut être attribuable à des facteurs physiologiques, psychologiques, sociaux et culturels.
- La baisse des taux de testostérone sérique après une ménopause causée par une intervention chirurgicale est plus dramatique qu'après une ménopause naturelle.
- Un timbre à la testostérone pourrait se révéler plus pratique pour les femmes que sous forme d'injections.
- Un timbre comportant 300-µg/d de testostérone, de concert avec une hormonothérapie de remplacement, peut contribuer à améliorer la fonction sexuelle et le bien-être chez la femme ayant subi une hystérectomie ou une ovariectomie.

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