Testosterone for low libido in postmenopausal women not using systemic oestrogen therapy

Susan R Davis

Results are promising but long-term safety remains uncertain

Hypoactive sexual desire disorder (HSDD; loss of desire that causes personal distress)[1] is common, with proposed prevalences ranging between 8% and 50% (wide variation is due to differences among populations surveyed and questionnaires used).[2,3] Women with HSDD have been observed to experience poor sexual self-image, feelings of unattractiveness, fear of disappointing their partners, depression, anxiety and diminished quality of life.[4,5] The effect of HSDD on quality of life has been reported as similar in magnitude to the effect of other common chronic conditions, such as diabetes and back pain.[5] Furthermore, both men and women reporting a discrepancy between their own and their partner's sexual desire have lower relationship satisfaction,[6] and individuals in sexually inactive marriages report less marital happiness.[7] Thus, HSDD merits recognition and intervention. In many cases, counselling and general sex education are helpful. However, the proportion of postmenopausal women who continue to experience HSDD despite good clinical care are left with few options, as there are no approved therapies presently available for this condition.

APHRODITE is the most recent of a series of randomised controlled trials (RCTs) evaluating the efficacy and safety of transdermal testosterone patch therapy in postmenopausal women with HSDD.[8] This large, multinational study, involving women with either natural or surgical menopause, differed from preceding studies in that participants were not receiving concurrent oestrogen therapy. The study was conducted and financed by Procter and Gamble Pharmaceuticals. However, it was instigated by the investigators, who were concerned that women may resort to off-label use of the testosterone patch Intrinsa (Procter and Gamble), when it becomes available, in the wake of the findings of the Women's Health Initiative Studies (these findings initially raised concerns about the safety of postmenopausal oestrogen therapy). As effects of testosterone use without concurrent treatment with systemic oestrogen are unknown, the investigators believed this study would provide much-needed data.

In this 52-week trial, 814 women with HSDD were randomly assigned to receive a patch delivering 150 μg or 300 μg of testosterone per day, or placebo. The primary end point was the number of self-reported sexually satisfactory events per month. The findings were interesting on several fronts.

At baseline, women reported engaging in sexual activity on average 5 times per month, with half these events reported as unsatisfying. Participants had low sexual desire and a high level of personal distress measured by validated scales. By 24 weeks, women treated with the testosterone 300 μg patch reported a mean of 4.5 satisfactory events per month compared with 3.2 satisfactory events per month for women in the placebo group. Sexual desire increased and distress diminished substantially for both groups of women receiving active therapy.

These findings have been interpreted by some as representing very little gain.[9] However, women treated with the 300 μg testosterone patch reported enjoying nearly all of their sexual encounters, whereas those who received the placebo experienced pleasure 65% of the time. It is worth noting that women treated with testosterone did not report a significant increase in total sexual activity; this may be an effect of strongly established relationship patterns, including interest and availability of partners.

In line with previous studies of transdermal testosterone therapy in postmenopausal and premenopausal women, efficacy did not manifest until after 8 weeks of therapy.[10,11]

Although women who received testosterone were more likely to report increased hair growth (20% of women receiving testosterone 300 μg v 10.5% of those receiving placebo), withdrawal from the study due to androgenic effects did not differ between the groups, and women treated with placebo were more likely to withdraw (19% of women receiving placebo v 14% of those receiving testosterone 300 μg). No significant adverse metabolic or endometrial effects were detected.

The main concern arising from this study was the finding of breast cancer in four women treated with testosterone and none in the placebo group; the ratio of participants receiving testosterone to those receiving placebo was 2:1. The relationship between these findings and testosterone use is unclear, with two of the cancers likely to have been pre-existing (one diagnosed within 4 months of randomisation and another in a woman who recalled symptoms before randomisation when diagnosed after 7 months of treatment). A third woman diagnosed with breast cancer had previously been treated with hormone replacement therapy for 25 years and had a sister with breast cancer. The fourth was diagnosed after completion of 24 months of the study. The literature regarding the breast cancer risk of exogenous testosterone does not illuminate this issue.

No other RCTs have been large enough or long enough to provide meaningful data. Observational data for oral methyltestosterone suggesting an increase in breast cancer risk[12] have major limitations — the data are from the 1990s when testosterone was commonly prescribed for mastalgia in postmenopausal women receiving oestrogen therapy and the comparator group comprised non-hormone users, such that any apparent risk may have been the risk of oestrogen or oestrogen plus progestin use. A subsequent study in fact suggests the latter may well be the case.[13] Two independent observational Australian studies have not found an increase in breast cancer risk with therapeutic testosterone use.[14,15]

Available data indicate transdermal testosterone can be useful for the treatment of HSDD in postmenopausal women. Short-term use appears to be safe, yet the effects of long-term use remain uncertain. Ideally, long-term safety should be evaluated in large longitudinal studies; however, as 70% of women who elect to use testosterone for HSDD do so for less than 3 years,[15] retention of women in such studies will be a challenge.

Competing interests

I was the principal investigator for APHRODITE. I have been a consultant to Acrux Australia, Procter and Gamble Pharmaceuticals, Novartis Oncology and AstraZeneca. I have received unrestricted research grants from Procter and Gamble Pharmaceuticals, Bayer Schering, Novartis Oncology and AstraZeneca. I have received honoraria from Organon and Bayer Schering.

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