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Treating Low Sexual Desire — New Findings for Testosterone in Women

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Decreased or low sexual desire is commonly reported by women from late adolescence through the seventh decade across a number of cultures. Estimates of prevalence range from 25 to 53%.[1-3] Low desire is not always a "problem" causing distress for women,[4,5] but it can have substantive negative effects on women's intimate relationships or their motivation to form them.[6] Low desire may be caused by a number of factors, many "nonphysiological," including relationship distress, a partner who has an illness or a disorder, neglect of the physical aspects of the relationship, or more global psychosocial problems, such as job loss or family crises. The optimal treatment of women who are bothered by low desire remains undefined, with few evidence-based treatments available. Earlier work focused on psychosocial and relationship-oriented approaches to improve desire,[7] but there has been little federal funding of research into this problem, and these treatments have not been as well studied as they deserve to be. More recently, possible pharmacologic treatment options have received greater attention, at least in part because of the increasingly common use of prescription drugs that frequently cause sexual disorders in women, such as the serotonergic drugs for depression. To date, however, no safe, reliable, fully tested product is available to treat low desire in women.

The use of exogenous testosterone, delivered in various ways, including injections and implants, has been studied in women with low sexual desire in a limited number of well-conducted, randomized, controlled trials, the majority of which have shown improvements (albeit rather modest overall) in desire, sexual responsiveness, and frequency.[8] The testosterone transdermal patch has been shown to favorably affect various domains of sexual functioning — desire, arousal, and orgasm, in particular — and to significantly increase the number of satisfying sexual episodes (an end point required by the Food and Drug Administration as evidence of efficacy).[9,10] However, these trials have tended to be rather brief, typically 3 or 6 months, which has worried those concerned about the potential for serious adverse effects from the use of hormonal products. In addition, these studies have been almost exclusively restricted to postmenopausal women taking estrogen or compounds of estrogen plus progesterone; long-term use of these products is now discouraged, given potential risks.

In this issue of the *Journal*, Davis and colleagues[11] report the results of a long-term, randomized, placebo-controlled, multicenter trial assessing the effectiveness and safety of a testosterone patch (Intrinsa, Procter & Gamble Pharmaceuticals) at a dose of 300 μg per day or 150 μg

per day in women with low sexual desire. Eligible women were naturally or surgically menopausal and not taking estrogen or progesterone. Efficacy was measured through week 24, and safety was evaluated through week 52, with a smaller subgroup (38.6% of the study patients from week 52) followed for an additional year.

At week 24, as compared with placebo, use of the patch providing 300 μg of testosterone per day resulted in significant improvements from baseline in several domains of sexual functioning (desire, arousal, orgasm, and pleasure), among other areas (including decreased distress and concerns), in women with natural or surgically induced menopause; use of 150 μg day resulted in significant changes only in desire and distress. The primary outcome — the 4-week frequency of satisfying sexual episodes at week 24 — significantly improved in the group receiving 300 μg of testosterone per day but not in the group receiving 150 μg per day; in subgroup analyses, the increase was significant in women who had natural menopause but not in women with surgically induced menopause, an observation that may simply reflect the smaller sample size and lower power for these analyses. A reasonable question is whether the absolute increase of satisfying sexual episodes of 2.1 per month (1.4 more events per month than in the placebo group) was of value. Although the report does not indicate whether the women were asked whether this change was meaningful for them, a review of the baseline data suggests it probably was, since the mean number of such episodes almost doubled for the high-dose group (an increase of 84%, vs. 28% for placebo). This is all good news.

All groups had similar rates of reaction at the application site (49.5 to 52.8%) and various androgenic events (e.g., acne, alopecia, and voice deepening, all occurring in less than 8% of women in each group). However, increased hair growth was significantly more common among women in the group receiving 300 μg of testosterone per day (19.9%, vs. 10.5% in the placebo group). This adverse effect seems unpleasant but is not a major cause of concern with respect to health, nor did it appear to substantively affect treatment adherence. Of greater concern is the occurrence of four cases of breast cancer in the groups receiving testosterone, including one case detected 3 months after the extension period had ended; there were no cases of breast cancer in the placebo group. The apparent excess of cases in the testosterone groups could simply be due to chance (the size of the groups is too small to allow for analysis), but this potentially worrisome signal cannot be ignored. More information on the cases (such as total and free testosterone levels, estradiol levels, body-mass index, and age) would be of interest and would help generate hypotheses for further testing.

Potentially related to efficacy and adverse events are the women's levels of testosterone. Although the range of most laboratory measures remained within normal limits in women receiving testosterone, the testosterone levels at weeks 24 and 52 appear high for women in the high-dose group. Mean levels of total, free, and bioavailable testosterone (not analyzed at week 52) were at or above the upper end of the reference range (based on premenopausal women 18 to 49 years of age), with the means in the 9th decile approximately double the figure at the upper end of reference range. A logical question is whether supraphysiologic levels in some of the subjects might underlie the positive effects on sexuality measures as well as the hair growth and breast cancer risk. If levels of testosterone (free or total) were more closely controlled to stay within range — perhaps difficult with a patch delivery system — would efficacy or adverse events be reduced? For women whose testosterone levels become particularly high, maintenance on the prescribed dose, especially over a period of months, may be ill-advised.

Although different testosterone compounds and delivery systems require separate evaluations, the results of the present report support previous findings that testosterone has positive effects on sexuality and that higher doses show greater effects. At the same time, the findings suggest the need for caution in using testosterone until we understand more about its possible link with breast cancer and are better able to predict which patients are more likely to be subject to negative effects.

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