Testosterone for women: green light for sex, amber light for health?

In 1950, Greenblatt and colleagues published findings of a randomised clinical trial of androgen therapy to manage menopausal symptoms.[1] After removal of the ovaries, postmenopausal women reported improved wellbeing, enhanced libido, decreased hot flushes, and amelioration of other symptoms when treated with methyltestosterone and diethylstilbestrol, versus either hormone alone or a placebo. Since then, androgen replacement for women—using effective and safe compounds—has been considered by health-care providers struggling to manage hypoandrogenic symptoms in women and to prevent medical conditions linked to hypoandrogenicity.[2] Many testosterone formulations are available to improve measures of sexual wellbeing including low sex drive and poor sexual function. However, currently, these compounds are available only as male formulations and their safety or adverse events, as well as their effect on general aspects of women's health, remain controversial because of scant published data.[3]

In *The Lancet Diabetes & Endocrinology*, Rakibul Islam and colleagues[4] report findings of a systematic review and meta-analysis of testosterone therapy for women, with the aim to assess the benefits and risks of this treatment at doses close to those achieved with a 300 µg transdermal patch—a dose that was effective in improving sexual function and psychosexual wellbeing against placebo in oophorectomised women with hypoactive sexual desire disorder.[5] In postmenopausal women, testosterone supplementation for at least 12 weeks improved several domains of sexual response, including satisfactory sexual event frequency, sexual desire, pleasure, arousal, orgasm, responsiveness, and self-image. Moreover, testosterone significantly reduced sexual distress in both postmenopausal and premenopausal women, although data were sparse in premenopausal women. These findings confirm those of a previous systematic review and meta-analysis,[6] which showed short-term efficacy—in terms of improvement of sexual function and the safety of transdermal testosterone—in naturally and surgically menopausal women affected by hypoactive sexual desire disorder and taking or not taking oestrogen–progestin hormone therapy.

Islam and colleagues' findings also add relevant information about cardiometabolic safety of testosterone. A significant increase in LDL-cholesterol, and a reduction in total cholesterol, HDL-cholesterol, and triglycerides, was noted with testosterone administered orally, but not for non-oral testosterone.[4] No effect of testosterone was recorded on blood pressure, blood glucose, and insulin, but testosterone treatment was associated with a significant increase in weight, irrespective of the route of administration. Mild adverse cosmetic effects (acne and hair growth) were also reported, but these side-effects did not lead to withdrawal from treatment. No other adverse effects of testosterone therapy were noted, including effects related to breast and endometrial safety. Finally, testosterone did not show an effect on cognitive performance, bone mineral density, body composition, muscle strength, depressed mood, and measures of psychological general wellbeing, although data are limited.

Several key messages can be taken from Islam and colleagues' analysis. First, in postmenopausal women with hypoactive sexual desire disorder or generalised female sexual dysfunction, testosterone provided at an appropriate dose is beneficial for sexual function when clinical judgment indicates its use.[7] Testosterone treatment should be prescribed to achieve physiological concentrations in blood for premenopausal women, although no cutoffs for any androgens have been defined to discriminate between women having or not having low sexual function.[8] Insufficient data are available in premenopausal women to support use of testosterone. Second, adverse events of testosterone are mild and restricted to clinical signs of hyperandrogenism. Third, available data do not support use of testosterone therapy to prevent bone loss at either the spine, total hip, or femoral neck or to protect postmenopausal women from sarcopenia. Further, there is no indication to use testosterone therapy to prevent cognitive decline or to ameliorate mood, general wellbeing, or physical and mental performance. Fourth, non-oral routes of testosterone administration have a better cardiometabolic profile in the short term, but this finding does not translate into

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cardiovascular safety[9] because of a paucity of long-term data and because selection criteria used in randomised controlled trials exclude high-risk women who are also candidates for oestrogen therapy. Finally, short-term use of testosterone does not modify either the breast or the endometrium, but data are insufficient to assess long-term oncological risks.

Notwithstanding these findings, we must gain insight into the therapeutic role of testosterone for women by designing adequate long-term studies to address benefits and risk in specific clinical conditions relevant to healthy female longevity. In particular, there is an urgent need in the area of sexual medicine to ensure gender equality in treating effectively those women with female sexual dysfunction clearly related to hypoandrogenic states. However, products specifically approved in women should become available to achieve this goal; at present, only male formulations are available, with clinicians adjusting the dose to the female circulating testosterone range.[10]

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1 Greenblatt RB, Barfield WE, Garner JF, Calk GL, Harrod JP Jr. Evaluation of an estrogen, androgen, estrogen-androgen combination, and a placebo in the treatment of the menopause. *J Clin Endocrinol Metab* 1950; **10:** 1547–58.
2 Bachmann GA. The hypoandrogenic woman: pathophysiologic overview. *Fertil Steril* 2002; **77** (suppl 4)**:** S72–76.
3 Davis SR, Wahlin-Jacobsen S. Testosterone in women—the clinical significance. *Lancet Diabetes Endocrinol* 2015; **3:** 980–92.
4 Islam RM, Bell RJ, Green S, Page MJ, Davis SR. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. *Lancet Diabetes Endocrinol* 2019; published online July 25. http://dx.doi.org/S2213-8587(19)30189-5.
5 Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000; **343:** 682–88.
6 Achilli C, Pundir J, Ramanathan P, Sabatini L, Hamoda H, Panay N. Efficacy and safety of transdermal testosterone in postmenopausal women with hypoactive sexual desire disorder: a systematic review and meta-analysis. *Fertil Steril* 2017; **107:** 475–82.
7 Simon JA, Davis SR, Althof SE, et al. Sexual well-being after menopause: an International Menopause Society White Paper. *Climacteric* 2018; **21:** 415–27.
8 Davis SR, Davison SL, Donath S, Bell RJ. Circulating androgen levels and self-reported sexual function in women. *JAMA* 2005; **294:** 91–96.
9 Armeni E, Lambrinoudaki I. Androgens and cardiovascular disease in women and men. *Maturitas* 2017; **104:** 54–72.
10 Nappi RE, Cucinella L. Advances in pharmacotherapy for treating female sexual dysfunction. *Expert Opin Pharmacother* 2015; **16:** 875–87.