Testosterone therapy in women

SHANANTHAN BALACHANDRAN MB BS, FRACP
SUSAN R. DAVIS AO, MB BS, PhD, FRACP, FAHMS

Transdermal testosterone therapy has received regulatory approval for the treatment of hypoactive sexual desire dysfunction (HSDD) in postmenopausal women. It is an effective treatment option for persistent low sexual desire that continues after exclusion or targeted management of reversible biopsychosocial factors.

Testosterone therapy has been shown to improve low sexual desire associated with distress in postmenopausal women. Until recently, the only options for testosterone therapy in women in Australia were a formulation for women approved only in Western Australia, testosterone formulations for men with dose modification, or compounded therapies. In November 2020, the TGA approved a transdermal testosterone 1% formulation for the treatment of hypoactive sexual desire dysfunction (HSDD) in postmenopausal women.[1] This article reviews the physiology of testosterone in women and the indications and prescribing details for transdermal testosterone therapy in women.

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Dr Balachandran is a Consultant Endocrinologist in the Department of Endocrinology and Diabetes, Eastern Health, Melbourne. Professor Davis is NHMRC Senior Principal Research Fellow, Director of the Women's Health Research Program, and Professor of Womens Health, School of Public Health and Preventive Medicine, Monash University, Melbourne, Vic.

Physiology of testosterone in women

The importance of androgens in female physiology is increasingly recognised, with roles in normal ovarian follicular development, bone and muscle health, and vascular endothelial and sexual function. Testosterone is the predominant circulating androgen in women as well as men. Dehydroepiandrosterone (DHEA) and androstenedione are testosterone precursors produced by the ovaries and adrenals that have little independent androgenic activity. Although testosterone itself is biologically active, it may also be reduced to the more potent androgen, dihydrotestosterone, or aromatised to oestradiol, resulting in pleiotropic effects.

In women, circulating testosterone is derived both from direct ovarian production and from peripheral production from adrenal and ovarian precursor hormones. Hormonal activation of intracellular sex steroid receptors modulates gene transcription, leading to subsequent downstream clinical effects.

Testosterone circulates in the blood predominantly bound to proteins, with about two-thirds bound to sex hormone binding globulin (SHBG). Previous assertions that unbound or 'free' testosterone represents the biologically active fraction have been challenged. Circulating testosterone levels do not approximate tissue levels or action, and free testosterone may instead simply represent the fraction available for degradation.[2]

Hypoactive sexual desire dysfunction

HSDD is a female sexual health problem that is characterised by persistent loss of motivation or desire to initiate or participate in sexual activity, causing significant personal distress.[3] The diagnosis is made after exclusion of other factors causing low desire or distress, such as relationship issues, dyspareunia and depression. HSDD is associated with impairments in body image, self-confidence and self-worth, as well as loss of connection to intimate partners.[4] HSDD is one of the most common female sexual health issues, with an Australian prevalence of 32.2% and 12.6% in women aged 40 to 64 years and 65 to 79 years, respectively.[5,6]

The Decreased Sexual Desire Screener is a helpful diagnostic tool that can be used to facilitate initial discussion to identify

HSDD.[7] Full assessment requires a thorough history to determine whether the underlying root cause of the sexual symptoms may be neurobiological, interpersonal or psychosocial, as initial management must be directed at any reversible factors. A diagnosis of HSDD cannot be made until such factors are addressed.

Transdermal testosterone therapy is the only approved pharmacotherapy for use in postmenopausal women with HSDD in Australia. It is appropriate for use when other strategies have been unsuccessful.

Effects of testosterone therapy in women

Testosterone levels decline in women between the third and fifth decades of life, do not vary with natural menopause and reach a nadir in the seventh decade.[8,9] Transdermal testosterone therapy that results in approximate physiological testosterone blood concentrations seen in premenopausal women is efficacious and appropriate for use in postmenopausal women with HSDD.[10]

Testosterone treatment has been shown to increase the number and frequency of satisfying sexual events as well as to significantly augment sexual desire, arousal, orgasm, pleasure, responsiveness and self-image.[11] There is also a reduction in sexual concerns and personal sexually associated distress, and hence effectiveness, for women with HSDD.[11] Benefits in these sexual health domains are seen in women who have experienced either natural or surgical menopause, and irrespective of concurrent oestrogen therapy.[11]

Although data are limited, there is no evidence that postmenopausal testosterone therapy improves cognitive performance, bone mineral density, muscle mass, general wellbeing or depressed mood.[10] Beyond its use in HSDD, there is presently no other indication for testosterone treatment in postmenopausal women.[10]

There is a paucity of studies evaluating testosterone treatment of premenopausal women with HSDD. However, no benefit in any sexual function domain has been demonstrated in this cohort. Treatment of premenopausal women with testosterone is not recommended without further study and evidence of efficacy.[10]

Testosterone prescribing for women

The preferred formulation for testosterone therapy is transdermal. Oral testosterone should be avoided because of a significant association with increased LDL-cholesterol and reduced HDL-cholesterol levels.[11] Injectable formulations may lead to peaks in testosterone level, increasing the risk of supraphysiological dosing and adverse effects. There is lack of evidence for efficacy and safety for compounded 'bioidentical' testosterone therapy, which is not justifiable now that a TGA-approved formulation is available.[10]

Transdermal 1% testosterone cream is the only TGA-approved female-specific testosterone therapy currently available in Australia. It can be prescribed as a private prescription and is widely available. Each 50 mL tube contains 500 mg of 1% testosterone (10 mg/mL). A dose applicator calibrated in 0.5 mL graduations is used to facilitate dose delivery.

Before treatment is initiated, women should have their baseline testosterone and SHBG levels measured

Initial dosing is 5 mg (0.5 mL) daily, applied to the upper outer thigh or buttock area. The cream is applied to clean dry skin and massaged in until absorption is complete, typically taking less than 30 seconds. Application should be followed by handwashing with soap and water, and the applicator should be rinsed in hot water after use.

An algorithm for prescribing testosterone for postmenopausal women with HSDD is shown in the Flowchart. Before treatment is initiated, women should have their baseline serum testosterone and SHBG levels measured. This is to exclude women with an unexpectedly high pretreatment testosterone level, such that treatment would put them into a supraphysiological range, and women with an elevated SHBG level. Women with a serum SHBG concentration above the upper limit of the reference range have been found to be unlikely to respond to treatment.[12] Women with a high SHBG level who are taking oral oestrogen (which increases SHBG) should first be switched to nonoral oestrogen, and the SHBG measured after about 12 weeks.

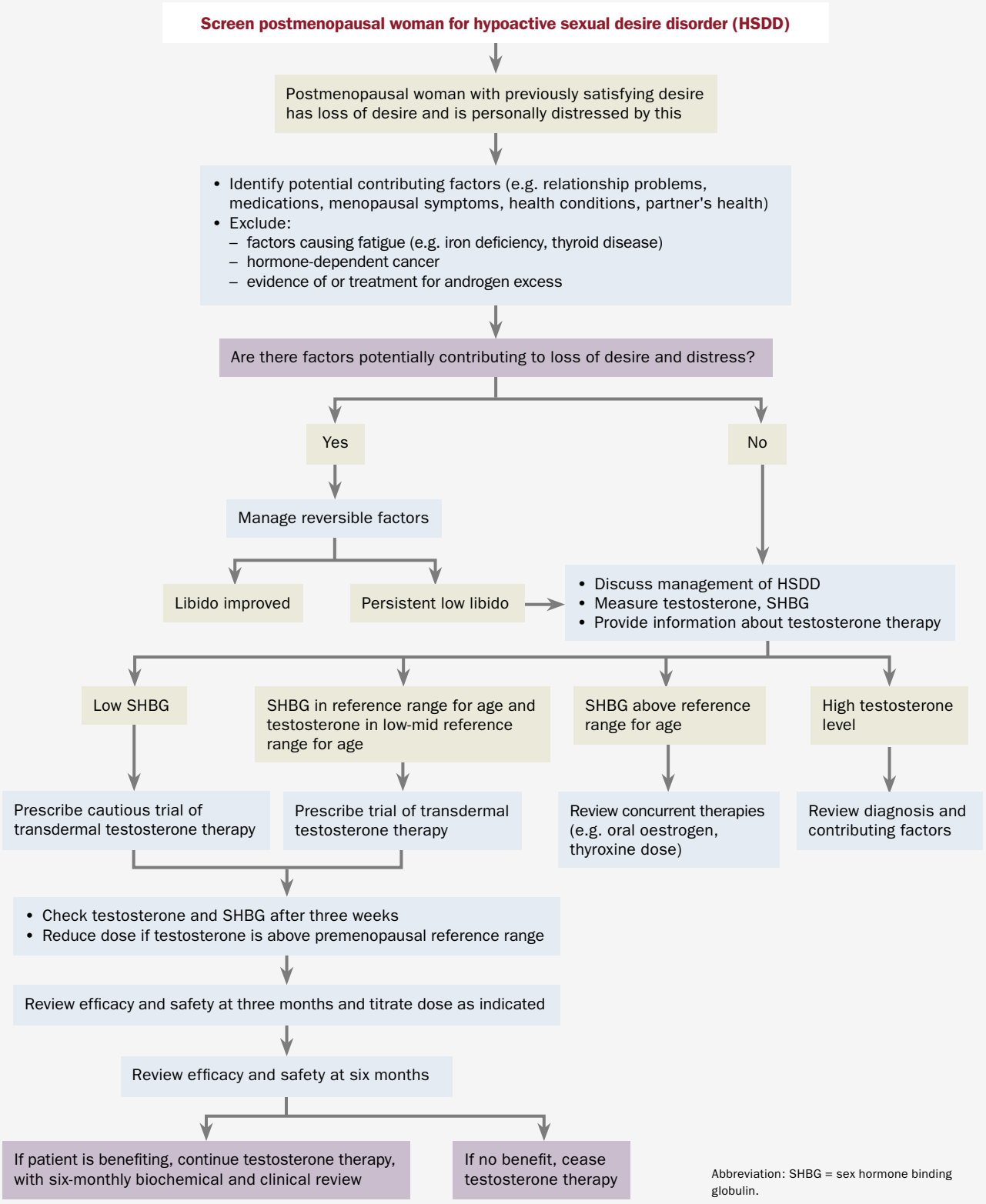
Treatment monitoring

The primary determinant of efficacy is based on improvement in sexual function considered relevant to each individual woman; however, this can take up to 12 weeks to be appreciated. After treatment begins, both biochemical and clinical reviews are essential. Clinical follow up includes monitoring of the response to therapy as well as assessment for signs of androgen excess. Total testosterone and SHBG levels must be measured three to six weeks after treatment initiation to ensure the testosterone concentration is within the premenopausal reference range.

Clinical and biochemical follow up should be repeated at 12 weeks. If the desired improvement in sexual function has not been attained and the testosterone concentration is within the premenopausal reference range, the testosterone dose may be titrated up as appropriate, up to 10 mg (1 mL). Doses exceeding 10 mg daily are rarely needed.

After a stable dose is reached, clinical and biochemical review of serum testosterone levels is required at six-monthly intervals. If the serum testosterone level exceeds the upper limit of the premenopausal range for the assay, clinicians should screen for clinical evidence of hyperandrogenism and consider dose reduction. If no benefit is experienced after six months of continuous therapy, treatment should be ceased and alternative options considered.[10,13]

PRESCRIBING TESTOSTERONE TO POSTMENOPAUSAL WOMEN WITH HYPOACTIVE SEXUAL DESIRE DISORDER



Abbreviation: SHBG = sex hormone binding globulin.

Safety of testosterone therapy

Transdermal testosterone therapy is generally well tolerated in doses that approximate physiological testosterone concentrations for premenopausal women. However, androgen-related effects may be encountered. Physiological levels may cause an increase in acne, oily skin and hair growth in some women.[11] Other effects such as alopecia, clitoromegaly and voice changes have not been seen with appropriate dosing but may be seen with supraphysiological therapy.[11]

Transdermal testosterone therapy does not lead to changes in liver function, lipids, insulin or glucose test results.[11] No increase has been seen in the risk of serious adverse events, including adverse endometrial and breast effects, with physiological dosing. However, randomised controlled trial data thus far are limited to 24 months of follow up, and longer-term safety remains uncertain.[10]

Although there is no evidence of increased cardiovascular risk with nonoral testosterone therapy, studies to date have not included high-risk populations. Caution should be exercised in patients with high cardiovascular risk.

Transfer of testosterone to others by skin-to-skin contact has been reported with the use of higher-dose therapy in men, resulting in increased testosterone serum levels and possible adverse effects. Testosterone doses are far lower in postmenopausal women than in men. However, close skin contact of a female partner or child with the area of application should be avoided. The risk of transfer is substantially reduced by wearing clothing covering the application area.

Contraindications

Testosterone therapy is contraindicated in women with clinical androgen excess, specifically acne hirsutism or androgenic alopecia, and in women being treated for androgen excess. As the current commercially available preparation contains almond oil, therapy should be avoided in those with tree nut allergy.

It is important for clinicians to be aware that women with a prior diagnosis of breast cancer were excluded from randomised controlled trials of testosterone therapy. Accordingly, testosterone therapy is not recommended in those with a history of hormone-sensitive breast cancer or other androgen-dependent neoplasia. Testosterone therapy should not be prescribed to prevent breast cancer.[10]

Drug interactions

Oral oestrogens, including oral postmenopausal oestrogen therapy, may result in an elevated SHBG level. As described above, oral oestrogen may need to be changed to transdermal oestrogen before consideration of testosterone therapy. Both tibolone and glucocorticoids lower the SHBG level, increasing testosterone clearance. This means the tissues are more exposed to testosterone while blood testosterone concentrations may appear deceptively low.

Conclusion

The only evidence-based indication for testosterone therapy in women is treatment of HSDD in postmenopausal women. HSDD must be formally diagnosed, and treatable factors should be excluded. Women should be advised that treatment is a therapeutic trial and that if no response is achieved by six months, treatment will be discontinued. MT

References

1. Lawley Pharmaceuticals. Australian product information – Androfeme 1 (testosterone) 1% w/v cream. Perth: Lawley Pharmaceuticals; 2020.
2. Handelsman DJ. Free testosterone: pumping up the tires or ending the free ride? Endocr Rev 2017; 38: 297-301.
3. Clayton AH, Goldstein I, Kim NN, et al. The International Society for the Study of Women's Sexual Health process of care for management of hypoactive sexual desire disorder in women. Mayo Clin Proc 2018; 93: 467-487.
4. Kingsberg SA. Attitudinal survey of women living with low sexual desire. J Womens Health (Larchmt) 2014; 23: 817-823.
5. Worsley R, Bell RJ, Gartoulla P, Davis SR. Prevalence and predictors of low sexual desire, sexually related personal distress, and hypoactive sexual desire dysfunction in a community-based sample of midlife women. J Sex Med 2017; 14: 675-686.
6. Zeleke BM, Bell RJ, Billah B, Davis SR. Hypoactive sexual desire dysfunction in community-dwelling older women. Menopause 2017; 24: 391-399.
7. Clayton AH, Goldfischer ER, Goldstein I, Derogatis L, Lewis-D'Agostino DJ, Pyke R. Validation of the decreased sexual desire screener (DSDS): a brief diagnostic instrument for generalized acquired female hypoactive sexual desire disorder (HSDD). J Sex Med 2009; 6: 730-738.
8. Skiba MA, Bell RJ, Islam RM, Handelsman DJ, Desai R, Davis SR. Androgens during the reproductive years: what is normal for women? J Clin Endocrinol Metab 2019; 104: 5382-5392.
9. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab 2005; 90: 3847-3853.
10. Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. Climacteric 2019; 22: 429-434.
11. 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; 7: 754-766.
12. Shifren J, Davis SR, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 study. Menopause 2006; 13: 770-779.
13. Wierman ME, Arlt W, Basson R, et al. Androgen therapy in women: a reappraisal: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99: 3489-3510.

COMPETING INTERESTS: Professor Davis is an NHMRC Senior Principal Research Fellow (Grant No. 1135843) and has been paid for developing and delivering educational presentations for Besins Healthcare, BioFemme and Pfizer Australia; has been on Advisory Boards for Theramex, Abbott Laboratories, Mayne Pharmaceuticals and Roche, and a consultant to Lawley Pharmaceuticals and Que Oncology; and has received institutional grant funding for Que Oncology research. Dr Balachandran: None.