Global consensus statement on testosterone therapy for women: an Australian perspective

There is more to female sexual function than circulating testosterone, and symptomatic women require a thorough clinical evaluation

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The 2019 global consensus position statement on the use of testosterone therapy for women[1] aims to provide guidance for clinicians managing women with female sexual dysfunction. The recommendations, graded according to levels of evidence, have been developed by an international taskforce with representatives from a range of organisations and societies, headed by Australian endocrinologist Professor Susan Davis, the current President of the International Menopause Society. The position statement bases many of its recommendations on a systematic review and meta-analysis of randomised controlled trials.[2]

The meta-analysis includes data from 36 randomised controlled trials with 8480 participants and includes studies with a testosterone treatment duration of at least 12 weeks. The primary outcome indicates an improvement in satisfying sexual events, measured as a mean increase of one event over 4 weeks with the use of testosterone. There were also improvements in other parameters associated with sexual function, including sexual desire, arousal and self-image. There were no cognitive, psychological, wellbeing or musculoskeletal (including bone mineral density) benefits. In doses that approximate physiological levels, the main adverse effects of testosterone therapy are significant increases in acne and hair growth but no difference in alopecia, clitoromegaly or voice change.

The position statement provides recommendations covering the assessment of women with female sexual dysfunction, laboratory measurement of testosterone, indications for treatment, and ongoing monitoring once treatment is commenced. It emphasises that the only evidence-based indication for the use of testosterone in women is the treatment of post-menopausal women who have been diagnosed with hypoactive sexual dysfunction disorder (HSDD) after formal biopsychosocial assessment. Doses that approximate physiological testosterone concentrations in pre-menopausal women are recommended. At these doses, testosterone therapy is not associated with serious adverse events. Notably there are no safety data for beyond 24 months of treatment. There are insufficient data regarding the use of testosterone therapy in pre-menopausal women. The position statement does not comment regarding women with premature ovarian insufficiency and recommends caution in women with a breast cancer diagnosis, reflecting the lack of data.[3,4]

The classification of female sexual disorders has been a source of controversy and debate. In the *Diagnostic and Statistical Manual of Mental Health Disorders, 5th Edition*, HSDD and female sexual arousal disorder (FSAD) have been amalgamated and classified as a single entity: female sexual interest/arousal disorder. The writing group for the position statement regards HSDD and FSAD to be distinct conditions, a view shared by experts in the field.[5,6] Diagnostic criteria for both conditions are outlined in Box 1.[7] It is important to understand this clinical distinction as the position statement does not consider FSAD to be an indication for testosterone therapy.

Serum testosterone levels decline during the reproductive years and are significantly reduced in women post-oophorectomy.[8] There was no reported correlation between androgen levels and reported sexual function in one study,[9] and there is no serum testosterone cut-off below which women are more likely to experience HSDD. The authors of the position statement comment that the relationship between endogenous androgen concentrations and sexual function remains uncertain because of issues related to androgen assays in some studies. Notwithstanding these factors, it is recommended that a baseline measurement of testosterone be taken to avoid overtreatment.[1] Serum total testosterone rather than free testosterone is the recommended biomarker. The significance of free testosterone in the context of female sexual dysfunction has not been evaluated. Most commercial assays in Australia use immunoassays to measure testosterone, while free testosterone and free androgen index are calculated from total testosterone and sex hormone-binding globulin. However, immunoassays are considered unreliable, particularly for low levels in the female reference range. Liquid and gas chromatography and mass spectrometry, while not yet in common use, are considered far more accurate and efforts are being made to increase availability.[10]

The position statement does not comment on whether menopausal hormone therapy should be used concurrently with testosterone therapy. However, a biopsychosocial model of treatment of female sexual dysfunction is recommended, which may include menopausal hormone therapy. Multiple studies have looked at the effect of oestrogen therapy alone, testosterone alone and a combination of the two on female sexual function, with variable outcomes. One of the main criticisms of studies demonstrating no improvement with oestrogen (alone or combined with testosterone) is that low therapeutic doses of oestrogen were used and circulating oestradiol levels were either not measured or were low and did not reach pre-ovulatory levels consistent with those seen in pre-menopausal women.[11] Only one of eight studies included in the meta-analysis did not include concomitant menopausal hormone therapy.[2] Systemic

1 Definition of hypoactive sexual desire disorder and female sexual arousal disorder[7]

Disorder	Definition
Hypoactive sexual desire disorder	Any of the following for a minimum of 6 months: • lack of motivation for sexual activity as manifest by reduced or absent spontaneous desire (sexual thoughts or fantasies); or reduced or absent responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity • loss of desire to initiate or participate in sexual activity, including behavioural responses such as avoidance of situations that could lead to sexual activity that is not secondary to sexual pain disorder AND is combined with clinically significant personal distress that includes frustration, grief, guilt, incompetence, loss, sadness, sorrow or worry
Female sexual arousal disorder*	
Female cognitive arousal disorder	Distressing difficulty or inability to attain or maintain adequate mental excitement associated with sexual activity as manifest by problems with feeling engaged, or mentally turned on or sexually aroused for a minimum of 6 months
Female genital arousal disorder	Distressing difficulty or inability to attain or maintain adequate genital response associated with sexual activity for a minimum of 6 months, including: • vulvovaginal lubrication • engorgement of the genitalia • sensitivity of the genitalia associated with sexual activity Disorders related to: • vascular injury or dysfunction, or • neurological injury or dysfunction

* Encompasses female cognitive arousal disorder and female genital arousal disorder ◆

oestrogen therapy is known to improve hot flushes, urogenital symptoms and mood disturbance, while topical vaginal oestrogen is effective in managing vulvovaginal atrophy.[12] Both improve wellbeing in menopausal women and may enhance libido such that other therapies are not required,[13] although an improvement in absolute terms has not been described. Our view is that menopausal hormone therapy with oestrogen with or without progestogen should be considered initially in all post-menopausal women who present with low libido before the initiation of testosterone.

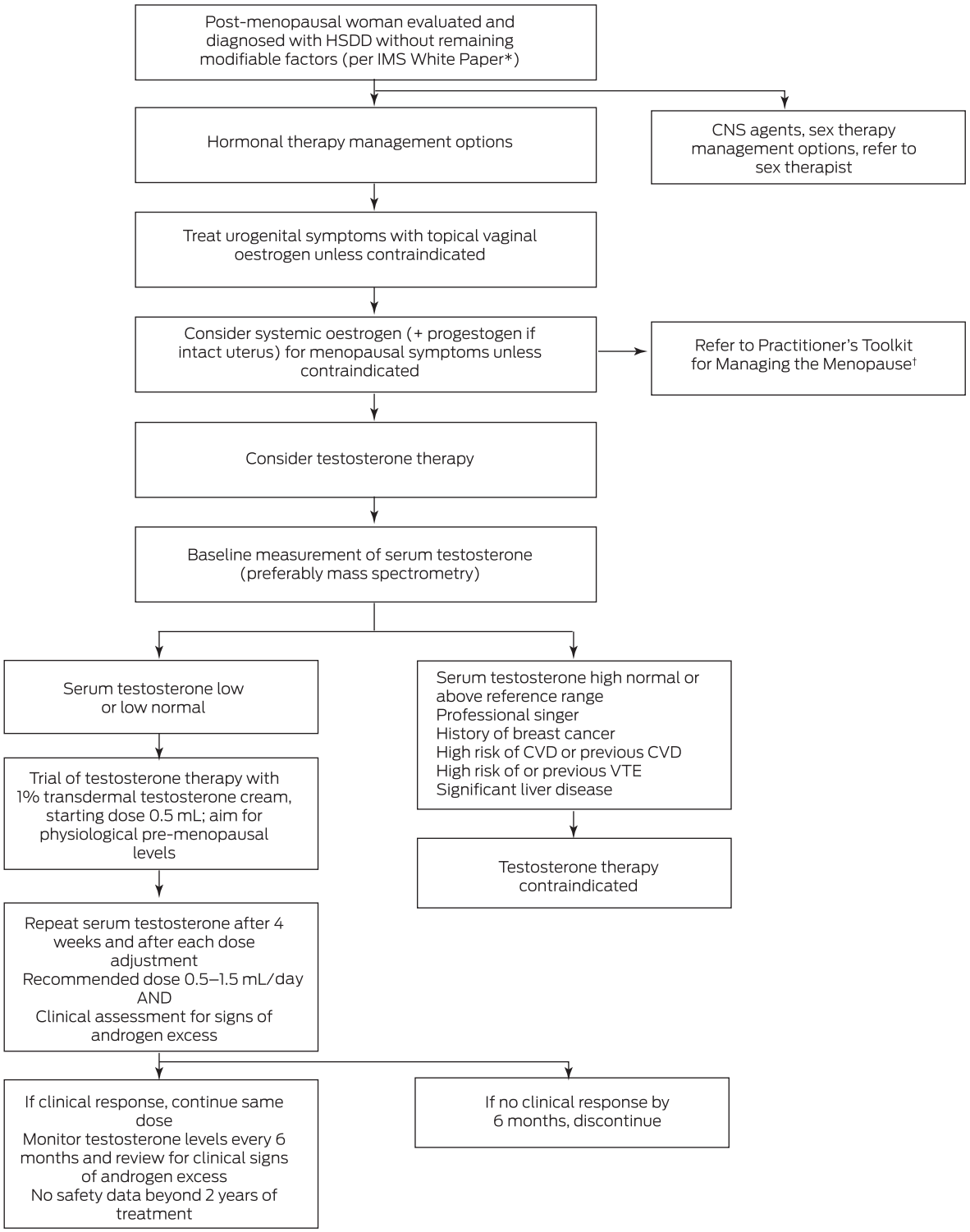
A significant issue is the clinical meaningfulness of the finding of a mean increase of one satisfying sexual event per month. Many will argue that such an outcome does not justify the use of testosterone therapy in clinical practice. In context, however, the meaningfulness will depend on the individual woman. For example, for a woman experiencing no satisfying sexual events, an extra one per month would equate to twelve extra events per year and could represent a significant improvement in her quality of life. Consumer involvement in the development of the position statement may have provided insight into this question. In the meta-analysis, testosterone therapy compared with placebo was found to reduce personal distress, a key component of HSDD, in all studies of post-menopausal women. Perhaps more relevant to the discussion is whether a satisfying sexual event is adequate as the primary measure of efficacy for treatment. The authors address this in the final part of the position statement. Appropriately, recommendations are made for the design of future clinical trials, including the development of a validated instrument for the screening and diagnosis of HSDD that can also be used as a marker of efficacy of treatment.

Australian perspective

Sexual dysfunction is common among Australian women. The prevalence of low sexual desire and HSDD was 69.3% and 32.2%, respectively, among a sample of community-based women aged 40–65 years in one study.[14] In older women, the prevalence of HSDD was reported to be one in seven women in a population of women aged 65–79 years living in the community.[15]

The use of testosterone for therapeutic purposes in women has been controversial. Despite this, clinicians in many countries including Australia have been prescribing testosterone off-label primarily for low sexual desire in women for several years.[16] Various formulations have been used, including subcutaneous pellets, transdermal gels and intramuscular injections that are designed for men, with dosing then adjusted for the female population. In this setting, there is greater potential for treatment to result in supraphysiological testosterone levels. The position statement suggests that "where approved female preparations are unavailable, off-label prescribing of an approved male formulation is reasonable".[1] Bio-identical and compounded products are not recommended. In Australia, a 1% transdermal testosterone cream is available, designed specifically for women and indicated for symptoms caused by testosterone deficiency. Although the product is unlicensed in Australia, it has been available on prescription from pharmacies within Western Australia since 1999 due to an exemption under section 6 of the *Therapeutic Goods Act 1989* (Cth). Women prescribed this treatment in other states are required to access it by mail order along with a prescription from their clinician. It was submitted for Therapeutic Goods Administration evaluation and inclusion

2 Testosterone therapy for post-menopausal women: proposed algorithm



CNS = central nervous system; CVD = cardiovascular disease; HSDD = hypoactive sexual desire disorder; IMS = International Menopause Society; VTE = venous thromboembolism. * Simon et al.[6] † Jane and Davis.[20] ◆

on the Australian Register of Therapeutic Goods as a registered product in 2019 for the proposed indication of treatment of hypoactive sexual desire dysfunction in post-menopausal women, and a response is expected by the end of 2020 (Michael Buckley, Medical Director, Lawley Pharmaceuticals, personal communications). Although limited by small sample sizes, pharmacokinetic and clinical studies of the recommended 5–10 mg daily dose of this cream demonstrated total and free testosterone levels within or above the pre-menopausal range.[17–19] Its availability in Australia overcomes the need to consider male preparations or compounded and bio-identical products.

The publication of the position statement will increase awareness of female sexual dysfunction in the medical community. Clinicians managing these patients will require education in practical terms about assessing such patients for HSDD and safely prescribing and monitoring testosterone therapy when indicated. Based on the authors' expertise and experience, we propose an algorithm for the assessment of women presenting with female sexual dysfunction and use of testosterone (Box 2), with women initially undergoing a biopsychosocial assessment.[6] We recommend information sheets for clinicians and patients written by local experts be made available on the websites of the Australasian Menopause Society, the Endocrine Society of Australia and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

Conclusion

The position statement is a timely addition to the literature regarding testosterone therapy for women. What is clear is that there is more to female sexual function than circulating testosterone and that symptomatic women require a thorough clinical evaluation, assessing for other factors which may be contributing to their presentation. Testosterone therapy is a small piece of the puzzle in the management of female sexual dysfunction. This position statement provides clarification regarding the indication, adverse effects and knowledge gaps. The availability in Australia of a transdermal testosterone preparation designed for women obviates the need to use male preparations, but further research regarding efficacy and safety is necessary. Future studies should address the safety of long term use of testosterone in women, particularly with respect to cardiovascular disease and breast cancer.

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