

Global Consensus Position Statement on the Use of Testosterone Therapy for Women

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Introduction

There are no clearly established indications for testosterone therapy for women. Nonetheless, clinicians have treated women with testosterone for decades, with the intention of alleviating a variety of symptoms, with uncertain benefits and risks. In most countries, testosterone therapy is prescribed off-label such that women are using either testosterone formulations approved for men with dose modification, or compounded therapies. Because of these issues, there is a compelling case for a global consensus Position Statement on testosterone therapy for women based on the available evidence from placebo/comparator randomized controlled trials (RCTs).

This Position Statement was developed, by consensus between the participating organizations, to inform health-

care professionals of the known benefits and potential risks of testosterone therapy for women. The aims were to provide clear guidance as to which women might benefit from testosterone therapy, to identify symptoms, signs, and conditions for which evidence does not support the prescribing of testosterone, to explore areas of uncertainty, and to identify any prescribing practices that have the potential to cause harm.

Methods

A Task Force of representatives of leading societies, whose international memberships include clinicians assessing and managing sex steroid therapy for women, was established. The Task Force agreed on the issues that needed to be

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addressed after which a systematic review and meta-analysis of the benefits and risks of testosterone therapy for women were conducted¹. The Task Force then met on 17th May 2019 in Berlin, Germany and drafted this consensus position statement.

Recommendations regarding the benefits and risks of testosterone therapy are based on findings from blinded placebo/comparator RCTs, of at least 12 weeks' duration for which data were available for inclusion in meta-analyses¹. The findings are reported with Levels of evidence and Grades of Recommendations². Clinical practice recommendations are agreed expert opinions of the panel. Through constructive discussion, unanimous consensus agreement was reached on all the Expert Opinion recommendations included here.

Recommendations

1. Measurement of testosterone, female sexual dysfunction and endogenous androgen levels

(1) Recommendations pertaining to the measurement of circulating testosterone in women

- (a) Testosterone may act directly via the androgen receptor (AR)/non-genomic androgenic action, or by reduction to the more potent androgen dihydrotestosterone (DHT) and/or aromatization to estradiol and their metabolites.
- (b) Testosterone concentrations decline during the reproductive years^{3,4} (Level IIB).
- (c) Testosterone concentrations appear to be maintained in women beyond the age of 65 years, but whether this confers a benefit is yet to be understood^{3,5} (Level IIB).
- (d) Total testosterone can be measured with high accuracy and reproducibility using liquid/gas chromatography and tandem mass spectrometry assays (LC/GC-MS/MS)⁶ (Grade B).
- (e) Direct assays for the measurement of total and free testosterone are highly unreliable in the female range^{6,7} (Grade A).
- (f) Reference laboratories should be 'harmonized' with biological standards in co-ordination with the Center for Disease Control⁸ (Expert Opinion).
- (g) Measurement of testosterone using direct assays in clinical practice is appropriate, if LC/GC-MS/MS is not available, to exclude high baseline concentrations and also to exclude supraphysiological concentrations during treatment (Expert Opinion).
- (h) Current research into testosterone physiology and clinical effects should mainly focus on measuring total testosterone as the main biomarker rather than 'free' testosterone, as evidence that 'free' testosterone is the biologically active testosterone fraction is lacking⁹ (Expert Opinion).

(2) Recommendations for the terminology for female sexual dysfunction (FSD)

- (a) Hypoactive sexual desire disorder/dysfunction (HSDD) and female sexual arousal disorder (FSAD) are distinct conditions which should be categorized separately

when considering the impact of androgens on their clinical presentation and response to treatment (Grade B).

- (b) While HSDD and FSAD overlap, they have distinct etiologies, risk factors, clinical features, and responses to psychological and biological interventions¹⁰ (Grade B).
- (c) Traditional specifiers, i.e. lifelong vs. acquired; generalized vs. situational, should be retained and utilized to further categorize and stratify treatments for HSDD and other female sexual disorders/dysfunctions¹⁰.
- (d) The diagnosis of HSDD in clinical practice should be based on thorough clinical assessment¹¹ guided by available diagnostic criteria such as ISSWSH^{12,13} or the International Classification of Diseases 11th Edition¹⁴ (Expert Opinion).

(3) Recommendations pertaining to the associations between endogenous androgen concentrations and female sexual function

- (a) The associations between endogenous androgen concentrations and sexual function in women remain uncertain due to issues relating to the sensitivity and specificity of androgen assays in some studies and insufficient data (Insufficient).
- (b) The physiology of androgens is complex due to their conversion in tissues and possible intracrine metabolism in multiple tissues (Insufficient).
- (c) No cut-off blood level can be used for any measured circulating androgen to differentiate women with and without sexual dysfunction¹⁵ (Grade C).

II. Recommendations regarding systemic testosterone therapy for postmenopausal women, in doses that approximate physiological testosterone concentrations for premenopausal women, based on findings from meta-analyses of placebo/comparator-controlled randomized clinical trials^{1,16}

There are insufficient data to make any recommendations regarding the use of testosterone in *premenopausal* women for treatment of sexual function or any other outcome (Insufficient).

(4) Recommendations regarding testosterone treatment of naturally or surgically postmenopausal women with HSDD, with/or without concurrent estrogen therapy

- (a) Testosterone therapy, in doses that approximate physiological testosterone concentrations for premenopausal women, exerts a beneficial effect on sexual function including increases, above the effects of placebo/comparator therapy, of an average of one satisfying sexual event per month, and increases in the subdomains of sexual desire, arousal, orgasmic function, pleasure and sexual responsiveness, together with a reduction in sexual concerns including sexual distress (Level I, Grade A).
- (b) As the majority of studies reporting on sexual function recruited women assessed as having HSDD or generalized FSD, the above recommendations cannot be

generalized to other subtypes of FSD or women without sexual dysfunction (Expert Opinion).

- (c) The recommendations of 4a do not apply to injectables, pellets or formulations that result in supraphysiological blood concentrations of testosterone, or compounded preparations (Expert Opinion).

(5) Recommendations regarding the effects of testosterone on wellbeing, mood and cognition in postmenopausal women

- (a) There is insufficient evidence to support the use of testosterone to enhance cognitive performance, or to delay cognitive decline, in postmenopausal women (Insufficient).
- (b) Available data show no effect of testosterone therapy on general wellbeing (Level I, Grade A).
- (c) Testosterone may improve wellbeing in premenopausal women but data are inconclusive (Level I, Grade B).
- (d) Available data do not show an effect of testosterone on depressed mood (Level I, Grade B).

(6) Recommendations regarding the musculoskeletal effects of testosterone

- (a) Few studies have evaluated the musculoskeletal effects of testosterone.
- (b) Of the studies that have reported musculoskeletal outcomes, the number of included participants has been small, all participants were taking concurrent estrogen therapy and no studies have been in women with osteoporosis.
- (c) The available data do not support an effect of testosterone treatment on bone mineral density at the spine, total hip or femoral neck at 12 months (Level I, Grade A).
- (d) No significant effect of testosterone administered in physiologic doses has been demonstrated on lean body mass, total body fat or muscle strength (Level I, Grade A).
- (e) There is a need for clinical trials to evaluate the impact of testosterone treatment on musculoskeletal tissues (Expert Opinion).

(7) Recommendations regarding possible androgenic side-effects of testosterone therapy

- (a) Systemic testosterone therapy for postmenopausal women, *in doses that approximate physiological testosterone concentrations for premenopausal women*, is associated with mild increases in acne and body/facial hair growth in some women, but not with alopecia, clitoromegaly or voice change (Level I, Grade A).

(8) Recommendations regarding testosterone therapy and cardiovascular health

- (a) Oral testosterone therapy is associated with adverse lipid profiles with negative effects on HDL-cholesterol

and LDL-cholesterol levels, and is not recommended (Level I, Grade A).

- (b) Studies of non-oral testosterone therapies (percutaneous and injectable), *in doses that approximate physiological testosterone concentrations for premenopausal women*, have shown no significant adverse effects on lipid profiles over the short term (Level I, Grade A).
- (c) Testosterone therapy has not been associated with increases in blood pressure, blood glucose or HbA1c levels (Level I, Grade A).
- (d) A non-significant trend for an increased risk of deep venous thrombosis (VTE) has been seen with testosterone therapy; however, the role of concurrent estrogen therapy in possible VTE risk cannot be excluded (Level I, Grade A).
- (e) Limited data preclude assessment of the effects of testosterone therapy on myocardial infarction or death (Insufficient data).
- (f) RCTs of testosterone therapy have excluded women at high cardiometabolic disease risk; most have included women taking concurrent estrogen therapy, and all have been of relatively short duration. Therefore, recommendations regarding the effect of physiologic doses of testosterone in postmenopausal women on cardiovascular health are not generalizable to a more 'at-risk' population or to long-term therapy.

(9) Recommendations regarding testosterone therapy and breast health

- (a) Testosterone therapy does not increase mammographic breast density (Level I, Grade A).
- (b) Available data suggest that short-term transdermal testosterone therapy does not impact breast cancer risk (Level I, Grade A).
- (c) Data from RCTs are insufficient to assess long-term breast cancer risk (Insufficient data).
- (d) There are no data to support the use of testosterone therapy to prevent breast cancer (Insufficient data).
- (e) Women with a prior diagnosis of breast cancer were excluded from the randomized trials for HSDD. Caution is recommended for testosterone use in women with hormone-sensitive breast cancer (Expert Opinion).

(10) Recommendations regarding testosterone therapy and serious adverse events

- (a) Testosterone therapy for postmenopausal women, *in doses that approximate physiological testosterone concentrations for premenopausal women*, is not associated with serious adverse events (Level I, Grade A).
- (b) As RCTs of testosterone therapy have excluded women at high cardiometabolic disease risk, and most have included women taking concurrent estrogen therapy, recommendation 10(a) is not generalizable to a more 'at-risk' population (Expert Opinion).
- (c) Safety data for testosterone in physiologic doses are not available beyond 24 months of treatment (Level I, Grade A).

III. Clinical care of postmenopausal women

(11) Recommendations regarding full assessment of FSD before commencing testosterone therapy

- (a) FSD including HSDD, FSAD and orgasmic disorder/dysfunction have multiple etiologies including biopsychosocial factors such as neuroendocrine imbalance, physical ill health or disease, interpersonal difficulties, psychological distress and sexually repressive cultural or religious values (Grade C).
- (b) Treatments should follow this biopsychosocial model and include pharmacologic options (hormone therapies and other pharmacologic agents), psychotherapy or multimodal treatments that combine both¹⁷ (Grade B).

(12) Recommendations regarding current testosterone therapy and postmenopausal women

- (a) The only evidence-based indication for the use of testosterone in women is for the treatment of postmenopausal women who have been diagnosed as having HSDD after formal biopsychosocial assessment (Level I, Grade A).
- (b) There is an unmet need for the provision and approval of testosterone treatments specific to women, formulated with the aim of approximating physiological testosterone concentrations for premenopausal women (Expert Opinion).
- (c) Where an appropriate approved female testosterone preparation is not available, off label, prescribing of an approved male formulation is reasonable, provided hormone concentrations are maintained in the physiologic female range (Expert Opinion).
- (d) Compounded 'bioidentical' testosterone therapy cannot be recommended for the treatment of HSDD, due to the lack of evidence for efficacy and safety, unless an authorized equivalent preparation is not available (Expert opinion). In the absence of an available approved product, if a compounded product is needed, the compounding pharmacy should be compliant with purity of Active Pharmaceutical Ingredients (API) and Good Manufacturing Practice (GMP) to meet industry standards for quality and safety. Dosing should be limited to achieving testosterone concentrations in the physiologic premenopausal range.
- (e) Use of any testosterone preparation that results in supraphysiologic concentrations of testosterone, including pellets and injections, is not recommended (Expert Opinion).
- (f) Should a trial of testosterone therapy be given for HSDD, a baseline total testosterone concentration should be measured before commencement, with a repeat level 3–6 weeks after treatment initiation (Level IIA, Grade C).
- (g) Patients should be monitored for their clinical response to treatment and assessed for signs of androgen excess with a serum total testosterone level every 6 months, to screen for overuse (Expert opinion).

- (h) If no benefit is experienced by 6 months, treatment should be ceased (Level IB, Grade C).

(13) Recommendations regarding other androgenic preparations

- (a) Systemic DHEA is not associated with significant improvement in libido or sexual function in postmenopausal women with normal adrenal function and cannot be recommended for women with HSDD¹⁸ (Level IA, Grade A).
- (b) In the absence of vulvovaginal atrophy, vaginal DHEA has not been tested and thus cannot be recommended for treatment of HSDD (Expert opinion).

(14) Recommendations regarding the design of future trials of physiologically dosed testosterone (Expert opinion for all)

- (a) More adequately powered, double-blind RCTs, without selection bias and with consistent reporting of standardized outcomes, are needed to comprehensively establish the benefits and risks of testosterone therapy for women.
- (b) For studies of testosterone and FSD:
 - (i) Relief of the distress associated with sexual dysfunction is a primary aim of FSD treatment.
 - (ii) Presently, no questionnaire covers all domains of female sexual function such that a combination of domains from different questionnaires should be used.
 - (iii) Satisfying sexual events should no longer be used as a primary efficacy measurement in clinical trials of women with FSD.
 - (iv) A set of clearly defined core outcomes needs to be established.
 - (v) There is a need for an instrument to assess sexual function with the following characteristics: general applicability; not disease-specific; high discriminant validity between women diagnosed with FSD and sexually functional women; validated, to measure FSD *per se* and as an instrument to screen for and diagnose FSD and demonstrating clinically meaningful response to intervention; cover different domains, with each domain comprising several items; translated and back-translated in a variety of languages; satisfies the most stringent assessment to gain approval by regulatory agencies.
- (c) There is a need for adequately powered RCTs of the effects of testosterone on the musculoskeletal health of women with normal bone mass, low bone mass, osteopenia/osteoporosis and sarcopenia, with outcomes including vertebral and total hip and femoral neck bone mineral density, trabecular bone score, serum biomarkers, fracture risk, body composition and muscle strength.
- (d) There is a need for adequately powered RCTs of the effects of testosterone on cognitive performance.

- (e) Studies must be undertaken to establish the longer-term cardiometabolic and breast safety of testosterone therapy for women.

Summary and key messages

The international panel concluded the only evidence-based indication for testosterone therapy for women is for the treatment of HSDD, with available data supporting a moderate therapeutic effect, in postmenopausal women. There are insufficient data to support the use of testosterone for the treatment of any other symptom or clinical condition, or for disease prevention.

Meta-analyses of the available data show no severe adverse events during physiological testosterone use, with the caveat that women at high cardiometabolic risk were excluded from study populations. The safety of long-term testosterone therapy has not been established.

It was considered of utmost importance that the diagnosis of HSDD involves a full clinical assessment and that other factors contributing to FSD must be identified and addressed before testosterone therapy is initiated^{10,11}. A blood total testosterone level should not be used to diagnose HSDD. Treatment should only be with formulations that achieve blood concentrations of testosterone that approximate premenopausal physiological concentrations. As no approved female product is presently approved by a national regulatory body, male formulations can be judiciously used in female doses and blood testosterone concentrations must be monitored regularly. The panel recommended against the use of compounded testosterone.

The panel highlighted the pressing need for more research into testosterone therapy for women and the development and licensing of products indicated specifically for women.

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Author contributions

Systematic review and meta-analysis of the literature, R.M. Islam and S.R. Davis; additional literature search, all co-authors; synthesis of information and draft statements, all co-authors; first manuscript draft, S.R. Davis, R. Baber, N. Panay; manuscript review, all co-authors.

Provenance and peer review: this is a global consensus position statement.

Conflict of interest

Dr Davis is a recipient of an NHMRC Partnership Grant (Grant no 1152778), NHMRC Senior Principal Research Fellow (Grant no 1135843), NHMRC Project Grant (Grant no 1105305), a National Breast Foundation: Accelerator Grant and the Grollo-Ruzzene Foundation. Dr Davis reports having received honoraria from Besins and Pfizer Australia and has been a consultant to Besins Healthcare, Mayne Pharmaceuticals, Lawley Pharmaceuticals and Que Oncology. She is an investigator for Que Oncology (money paid to her institution).

Dr Baber has received funding from Que Oncology for a clinical research trial. Dr Baber reports having received honoraria or consultation fees from Besins Pharmacology and Pfizer Australia for educational lectures and participated in speaker's bureaus for Besins Pharma and Pfizer.

Dr Bitzer reports having received honoraria or consultation fees from Bayer AG, Libbs, Gedeon Richter, Jenapharm, Ava, Natural Cycles, Exeltis, Theramex, Mithra, Effik, Merck and Mitsubishi. Dr Bitzer has participated in company-sponsored speaker's bureaus for Bayer AG, Libbs, Gedeon Richter, Jenapharm, Ava, Exeltis, Theramex and Effik.

Dr Kingsberg is a consultant who has participated in investigator or on scientific advisory boards for AMAG, Daré, Duchesney, Emotional Brain, Valeant, Endoceutics, IVIX, Palatin Technologies, Mitsubishi and has stock options with Viveve. Dr Kingsberg is in receipt of grants/research support from Endoceutics, Palatin, receives honoraria from the above listed and has participated in a company-sponsored speaker's bureau for TherapeuticsMD.

Dr Liu has received funding from AbbVie, AMAG, Femsys for clinical trials. Dr Liu also reports having received honoraria or consultation fees as a Consultant to Allergan, TherapeuticsMD, Ferring, Daré and Mitsubishi-Tanabe.

Dr Panay has received funding for the following: Abbot/Mylan (OPTIMISE study), Asarina (SEPRANOLONE study), Lawley Pharmaceuticals (T-BONE study), Pharm Olam/NeRe (SWITCH 1 study), PregLem (ESMYA study), Yes Company (REVIVE Me study). He has received honoraria or consultation fees from Abbott, Bayer, Besins, Glenmark, Kora, Meda, Mithra, MSD, Mylan, Novo Nordisk, Pfizer, SeCur and Shionogi. Dr Panay has participated in company-sponsored speaker's bureaus for Abbott, Bayer, Besins, Glenmark, Meda, MSD, Mylan, Novo Nordisk, Pfizer, Shionogi and Theramex.

Dr Parish reports having received honoraria or consultation fees for participating in Scientific Advisory Boards for Allergan, AMAG, Valeant, Duchesnay Pharmaceuticals and scientific consultancy for AMAG, Daré Bioscience, JDS Therapeutics, Strategic Science Technologies, Proctor and Gamble, and TherapeuticsMD. Dr Parish has participated in sponsored speaker's bureaus for AMAG Pharmaceuticals – two lectures, and Valeant Pharmaceuticals – two lectures. Dr Parish's partner is the recipient of a Valeant Pharmaceuticals unrestricted grant to develop HSDD educational materials.

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