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Androgen-based therapies in women

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Androgens play a key biological role in libido and sexual arousal in women, and knowledge about their complex role in other systems remains ambiguous and incomplete. This narrative review examines the role of endogenous androgens in women's health throughout the life span before focusing on evidence surrounding the use of androgen-based therapies to treat postmenopausal women. The role of testosterone as a therapeutic agent in women continues to attract controversy as approved preparations are rare, and use of off-label and compounded formulations is widespread. Despite this androgen therapy has been used for decades in oral, injectable, and transdermal formulations. Responses to androgen therapy have been demonstrated to improve aspects of female sexual dysfunction, notably hypoactive sexual desire disorder, in a dose related manner. Substantial research has also been conducted into the role of androgens in treating aspects of the genitourinary syndrome of menopause (GSM). Evidence for benefits beyond these is mixed and more research is required regarding long-term safety. However, It remains biologically plausible that androgens will be effective in treating hypoestrogenic symptoms related to menopause, either through direct physiological effects or following aromatization to estradiol throughout the body.

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Overview of androgens

The major circulating androgens in females are dehydroepiandrosterone (DHEA), its metabolite DHEA sulphate (DHEAS), androstenedione, testosterone, and dihydrotestosterone (DHT). DHEA, DHEAS and androstenedione are considered pro-hormones as they require conversion to testosterone to exert androgenic effects. DHEAS is produced almost exclusively by the adrenal glands and is peripherally converted to DHEA. Around half of DHEA production comes from the adrenal glands, 20% from the ovaries, and the remaining from the conversion of DHEAS. Androstenedione is equally produced by the adrenal glands and ovaries, and the peripheral conversion of this pro-hormone contributes about 50% of testosterone production. The remaining production of testosterone is equally derived from the adrenal glands and ovaries.

Testosterone has direct action via androgen receptors (AR). It also acts through its conversion to DHT via 5α-reductases 1 and 2 present in target cells, including skin, sweat glands, hair follicles and genital skin, and by aromatization to estradiol. Aromatase is present throughout the body including brain, bone, adipose tissue, skin, vasculature, vagina, breast and ovary [1].

The relative androgenic potency of DHEA, androstenedione, testosterone, and DHT are roughly 5:10:100:300, respectively [2]. Along with being the most potent, DHT has the highest affinity for the AR. Testosterone and DHT induce genomic effects by binding to intracellular AR, leading to DNA transcription of various genes, and nongenomic effects via membrane receptors and activation of various signalling pathways [3].

In women, only around 1% of testosterone is free or unbound. 66% is bound to sex hormone binding globulin (SHBG) and 33% weakly bound to albumin [4]. Very small amounts will also bind to cortisol binding globulin and orosomucoid. It has long been thought that the androgenic effects of testosterone relate mainly to the amount of free testosterone. The relatively small proportion of testosterone available to bind to the androgen receptor is a complex combination of free or unbound testosterone, a portion of testosterone weakly bound to albumin and that which is produced locally at the cellular level from its precursors [5].

The free fraction of testosterone is determined by the level of SHBG, and the balance between production and clearance [6]. Any increase in SHBG, and therefore the binding capacity of testosterone results in less free testosterone and less clearance into tissue. SHBG levels rise in response to oral estrogens and thyroid hormone, as well as other conditions including anorexia and liver disease. Androgens themselves lower SHBG and increase free circulating levels of multiple sex steroids [7].

Measurement of testosterone in women has been hampered by poor precision and low specificity when using radioimmunoassays [8]. Liquid or gas chromatography and tandem mass spectrometry assays tend to be more reliable and give reproducible results and are increasingly available. In general Total testosterone and SHBG levels should be measured [9].

Endogenous androgens in women prior to menopause

Adrenal androgen production increases in children around 6 years of age. This developmental stage, called adrenarche, is generally marked by a serum DHEAS concentration of 40 ug/dL, and ultimately stimulates pubarche, the appearance of pubic and axillary hair [10].

During puberty, cyclical ovarian testosterone production is seen with the onset of ovulation [6]. Androgen levels fluctuate within the menstrual cycle, with serum testosterone and androstenedione levels increasing after ovulation [11,12]. During the follicular phase, the adrenal precursors account for more than 60% of total testosterone production and half of DHT production. During midcycle, the ovarian contribution increases, and adrenal precursors account for 40% of testosterone production [2,6].

Peak levels of DHEAS are seen in women in their 20 s and decline progressively thereafter. Sulcova et al. measured DHEA and DHEAS in both sexes and saw a peak in females at age 24 years, a rapid decline until age 50 and moderate decline after 50 years [13]. In an Australian cross-sectional study of 588 women aged 18–39 years, all androgens were seen to decline with age before menopause [12]. Testosterone levels fell spontaneously by 25%, androstenedione by 31% and DHT by 36%, even when adjusting for BMI and cycle stage.

Endogenous androgens in women beyond menopause

After menopause, the principal steroid secreted by the ovary is androstenedione. Total androstenedione levels fall after menopause and most androstenedione production comes from the adrenal glands. Similarly, circulating levels of DHEA and DHEAS are less than that seen in young adult life [14–16].

In the early post-menopausal period, the ovary secretes more testosterone than in premenopausal years [12]. This is thought to be driven by the elevated gonadotrophins, particularly luteinizing hormones (LH) since treatment of postmenopausal women with GnRH agonists or antagonists results in a significant reduction in circulating testosterone levels [17]. Despite the increase in ovarian testosterone production, overall production is lower as there is less androstenedione available for peripheral conversion to testosterone.

Although testosterone levels in women decline in their 40 s these changes do not appear to be related to the menopause. Burger, et al. reported no change in testosterone levels in a longitudinal study of women 5 years prior to, and 7 years beyond their final menstrual period [16]. The free androgen levels in these women were in fact reported to be higher, along with reduced SHBG levels. Similarly, other longitudinal studies of women in perimenopause found relatively constant concentrations of testosterone, DHT, androstenedione, DHEA and DHEAS as the time from the last menses increased [18].

Declines in androgens are steepest in early reproductive life and tend to plateau at midlife. One cross-sectional study suggested a nadir in testosterone levels occurs around the age of 62 years, with a tendency for a very small increase in the later years [19].

The midlife decrease in ovarian estrogen production far exceeds the decrease in androgen production, and the postmenopausal ovary is primarily an androgen producing organ [20]. Ovarian androgen production reduces with time however, and eventually ceases altogether. Adrenal androgen production also declines with age, so that the DHEA level has decreased by 80–90% of peak production by the eighth or ninth decade of life, well beyond the age of menopause [2].

More recent data supports the tendency for a small increase in testosterone in later life, despite a steady decline in its primary precursor, DHEA [21]. A large cross-sectional study of 5300 women aged 70–95 years found an 11% increase in testosterone, with the median level being similar to that for healthy premenopausal women (0.38nmol/L [0.035–8.56]) [21]. The authors speculated the potential for testosterone being used as a marker of longevity, having a survival benefit or contributing to healthy ageing.

Actions and effects of androgens in women

Sexual function

Testosterone plays a key role in female sexual function but our understanding of the effects of androgens on female sexuality are far from complete and studies are conflicting [22].

Androgens are thought to affect sexual motivation and desire, and low testosterone levels have been correlated with sexual infrequency and reduced libido [7]. In a study of perimenopausal women aged 42–52 years not using any exogenous hormones, frequency of masturbation, sexual desire and arousal had a modest positive association with serum testosterone levels but there was no association with pain with intercourse or the ability to climax [23]. The authors concluded that the relationships between reproductive hormones and female sexual function are subtle and may be of limited clinical use [23]. In a cross-sectional study of more than 1000 women aged 18–75 years, Davis et al. found no association between low scores for any of the self-reported sexual domains evaluated and low serum total and free testosterone [24].

Androgen receptors are present in nearly every tissue of a woman's body making it prudent to review the effects of endogenous and exogenous androgens on other health aspects.

Breast

Testosterone appears to have anti-proliferative and pro-apoptotic effects in the breast. This is despite an abundance of aromatase and androgen receptors being present in breast cells. It is generally accepted that androgens counteract estrogen and inhibit thelarche in boys, and in girls with pathologically

elevated androgen levels [25]. Androgen excess due to adrenal tumour or hyperplasia suppresses normal breast development in girls, despite adequate estrogen levels. In addition, males may develop gynecomastia with an increase in the ratio of estrogen to androgens secondary to increased aromatization or low androgen production [25].

The relationship between testosterone and breast cancer remains unclear. ARs are abundant in most breast cancer specimens and cell lines [25]. Studies looking at testosterone use for up to 24 months have not shown an increased risk of breast cancer amongst participants. Long term data is lacking.

Women with polycystic ovarian syndrome (PCOS) who have a higher endogenous androgen levels do not have an increased incidence of breast cancer [26]. Similarly, transgender men using exogenous testosterone therapy do not appear to have more breast cancers. Testosterone therapy does not appear to cause an increase in mammographic breast density [27].

There has long been interest in androgens being used in the treatment of breast cancer. Some studies suggest that AR expression may be a favourable prognostic factor, and that it's mechanism of action may alter according to estrogen receptor (ER) tumour status [28,29]. AR is expressed in 90% of ER^+ tumours, and only 20–30% of ER^- tumours. Nevertheless, understanding is far from complete, and epidemiological data and clinical studies are conflicting. The Global Consensus Position Statement on the Use of Testosterone Therapy for Women advises there is not data to support the use of testosterone to prevent breast cancer [27].

Endometrium

The endometrium is an androgen target tissue with ample AR expression. Testosterone is anti-proliferative to the endometrium, and evidence supports that local activation and conversion of androgens is essential for endometrial competence during the establishment of pregnancy [30].

In transgender males using high doses of testosterone for an average of 3 years prior to hysterectomy, endometrial sampling showed inactive endometrium with no evidence of endometrial proliferation [31]. In fact, atrophic endometrium was the likely cause of bleeding in a study of postmenopausal women using testosterone alone for 12 months. In this double-blind, placebo-controlled trial the testosterone group experienced more bleeding than the placebo group (10.6% compared to 2.6%). No cases of endometrial hyperplasia or cancer were diagnosed [32].

Cardiovascular health

Testosterone acts predominantly on the vascular smooth muscle and vascular endothelium in a dose dependent manner. At physiological levels, testosterone promotes vasorelaxation through stimulating nitric oxide production and action on potassium and calcium channels [3]. Extremes of endogenous testosterone however are associated with detrimental cardiovascular effects.

Low testosterone levels have unfavourable cardiovascular outcomes in men, including associations with abdominal obesity, metabolic syndrome, type 2 diabetes, increased inflammatory markers and dyslipidaemia [33]. There is some evidence to suggest that this is also the case in women, with a large prospective cohort study of 2914 women aged 18–75 years (mean age 58) revealing that lower testosterone was associated with all-cause mortality and cardiovascular events with 4.5-year follow-up [34].

Supraphysiological testosterone levels promote vasoconstriction and may be associated with adverse cardiovascular health [9,35]. A prospective, population-based study of postmenopausal women [36] suggested a U-shaped association between bioavailable testosterone and incident coronary heart disease [35].

Prospective RCTs have illustrated no adverse cardiovascular events in women using testosterone therapy when levels remain within normal physiological range [36,37]. At these levels, oral and transdermal testosterone therapy have not been associated with adverse effects on glycaemic markers, blood pressure, body mass index, haematocrit, coagulation factors or C-reactive protein [27,38]. Oral therapy however is associated with adverse lipid profiles and is not recommended [27]. Transdermal preparations appear to have a more favourable effect on lipid profile, with no increase in low-density lipoprotein (LDL) and a reduction in triglycerides. A nonsignificant trend towards venous thromboembolism has been noted in studies, but this effect is thought to be due to concurrent estrogen use [1,27].

Interestingly, elderly women with stable chronic heart failure who received testosterone therapy had improved exercise capacity, insulin resistance and muscle strength compared to those randomised to placebo [39].

Experimental evidence for potential beneficial or adverse effects of exogenous testosterone therapy on the cardiovascular system in women is rather limited, with most studies being of limited duration (< 2 years) and excluding women at high risk of cardiovascular disease [3,9]. Therefore recommendations regarding the effects of physiological doses in postmenopausal women are not necessarily generalizable to women at risk of cardiovascular disease or to longer term therapy [27]. Nonetheless, there is no evidence that testosterone, when being used to treat HSDD, is associated with adverse cardiovascular effects with some data suggesting benefit [6,8,38].

Bone

Androgen receptors are present in growth plate cartilage cells, and in bone cells. They are found on osteoblasts and osteocytes, and many studies have shown that androgens upregulate AR osteoblast expression [40]. Androgens have also been found to promote osteoclast apoptosis in-vitro.

Gonadal, adrenal and exogenous androgens all have effects on bone via the AR, but it is their indirect effects via aromatization to estradiol that probably has a greater effect in the maintenance of skeletal health [40].

Androgens have been found to help prevent osteoporosis and bone loss in ageing men, but aromatisation to estrogens appears to provide the greatest effect [40]. In menstruating, perimenopausal and postmenopausal women, low endogenous androgen levels have been associated with low bone mass [41,42]. Antiandrogen treatment in young women with androgen excess was also associated with a reduction in BMD [43].

Higher levels of endogenous testosterone in postmenopausal women are associated with a lower risk of hip fracture, independent of SHBG, estradiol concentration and other putative risk factors [44]. Small studies exist to show that testosterone therapy in this population improves BMD. In a double-blind, prospective study, when combined with sublingual micronized hormone replacement therapy, 12 months of testosterone therapy was associated with a significant increase in hip BMD, but not spine [45].

There is a paucity of trial evidence on the effect of testosterone therapy on fracture risk, and of the studies that do exist, participants were taking concurrent estrogen therapy. No studies have been conducted in women with osteoporosis. A systematic review and meta-analysis of trials reported no benefit of testosterone regimens on BMD when compared to testosterone-free regimens. The Global Consensus Position Statement on the Use of Testosterone Therapy for Women states that data does not support an effect of testosterone treatment on BMD at 12 months [27].

Cognition and mood

AR are found throughout the central nervous system, and androgens are through to have neuroprotective and anti-inflammatory effects throughout the brain. Androgens promote neuron viability during development and following injury or toxicity and promote neuron survival in vulnerable areas such as the hippocampus and cortical brain regions [46]. Testosterone may also help to regulate β-amyloid protein accumulation in the brain [46].

Data on the effects of exogenous testosterone on various domains of cognition are limited by small numbers and often concurrent estrogen use, and findings are mixed. Significant improvements in verbal learning and memory were seen in postmenopausal women who took testosterone therapy alone for 26 weeks compared to placebo, but no difference was seen in general wellbeing [47]. Small observational studies have reported higher endogenous testosterone levels in postmenopausal women to be associated with better verbal fluency and memory scores [8,48].

In a 16-week trial of 61 postmenopausal women using transdermal oestrogen and daily testosterone gel, half were randomized to 2.5 mg letrozole daily and half to placebo. No difference in cognitive outcomes were found between those that received the aromatase inhibitor or placebo [49]. There were significant improvements in all participants for visual and verbal memory and simple concentration,

Box 1
Conditions that may represent androgen deficiency syndromes in women.

▪ Ovarian insufficiency	Premature ovarian insufficiency, bilateral oophorectomy, chemotherapy, radiotherapy
▪ Primary adrenal insufficiency	Autoimmune, adrenal, congenital adrenal hyperplasia, drug-induced, other metabolic disorders
▪ Hypopituitarism	Primary or secondary; particularly with corticotropin and gonadotropin deficiencies
▪ Anorexia nervosa	Associated with low free and total testosterone
▪ Medications	Corticosteroids, combined oral contraceptive pills, Depo-Provera, anti-androgenic agents, oral estrogen, opioids

with testosterone therapy, but not for attention, working memory, psychomotor speed, or executive function [49].

Available evidence does not show an effect of testosterone therapy on anxiety or depressed mood, and there is insufficient evidence to suggest use for enhancing cognitive performance or delaying cognitive decline [27].

The effects of low levels of androgens in women

There is no defined syndrome of androgen deficiency in females with no consensus as to the biochemical or clinical criteria that may be diagnostic [7,24]. Androgen levels decline during reproductive years, and probably plateau or even increase slightly in later life. Low levels are not necessarily abnormal, and it remains unclear whether they are even associated with abnormalities in mood, sexual function, or other outcomes considered secondary to androgen deficiency [50].

Nevertheless, Testosterone therapy, particularly in postmenopausal women has been used to treat a range of symptoms including sexual dysfunction, chronic fatigue, dysphoric mood, and a general diminished sense of well-being [51]. Clinical trial evidence suggests that androgen replacement in women may result in improvement in libido, hypoactive sexual desire disorder and wellbeing [7].

Some of this evidence comes from testosterone replacement given to women with surgical menopause post oophorectomy, where androgen levels are generally lower than in women experiencing a natural menopause [52,53].

Conditions associated with androgen deficiency are listed in Box 1.

Androgen therapy in women

Indications

The principal androgen treatment used in women is testosterone. The only evidence-based indication for testosterone therapy in women is to treat hypoactive sexual desire disorder (HSDD) after menopause. The 2019 Global Consensus Position Statement on the use of testosterone therapy for women reported that available data supports a moderate therapeutic effect of systemic transdermal testosterone for this indication only and is recommended only in doses that approximate physiological testosterone concentrations for premenopausal women [27]. HSDD is detailed below.

Despite evidence of therapeutic benefit, no testosterone formulation for women has been approved for use in most countries, the exception being Australia where a 1% testosterone cream was approved for use in women in 2021. This has not impeded widespread use of testosterone with clinicians prescribing therapy off-label to women who are using either dose-adjusted approved male formulations or compounded therapies [6].

There is no consensus regarding the use of any form of DHEA in women at menopause although a low dose DHEA vaginal preparation is approved in the US and Canada for the treatment of moderate to severe dyspareunia in menopausal women [54].

Hypoactive sexual desire disorder

Hypoactive sexual desire disorder (HSDD is defined as a marked reduction in desire or motivation to engage in sexual activity, which has occurred episodically or persistently over a period of at least several months and is associated with clinically significant distress [55]. Before the diagnosis can be made a thorough biopsychosocial assessment must be made [55]. Clinical history should include a validated screening questionnaire such as the Decreased Sexual Desire Screening Questionnaire [56]. Physical examination is not commonly required, and serum levels of testosterone and SHBG are not useful as there is no lower limit to define HSDD [57].

HSDD is not limited to postmenopausal women and is seen at all reproductive ages. It is a relatively common but underdiagnosed condition affecting approximately 12.3% of women aged 45–64 years and 7.4% over 65 [58,59]. Prevalence is significantly higher however in surgically induced menopausal women (16–26%) than age-matched premenopausal women (7–14%) although this difference does not persist in women aged 50–70 [60,61].

Evidence suggests that testosterone improves sexual function in women with HSDD when given in doses that approximate physiological testosterone concentrations for premenopausal women [27]. Treatment with testosterone should be considered a trial as there is no way to predict who will benefit. If no improvement is seen after the first six months therapy should be ceased. Recommendations are that baseline serum total testosterone and SHBG levels are measured prior to commencing therapy and repeated at 3–6 weeks. Concentrations should be monitored 6 monthly throughout use, to ensure supraphysiological levels are not reached [27].

Studies show that improvements in symptoms of HSDD take some time. In doses which achieve or approximate physiological levels of total testosterone in serum, improvements in total satisfying sexual activity, sexual desire and reduction in distress begin at 4 weeks and peak at around 12 weeks [19]. With continued use the effects appear to be sustained. Ongoing review 6–12 monthly is advised. Monitoring should include blood levels, and assessment of clinical response to treatment and signs of androgen excess [27].

Systemic DHEA does not result in improvement in sexual function versus placebo and cannot be recommended for women with HSDD [27,62].

Genitourinary syndrome of menopause

Genitourinary syndrome of menopause (GSM) affects up to 84% of postmenopausal women [54]. It describes the multiple changes occurring in the external genitalia, pelvic floor tissues, bladder, and urethra secondary to the hypoestrogenic state of menopause. It may include symptoms of dryness, burning, and irritation, sexual symptoms of lack of lubrication, discomfort or pain, and impaired function, and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections [63].

Over the counter, non-hormonal vaginal lubricants and moisturisers may alleviate symptoms of GSM however data for effectiveness is sparse. Systemic and local vaginal estrogen are effective in managing urogenital symptoms and vulvovaginal atrophy [64,65]. Vaginal oestrogen is considered first-line therapy in women choosing hormone treatment when GSM is their main symptom. Its safety is well-established and usually results in minimal systemic absorption [66]. A history of hormone dependent malignancy is not considered an absolute contra-indication to some forms of vaginal estrogen therapy [53].

Androgen receptors are abundant in all layers of the vagina, smooth muscle (vaginal, urethral and bladder) and vascular endothelium in both pre and postmenopausal women although one study reported a decline in AR expression with age [9,67]. Testosterone administration appeared to increased expression of the AR gene in both the vaginal mucosa and stroma and also the volume of urethrovaginal tissue [67,68].

Testosterone therapy in women

The sole evidence-based indication for the use of testosterone therapy in women is for the treatment of diagnosed HSDD [27]. Testosterone preparations should be delivered in doses that will approximate

premenopauusal testosterone concentrations, and do not apply to injectables, pellets, compunded preparations, or other formulations that result in supraphysiological blood testosterone concentrations [27].

There is no blood level of testosterone that is a treatment goal for therapy and serum concentrations do not predict treatment efficacy [22].

The widespread use of male testosterone formulations where female products are not approved or available additionally highlights the need to monitor, to ensure appropriate physiological dosing and minimise unwanted adverse effects [27].

Transdermal patches and topical gels or creams are advised, and oral products avoided because of undesirable first-pass hepatic effects documented with oral formulations [69]. Transdermal application via a patch delivers testosterone continuously by passive diffusion, whereas gels create a drug depot within the outer layers of the skin, and testosterone is absorbed at the dermal capillaries [70]. Very little 5α-reductase and aromatase activity occurs in non-genital skin, therefore there is little metabolism to DHT or estradiol. This, along with absent, or at the very least reduced, hepatic first-pass effects, mitigates the adverse effects that non-topical testosterone administration may have on SHBG, thyroid binding globulin and cholesterol levels [70].

Vaginal testosterone cream, although not approved for use for any indication in women, has limited data supporting treatment of GSM symptoms [54].

Transdermal testosterone

The US FDA has previously evaluated gel and patch testosterone products but approval was declined based on lack of efficacy over placebo and safety concerns [22]. A testosterone patch was approved for use by the European Medicines Agency in 2006 for the treatment of HSDD in women who have had oophorectomy and were already taking oestrogen replacement but was withdrawn for commercial reasons in 2012 [22].

Several studies have evaluated the efficacy and short-term safety of transdermal testosterone therapy in women using doses designed to produce levels of testosterone approximating physiological premenopausal levels in women. Shifren and colleagues randomized 483 naturally menopausal women with HSDD already taking oral oestrogen + /- progestin, to receive a testosterone or placebo patch for 24 weeks [71]. Testosterone treatment was associated with increased frequency of satisfying sexual activity and sexual desire and decreased personal distress. Simon et al. treated surgically menopausal women receiving estrogen therapy with transdermal testosterone for 24 weeks [72] A significant increase in satisfactory sexual encounters was reported in the treatment arm compared to placebo whilst 30% of women reported, mostly mild, application site reactions with 5% discontinuing study participation due to the reaction.

Davis et al. evaluated transdermal testosterone therapy in postmenopausal women with HSDD, not using estrogen replacement therapy. This randomised controlled trial (RCT) of 814 women reported a modest improvement in sexual function at 24 weeks in those who received a 300 μg per day testosterone patch, but not in the 150 μg patch group, when compared with placebo [32]. Both groups receiving testosterone had significant increases in scores for sexual desire and decreases in scores for personal distress, and treatment effect did not differ between those that had natural versus surgically induced menopause. Application site reaction occurred in over 50% of women in this study, with approximately 6% withdrawing due to this adverse event.

A recent review of trials evaluating the effectiveness of testosterone in women with HSDD reported that transdermal therapy improved the frequency of satisfying sexual events, arousal, orgasm frequency, pleasure, responsiveness, and self-image, and reduced sexual concerns [38]. This confirms the findings of a previous systematic review and meta-analysis on the same topic [61]. These studies reported few adverse outcomes and were reassuring regarding short-term safety [61].

Longer term safety has also been evaluated, but evidence remains inconclusive. With up to 4 years use of the 300 μg per day transdermal testosterone patch, Nachtigall et al. in a study of 900 surgically menopausal women aged 20–70 receiving estrogen replacement therapy, reported no clinically significant changes in serum chemistry, haematology, lipid profile, carbohydrate metabolism, renal and liver function, or coagulation parameters, or serious adverse outcomes or withdrawals from adverse

outcomes. Three cases of invasive breast cancer were observed within the 900 participants, consistent with population background rates of breast cancer [73].

Short-term data describes no increased risk of breast cancer in postmenopausal women using transdermal testosterone for up to 2 years [27].

Expert opinion declares there is an unmet need for the provision and approval of testosterone therapy for use in women [27]. Topical compounded testosterone cream, ointment or gel is used widely due to the lack of an approved transdermal preparation in many countries. Caution should be used when prescribing a compounded testosterone therapy. Limitations of these formulations include the inconsistency of testosterone concentration in the product, and variability in absorption and bioavailability, in a largely unregulated industry.

Oral testosterone

Many older studies that demonstrate beneficial effects of testosterone in postmenopausal women involved supraphysiological doses of oral testosterone with estrogen. Use of oral formulations is limited by adverse events associated with first pass metabolism including decreasing high-density lipoprotein (HDL) and increasing LDL concentrations [38,74]. On the other hand, oral therapy lowers triglycerides.

A combined oral estrogen and testosterone product is available in the USA, containing either 1.25 mg or 0.625 mg of esterified estrogens and either 2.5 mg or 1.25 mg of methyltestosterone. The labelled indication for use is for the treatment of moderate to severe vasomotor symptoms associated with menopause not improved by estrogens alone. It has not received pre-market approval by the FDA.

Studies examining benefit of combines estrogen and testosterone therapy (ET) over estrogen alone are few and results are inconsistent [75].

Similarly, safety data regarding breast cancer risk is mixed. Mammographic breast density has not been shown to increase with short-term transdermal testosterone treatment [27,38]. Short-term data describes no increased risk of breast cancer in postmenopausal women using transdermal testosterone for up to 2 years [27].

Analysis of data from the Nurses' Health Study reported that women with natural menopause using ET therapy had a 2.5 times higher risk of breast cancer compared with never users of hormone therapy [76]. Women's Health Initiative Observational Study data illustrated a modest non-significant elevation in invasive breast cancer among women using ET compared to no-hormone users, after adjustment for confounding variables [77] Risk appeared to be greater for short term than long term users suggesting that risk was not strongly related to combined hormone use.

There are mixed findings on the effect that ET has on BMD, when compared to estrogen alone. In an RCT of 311 postmenopausal women, improved hip and spine density was seen after 2 years of use, [78] whilst another found no statistically significant difference in BMD at the hip or lumbar spine over estrogen alone [79]. This study also reported a significant reduction in HDL cholesterol, triglycerides, and total cholesterol in the ET group.

Testosterone implants

Injectable or implantable testosterone preparations, available for use in male hypogonadism, should be avoided as they expose women to supraphysiological dosing which may be prolonged [27].

However, there is a long history of subcutaneous testosterone use for the treatment of hormone deficiency in women, and compelling data exists from groups that support its use. Glaser et al. reported on data from 1300 female patients who received 16,000 testosterone pellet implants over a 7-year period. The average starting dose was 2 mg/kg. a dose determined by the clinicians based on a need for adequate symptom control [5]. Androgenic side effects were reported to be the only adverse side effect and clinicians claimed many patients prefer the clinical benefits of a higher testosterone level, choosing to treat the androgenic side effects. No control group was available.

The same group published a 10-year prospective cohort study of 407 pre- and post-menopausal women receiving subcutaneous testosterone implants, with or without anastrozole. The vast majority did not receive concurrent estrogen + /- progestogen therapy. Findings demonstrated a significantly lower incidence of invasive breast cancer when compared to age-matched peers [80]. Enrolled

participants had initially presented with symptoms of androgen deficiency, and with levels of breast cancer risk like population levels.

Testosterone pellets show considerable interindividual variation in absorption and degradation and may remain effective for from 4 to 12 months. Confirmation of a return to normal serum testosterone levels before reimplantation is recommended [8]. Androgenic side effects of testosterone therapy are largely dose related and when supraphysiological testosterone levels are being used, patients should be made aware of these risks.

Vaginal testosterone

Limited data exists for the use of vaginal testosterone cream for the treatment of HSDD or GSM, and globally, it is not approved for any indication in women. It has been used for various vulvovaginal conditions in premenopausal and menopausal women, including lichen sclerosis and vestibulodynia, but limited efficacy data exists [54].

Small studies have reported improvements in multiple domains of sexual function with the use of vaginal testosterone for up to 12 weeks. In a randomised controlled trial of 75 postmenopausal women, 0.625 mg vaginal conjugated equine estrogen plus 0.5 g 2% testosterone resulted in greater improvement in sexuality scores when compared to oestrogen alone. Serum testosterone levels were in the normal physiological range [81]. A study of 300 ug vaginal testosterone propionate compared to 0.625 mg conjugated estrogen cream polyacrylic lubricant or placebo revealed significant improvements in sexual desire, lubrication, satisfaction, and reduced dyspareunia amongst the testosterone users [82].

Safety of vaginal testosterone cream was evaluated in women with early stage breast cancer who were taking an aromatase inhibitor [83]. Patients were randomized 1:1 to receive either 0.5 g of 1% testosterone cream intravaginally or a 2 mg vaginal estrogen ring, and outcomes included oestradiol levels, adverse events, and sexual quality of life. More women in the testosterone group had transient elevations in oestradiol levels, but results were difficult to interpret due to elevated oestradiol levels at baseline, raising questions surrounding aromatase inhibitor efficacy and compliance. Total testosterone levels in the vaginal testosterone group were significantly elevated when compared to baseline for the duration of the 12-week trial and were elevated outside of the normal postmenopausal range (mean 171 ng/dL, median 67 ng/dL at 12 weeks). Improvements were seen in sexual desire and symptoms of GSM in both groups, whilst only the vaginal ring improved sexual satisfaction [83].

A similar study evaluated the effect of 300 μg or 150 μg compounded testosterone propionate on vaginal atrophy in 20 postmenopausal women with a history of breast cancer who were taking aromatase inhibitors [84]. All women had moderate to severe symptoms of vaginal atrophy at baseline, and all showed improvement after 28 days of testosterone use, at both treatment doses. A small but significant clinical improvement persisted at 1 month after treatment. Importantly, estradiol levels remained low after therapy for both groups, and there was no significant difference between the dosing groups [84].

In healthy premenopausal women, a single vaginal dose of 2 mg testosterone propionate induced a significant rise in serum testosterone levels, but no increase in oestradiol levels [85]. The rise was seen within 6 h of administration, reached supraphysiological levels, and was not associated with an effect on the genital or subjective sexual response in participants [85].

Overall, available evidence of a role for testosterone vaginal cream is limited by small sample sizes and lack of power. The available data justifies further studies to investigate appropriate dosage, delivery, effectiveness and short and long-term safety of vaginal testosterone for symptomatic postmenopausal women, with or without breast cancer.

DHEA therapy

DHEA is widely available worldwide as a dietary supplement or compounded by prescription. Because of its role as a prohormone in the biosynthesis of steroid hormones, it has been proposed as a hormone replacement therapy.

Suggestions are that DHEA may yield benefits mediated by oestrogen, including improvements in vasomotor symptoms, and testosterone, including increased libido and wellbeing [62]. Wider claims

exist for a role in improving immune response, bone health and cognitive outcomes with ageing, but data are conflicting [86].

An approved vaginal DHEA is available in the US for the treatment of moderate to severe dyspareunia in menopausal women, and otherwise compounded formulations are readily accessible. Similarly, oral compounded preparations are widely available, but none approved or recommended for use in the treatment of HSDD or symptoms of menopause [27].

Vaginal DHEA

The 2019 Global Consensus Position Statement on the Use of Testosterone Therapy for Women advises that vaginal DHEA is an effective treatment for women with dyspareunia associated with GSM but should not be used for women without this symptom [27]. The only approved androgen therapy for use in women is a vaginal DHEA cream (Prasterone) approved for use in the USA and Canada [54]. Use of Prasterone is associated with slight increases in circulating levels of DHEA, testosterone and estrone which, nevertheless, remain within normal postmenopausal values [87].

Studies have shown that vaginal DHEA improves vaginal cell maturation, dyspareunia, and sexual function, lowers pH, and may increase local nerve density [88,89]. Improvements have also been reported with use up to 52 weeks in symptoms of dyspareunia, dryness and irritation or itching [90].

The 2022 care pathway from the European Menopause and Andropause Society on menopause, wellbeing and health advises that women with vulvovaginal atrophy be treated with low-dose vaginal estrogen or vaginal DHEA [91].

One study of 482 postmenopausal women with moderate to severe dyspareunia reported improvements in the Female Sexual Function Index (FSFI) in the Prasterone group after 12 weeks therapy [92]. Vaginal discharge was reported in around 6% of participants and was the most common adverse effect.

Endometrial safety has been demonstrated for this duration of use also. Biopsies of 422 women receiving vaginal DHEA all showed inactive or atrophic endometrium after 52 weeks of use [93].

The mechanism of action of vaginal DHEA likely relates to its intracrine action and function as a prohormone of androgens and estrogens [94]. DHEA is converted to androstenedione and testosterone which can undergo aromatisation within the vaginal mucosal cells to estrone and oestradiol [88]. It will therefore have agonistic action at the estrogen and androgen receptors of the vagina.

The small elevations in serum oestrogen seen in women using Prasterone may raise some concern, especially when used in those with a history of an oestrogen responsive malignancy. In a randomized controlled trial of postmenopausal women with a history of breast or gynaecologic cancer, who had completed primary treatment, had no evidence of disease, and reported at least moderate vaginal symptoms, there was improvement in dryness or dyspareunia with use of 3.25 mg DHEA, 6.5 mg DHEA and plain vaginal moisturiser [95]. No significantly greater improvement was seen between groups although the higher dose DHEA group reported significantly better sexual function. Serum DHEAS and testosterone were significantly increased in the vaginal DHEA groups in a dose dependent manner, and oestradiol was slightly higher in the 6.5 mg DHEA group, but not the lower dose group [96].

The well-established effectiveness and availability of vaginal estrogens for GSM ensure that vaginal DHEA remains a second line option. Although Prasterone has been shown to be effective, its efficacy has not been compared directly with vaginal estrogen. Moreover, Prasterone requires daily dosing compared to the usual recommendation of twice weekly application of vaginal oestrogen, a factor which probably affects compliance.

Oral DHEA

DHEA is widely available in many countries as a dietary supplement, despite not being found in any food. It is proposed to have several potential benefits on mood, cognition, inflammation and sexual function, and even sprouted as an anti-ageing tonic [96]. Much of the available evidence suggests the contrary, however [62,97].

Oral DHEA has been evaluated for its effect in treating HSDD in postmenopausal women. Large RCT data of sufficient duration demonstrates no benefit for the treatment of menopausal symptoms or sexual dysfunction in postmenopausal women with intact adrenal function [97]. Multiple reviews of the

Box 2
Summary of the main safety aspects to consider.

▪ Androgenic side effects	▪ Women treated at doses that approximate physiological testosterone concentrations for premenopausal women may report acne or body hair growth, but not hirsutism ▪ No evidence that testosterone across studies resulted in alopecia, clitoromegaly, voice change ▪ No increase in drop out due to androgenic effects. More placebo women dropped out
▪ Cardiometabolic effects	▪ Overall, there is a trend for oral androgens to reduce HDL cholesterol (testosterone and DHEA) ▪ Recommend not to use oral testosterone in women (and men) ▪ Transdermal and injectable testosterone showed no adverse effects on lipid profiles over the short term, up to 2 years, in doses that approximate physiological testosterone concentrations for premenopausal women, and no change in any other metabolic effect
▪ Breast effects	▪ Testosterone therapy does not increase mammographic breast density ▪ Short-term transdermal testosterone does not impact breast cancer risk ▪ Data from RCTs are insufficient to assess long-term breast cancer risk; but there was no increase in breast cancer risk in observational studies ▪ Testosterone implants should not be used to prevent breast cancer
▪ Endometrial effects	▪ No evidence that testosterone increases the risk of endometrial hyperplasia or malignancy
▪ Overall serious adverse events	▪ In doses that approximate physiological concentrations for premenopausal women, testosterone is not associated with serious adverse events

literature on this topic have concluded that the evidence does not support a benefit of oral DHEA therapy for postmenopausal women [62,98].

The 2014 Endocrine Society's Clinical Practice Guideline on the use of androgens in women, clearly recommends against the generalised use of DHEA for women because the indications are inadequate, and evidence of efficacy and long-term safety data are lacking [50].

Safety of androgen therapy in women

Safety data for the use of testosterone therapy in doses that approximate physiological concentrations for premenopausal women is largely reassuring, certainly for short-term use. Islam et al. published a comprehensive systematic review and meta-analysis on the safety and efficacy of testosterone for women in 2019, and this preceding the internationally endorsed Global Consensus Position Statement on the Use of Testosterone Therapy for Women published in the same year [27,38]. Together these two pivotal publications summarize the available high quality evidence and provide clear recommendations based on the evidence and expert opinion for the safe use of androgens in women. Box 2 summarises the main safety aspects to consider in women using androgen therapy.

Conclusion

Androgen therapy has been widely used for decades in women, largely without adequate regulatory body approval and poor availability of regulated preparations. Suspicion about its effectiveness and safety are likely compounding by these factors, despite clear benefits shown in treating various symptoms and disorders associated with menopause.

Prescription of hormone therapy in women at all life stages requires shared decision making, and commencing androgen therapy should employ the same principle. Women with HSDD should be offered an approved female transdermal testosterone therapy where it is available after appropriate biopsychosocial assessment.

There is an obvious unmet need for more good quality long term research and availability of appropriate approved female androgen formulations.

Practice points

- The only evidence-based indication for testosterone therapy in women is to treat HSDD in postmenopausal women.
- Testosterone therapy is associated with improvement in symptoms of HSDD in a dose-related manner.
- Testosterone preparations should be delivered at doses that will approximate premenopauusal testosterone concentrations in women.
- Use of male testosterone formulations must be done with caution and only when an approved female formulation is not available.
- Serum testosterone concentration must be regularly monitored in women using any form of testosterone therapy to ensure supraphysiological levels are not reached and avoid unwanted side effects.
- Transdermal testosterone is considered the safest form of testosterone therapy.
- Before androgen therapy is considered, a full biopsychosocial assessment of general and sexual health should be conducted.

Research agenda

- Research into the long-term safety of androgen therapy for women is required.
- Trials are needed to determine the efficacy of vaginal testosterone for the treatment of GSM in women.
- Large-scale RCTs are needed to explore other possible roles for androgen therapy in women including cardiovascular, bone, and mental health.
- Development and approval of testosterone preparations, specifically for use by women, are needed.

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