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Testosterone therapy in women: a review

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Female sexual dysfunction is a complex problem with multiple overlapping etiologies. Androgens play an important role in healthy female sexual function, especially in stimulating sexual interest and in maintaining desire. There are a multitude of reasons why women can have low androgen levels with the most common reasons being age, oophorectomy and the use of oral estrogens. Symptoms of androgen insufficiency include absent or greatly diminished sexual motivation and/or desire, that is, libido, persistent unexplainable fatigue or lack of energy, and a lack of sense of well being. Although there is no androgen preparation that has been specifically approved by the FDA for the treatment of Women's Sexual Interest/Desire Disorder or for the treatment of androgen insufficiency in women, androgen therapy has been used off-label to treat low libido and sexual dysfunction in women for over 40 y. Most clinical trials in postmenopausal women with loss of libido have demonstrated that the addition of testosterone to estrogen significantly improved multiple facets of sexual functioning including libido and sexual desire, arousal, frequency and satisfaction. In controlled clinical trials of up to 2 y duration of testosterone therapy, women receiving androgen therapy tolerated androgen administration well and demonstrated no serious side effects. The results of these trials suggest that testosterone therapy in the low-dose regimens is efficacious for the treatment of Women's Sexual Interest and Desire Disorder in postmenopausal women who are adequately estrogenized. Based on the evidence of current studies, it is reasonable to consider testosterone therapy for a symptomatic androgen-deficient woman with Women's Sexual Interest and Desire Disorder.
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Introduction

According to the National Health and Social Life Survey, approximately 43% of women have experienced sexual dysfunction, most commonly a lack of interest in sex, that is, lack of libido, which was present at some time in 32% of the women surveyed. This low sexual desire was associated with low feelings of physical and emotional satisfaction and low feelings of general happiness toward their partners.[1]

Hypoactive sexual desire disorder (HSDD) refers to a persistent or recurring deficiency or absence of sexual fantasies or thoughts and desire for or receptivity to sexual activity that causes personal distress according to DSM-IV.[2] Recently, it has been recommended that the definition be broadened and be termed Women's Sexual Interest/Desire Disorder.[3] It is defined as the lack of or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies, and a lack of responsive desire. Motivations for attempting to become sexually aroused are scarce or absent and the lack of interest is considered to be beyond a normative lessening with life cycle and relationship duration.[4]

Hormonal modulators of libido

A woman's libido is determined by environmental, emotional, cultural and hormonal factors. Based on animal data, the preoptic area of the brain is presumed to be involved in the initiation of sexual activity and mating behavior.[5] Androgen receptors

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have been identified in this area and in the hypothalamus.[6,7] Effects of testosterone on the brain are mediated both directly via androgen receptors and indirectly via the aromatization of testosterone to estrogen.

Androgens play an important role in healthy female sexual function, especially in stimulating libido and sexual interest and in maintaining desire.[8] There have been a number of studies that have shown a correlation between testosterone levels and sexuality of women.[9–12]

Additionally, studies in women who have undergone bilateral oophorectomy and experience an approximately 50% drop in testosterone levels have shown that these women experienced a decrease in libido and sexual activity as compared with women who underwent hysterectomy, but had their ovaries preserved. The differences were especially apparent in women who were premenopausal at the time of the procedure.[13]

Testosterone might also have additional direct effects on the genitalia in women. Testosterone receptors have also been identified on vulvar epithelium, vaginal mucosa, submucosa, stroma, smooth muscle and vascular endothelium, with the greatest degree of expression in vaginal submucosa. A negative correlation existed between age and androgen receptor density.[14,15] The function of these receptors is unknown, although they may be involved in vaginal smooth muscle relaxation. It is also unknown whether nitric oxide synthetase activity in the clitoris is under testosterone regulation as it is in the cavernosal smooth muscle in the penis.

Other hormones involved in the sexual response cycle include estrogens, progestins and prolactin.[16] Libido is inhibited by progestins and high levels of prolactin. Estrogen is essential for the maintenance of urogenital health. A decline in serum estrogen levels results in thinning of vaginal mucosal epithelium and atrophy of vaginal wall smooth muscle. Decreased estrogen levels also result in a less acidic environment in the vaginal canal, as well as a decrease in vaginal secretions. These changes can predispose women to increase frequency of vaginal infections, urinary tract infections, incontinence and dyparunia.[17]

Androgen biosynthesis in women

There are five main androgens or androgen precursors in women as follows: testosterone, dihydrotestosterone, androstenedione (A), dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEA-S). Testosterone can be produced by the ovaries, adrenal gland and peripheral tissue such as adipose, muscle and skin. In premenopausal women, approximately 25% of testosterone comes from the ovaries; 25% from the adrenals and 50% is the result of local production from androgen precursors produced by the adrenals and ovaries. This ratio changes after menopause (as long as ovaries are retained), so that 50% is produced by the ovaries, 10% from the adrenal glands and 40% is converted from A, DHEA or DHEA-S. As some tissues have the ability to produce testosterone locally, serum levels of testosterone may not accurately reflect the true androgen status of a patient.

Hormones travel through the body either in the free form or bound to carrier proteins such as sex hormone binding globulin (SHBG) or albumin. SHBG has a high affinity and binds tightly to testosterone, effectively preventing the SHBG-bound testosterone from being biologically active. SHBG levels are an important factor in androgen status as they determine the level of free testosterone. Bioavailable testosterone includes the fraction of testosterone that is unbound (ie free) and the fraction that is bound to albumin, the latter being able to dissociate from the albumin easily to enter cells.

Changes to androgen status with age, menopause and medications

Age, menopausal status and medications can highly impact androgen synthesis, bioavailability and clearance. Since SHBG levels are critical in determining free testosterone levels, factors affecting SHBG levels are important to consider as these factors may be less apparent causes of low free or bioavailable testosterone levels.

Normal aging has the greatest impact on androgen levels in women. Women in their 40's have been found to have half the testosterone level as women in their 20's.[18] Additionally, a large prospective trial of over 3000 women demonstrated a 26% decline in mean testosterone levels between the ages of 42 and 50 y old, but the majority of this drop in androgen occurred in the early 40's.[19] Another longitudinal study, of women 45–55 y old, found that during the menopausal transition there was no reduction in serum testosterone levels from 4 y before to 2 y after the FMP.[20] Thus, the decline in serum testosterone levels during the menopausal years reflects an age-related decline rather than the menopausal transition *per se*.

The acute drop in estrogen levels postoophorectomy in premenopausal women is commonly acknowledged. Less frequently appreciated is the significant decline in plasma testosterone in this same population. Judd and co-workers[21] demonstrated that testosterone levels decreased by 50% or more in both pre- and postmenopausal patients

undergoing bilateral oophorectomy. Similar findings were reported by Hughes *et al*.[22] The Rancho Bernando Study reported that bioavailable testosterone levels were 40–50% lower in elderly postmenopausal women who had had oophorectomies compared to their counterparts who had intact ovaries.[23]

Additionally, oral estrogen replacement therapy can also have a significant impact on free androgen levels. Oral estrogens lead to an increase in SHBG, which binds testosterone, and decreases the amount of free or bioavailable testosterone. A daily dose of 0.15 mg of conjugated equine estrogens is sufficient to increase the SHBG levels.[24] On the other hand, transdermal estrogens does not raise serum SHBG levels nor lower free testosterone levels as it does not undergo hepatic first pass effect.[25]

SHBG levels can increase with advancing age, pregnancy, cirrhosis and anorexia nervosa.[23] The menopausal transition lowers SHBG levels, presumably through lowered estrogen levels.[20] Medications that can increase SHBG levels include oral estrogens such as those found in oral contraceptives and menopausal hormone therapy, excess thyroid hormone and certain antiepileptic drugs. Any increase in SHBG levels can lead to a decrease in the free and bioavailable fractions of testosterone.

Progestins can also affect androgen levels. In premenopausal women, medroxyprogesterone acetate decreases the production rate and increases the metabolic clearance rate of testosterone, leading to lower serum concentration of testosterone.[21]

There are a multitude of reasons why women can have low androgen levels. Table 1 is a list of conditions associated with a decline in androgen levels in women.

Table 1 Potential causes of low androgen levels in women

Age-related decline
Premature ovarian failure
Iatrogenic menopause
Owing to chemotherapy
Owing to radiation therapy to the pelvis
Owing to bilateral oophorectomy
Conditions causing rise in SHBG
Age
Pregnancy
Oral estrogen therapy
Antiepileptic drugs
Anorexia nervosa
Cirrhosis
Hyperthyroidism
Treatment with glucocorticoids
Hypopituitarism
Addison's disease

Androgen insufficiency syndrome: signs, symptoms and diagnosis

Symptoms of androgen insufficiency include absent or greatly diminished sexual motivation and/or desire, that is, libido, persistent unexplainable fatigue or lack of energy, and a lack of sense of well being.[26] Signs of androgen insufficiency include thinning or loss of pubic hair, decreased lean body mass, and osteopenia or osteoporosis.[26] Owing to the impact that low androgen levels can have on libido, androgen insufficiency is an important cause of low desire. A consensus conference concluded that it is reasonable to consider a woman to have androgen insufficiency if she:[27]

a. has signs and symptoms consistent with this syndrome;
b. she is adequately estrogenized (as estrogen effects are also strongly linked to well being and sexual function);
c. free testosterone or free androgen index are at or below the lowest quartile of the normal range of reproductive women;
d. other potential etiologies of these symptoms have been excluded. Such problems include major life stressors including relationship issues, thyroid disease, major metabolic or nutritional disorders (such as iron or Vitamin D deficiency), other causes of chronic fatigue (Lyme disease, chronic fatigue syndrome) and psychiatric disorders (eg major depression); and
e. consideration is made to identify a specific etiologic factor in the development of androgen insufficiency (such as oophorectomy, adrenal disease, hypothalamic or pituitary dysfunction, medications, etc).

Many clinicians have argued that there is no need to measure testosterone levels to make a presumptive diagnosis of androgen insufficiency for several reasons: First, most commercial assays for the measurement of total and free testosterone levels were developed to measure the much higher circulating concentrations in men; thus, these assays lack the sensitivity and precision required to measure the low levels prevalent in androgen-deficient women.[28] Second, there is a lack of normative data of normal testosterone ranges in women, and there are no epidemiological studies that have shown a difference in carefully measured free testosterone levels between women with normal sexual function and those with HSDD when matched for age, menopausal status and other factors.[28] Evaluation of androgen status is further complicated by peripheral androgen biosynthesis primarily from adrenal androgen precursors, which allows for local androgen production and action without a rise in serum androgen levels. Owing to

these limitations, it is reasonable to give a therapeutic trial of androgens to women who exhibit the symptoms and signs of androgen insufficiency in an appropriate clinical setting. However, before initiating therapy, other possible causes of the symptoms of androgen insufficiency should be considered and evaluated. These include evaluation of thyroid function, iron deficiency and hyperprolactinemia. The measurement of SHBG levels in women taking oral estrogen therapy may be also be beneficial to evaluate the effects of oral estrogen on hormonal status. If SHBG levels are elevated in women taking oral estrogen therapy, consideration should be made to switching to transdermal estrogen to lower SHBG levels and increase free testosterone concentrations.[29]

Testosterone therapy for sexual dysfunction in women

The first randomized, double-blind, placebo-controlled trial of the effects of testosterone therapy for the treatment of low libido came in 1950 when Greenblat *et al*[30] reported an improvement in libido and well being in women treated with methyltestosterone (MT). Since that time there have been a number of studies looking at the effects of testosterone for the treatment of low libido and sexual function. A summary of these trials can be seen in Table 2. The majority of the trials have looked at the treatment of sexual dysfunction in menopausal women. Many of the trials followed women who had already been on estrogen therapy, but all the trials had women on concurrent estrogen therapy.

Most of these trials demonstrated that the addition of testosterone to estrogen significantly improved multiple facets of sexual functioning including libido and sexual desire,[29–31,34–36,38,41–43] arousal,[31,36,37,42–44] frequency[36–38,42,46] and satisfaction[39] in postmenopausal women. Testosterone therapy was even effective in patients who were not seeking treatment for libido problems to improve their libido and well being in one trial,[39] although another study did not show significant benefit of the use of oral testosterone on measures of sexual function, possibly because most of the patients enrolled did not consider themselves to have a sexual dysfunction at the start of the study.[40] In women with high normal initial SHBG, correlations were observed with changes in parameters of sexual function score and an increase in bioavailable testosterone through a lowering of SHBG levels.[29,32,35,37] Additionally, several of the trials demonstrated that the addition of androgens improved sense of well being and other 'psychological factors'.[30,38,42,43,46] In the one trial of premenopausal women, testosterone therapy was also found to be effective in improving sexual desire, arousal and satisfaction.[33]

Administration of testosterone

There is no androgen preparation that has been specifically approved by the FDA for the treatment of Women's Sexual Interest/Desire Disorder or for the treatment of androgen insufficiency in women, although androgen therapy has been used off-label to treat low libido and sexual dysfunction in women for over 40 y.[47] There are multiple means of administering testosterone with the most common being oral pills (MT and testosterone undecanoate); subcutaneous pellets; intramuscular injection; transdermal patches, gels, creams and sprays; and sublingual drops.

The only FDA-approved androgen for women is a product composed of MT combined with esterified estrogen (EE) in doses of either 1.25 mg MT/0.625 mg EE or 2.5 mg MT/1.25 mg EE (Estratest HS and Estratest, Solvay Pharmaceuticals, Marietta, GA), and it is only approved for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients whose symptoms did not improve by estrogens alone. MT has been used in postmenopausal women since the 1930s, although today the doses of testosterone used in treating women are only 1–20% of the oral doses used in the 1940s and 1950s.[29] MT is as biologically potent as testosterone, and likely exerts its action in part by reducing both the production of SHBG and the androgen binding capacity of SHBG. A potential disadvantage of oral MT is that it undergoes hepatic first pass metabolism and thus has the potential to induce hepatotoxicity. Since testosterone assays do not crossreact with MT, the measured serum testosterone levels will continue to reflect only the endogenous testosterone production.[40]

An oral testosterone that avoids hepatic first pass metabolism is testosterone undecanoate, an ester with a long-chain fatty acid linked to testosterone. It was initially developed to overcome the low oral bioavailability and hepatic side effects of oral testosterone preparations. It is mainly absorbed by intestinal lymphatics rather than into the portal vessels, thereby avoiding hepatic first pass metabolism.[37]

Injectable preparations of testosterone (cypionate, propionate and enanthate in doses of 25–50 mg) have the benefit of having a slower metabolism, thus requiring less frequent dosing (every 2–4 weeks), but have the disadvantage extreme peaks and troughs in testosterone levels and patient discomfort in getting an injection.

Pellet implants not only have the slow metabolism, which results in elevated testosterone levels for up to 6 months, but they also have the benefit of providing stable testosterone levels during this period of time.

Three new formulations, the testosterone transdermal matrix patch, testosterone gel and testoster-

Table 2 Review of clinical trials of androgen therapy (adapted from Braunstein and Cameron[48] and Cameron and Braunstein[61])

Trial	*Population* (n)	*Therapy/mode of administration*	*Rx duration*	*Effect*	*Study design*
Simon *et al*[31]	SMP only (562)	Placebo *vs* 300 μg T patch	6 mo	↑satisfying sexual activity ↑desire ↑arousal ↑orgasm ↑pleasure ↑responsiveness ↓personal distress	Parallel Double-blind RCT
Goldsmith *et al*[32]	Not reported (323)	CEE (0.625–1.25 mg) *vs* CEE (0.625–1.25 mg)/MT (1.25–2.5 mg)	Not reported	↑sexual interest	Parallel Double-blind RCT
Goldstat *et al*[33]	Premenopausal (31)	Placebo *vs* 10 mg of 1% testosterone cream daily	3 mo	↑sexual interest ↑activity ↑satisfaction ↑pleasure ↑fantasy ↑orgasm	Crossover Double-blind RCT
Braunstein *et al*[34]	SMP only (447)	Placebo *vs* 150 μg T patch *vs* 300 μg T patch *vs* 450 μg T patch	6 mo	↑total satisfying sexual events *1 ↑desire *1	Parallel Double-blind RCT
Lobo *et al*[35]	NMP and SMP (218)	CEE 0.625 *vs* CEE 0.625/1.25 MT	4 mo	↑desire ↑responsiveness	Parallel Double-blind RCT
Davis *et al*[36]	SMP Only (77)	Placebo *vs* 300 μg T patch	6 mo	↑sexual desire ↑frequency ↑orgasm ↑sexual arousal ↑sexual responsiveness ↑sexual self-image ↓distress	Parallel Double-blind RCT
Floter *et al*[37]	SMP only (44)	Placebo *vs* E valerate 2 mg *vs* E valerate 2 mg/T undeconate 40 mg	6 mo	↑lubrication ↑interest in sex ↑sexual thoughts and fantasies (both groups for all of above) ↑arousal ↑orgasm ↑frequency of sex ↓dysparunia	Crossover Double-blind RCT
Shifren *et al*[38]	SMP only (75)	Placebo *vs* 150 μg T patch *vs* 300 μg T patch	3 mo	↑sexual function *1 ↑sexual desire *1 ↑frequency of sexual *1 ↑activity *1 ↑orgasm *1	Crossover Double-blind RCT
Sarrel *et al*[29]	SMP and NMP (20)	CEE 1.25 *vs* CEE 1.25/MT 2.5	2 mo	↑sexual sensation ↑sexual desire ↑sensation No change: vaginal moisture and pain rates of sexual fantasy	Placebo lead in: parallel double-blind RCT
Tuiten *et al*[12]	Premenopausal women with hypothalamic secondary amenorrhea (16)	Placebo *vs* 40 mg testosterone undecanoate	2 mo	↑genital vasocongestion No difference: sexual fantasy sexual excitement lust	Crossover Double-blind RCT
Davis *et al*[39]	SMP and NMP (32)	E2 50 mg pellet *vs* E2 50 mg/T 50 mg pellet	2 yr	↑activity ↑satisfaction ↑pleasure ↑orgasm ↑relevancy	Parallel Single-blind trial
Myers *et al*[40]	SMP and NMP (40)	Placebo *vs* CEE 0.625 mg *vs* CEE 0.625/MPA 5 mg *vs* CEE 0.625/MT 5 mg *vs* MT 5 mg	2 mo	↑masturbation ↑orgasm with masturbation -No difference: -pleasure from intercourse -dysparunia -sexual desire	Parallel Double-blind RCT

Table 2 Review of clinical trials of androgen therapy (adapted from Braunstein and Cameron[48] and Cameron and Braunstein[61])

Trial	*Population* (n)	*Therapy/mode of administration*	*Rx duration*	*Effect*	*Study design*
Burger *et al*[41]	SMP and NMP (20)	E2 40 mg pellet *vs* E 40 mg/T 50 mg pellet	6 mo	↑libido ↑enjoyment	Single blind Randomized
Sherwin and Gelfand[42]	SMP only (44)	Placebo *vs* i.m. E2 *vs* i.m. E2/T	2 yr	↑sexual desire *2 ↑sexual fantasy *2 ↑sexual arousal *2 ↑orgasm *2 ↑sexual activity *2	Parallel Nonrandomized Controlled trial
Sherwin *et al*[43] and Sherwin and Gelfand[44]	SMP only (53)	Control hysterectomy *vs* placebo *vs* E 10 mg *vs* E 8.5 mg/T 150 mg i.m. *vs* T 150 mg i.m.	3 mo	↑desire *3 ↑fantasty *3 ↑arousal *3↑well being *3 ↑energy level *3 ↑sexual appetite *3	Crossover RCT
Burger *et al*[45]	SMP and NMP (17)	E 40 mg/T 100 mg pellet	6 mo	↑libido ↑enjoyment of sex	Open study
Dow and Hart[46]	SMP and NMP (40)	E 50 mg pellet *vs* E 50 mg/T 100 mg pellet	4 mo	↑orgasm frequency (at 2 mo in low dysparunia pts. only) ↑'psychological factors' (in low dysparunia pts. only)	Parallel Double-blind RCT
Greenblatt *et al*[30]	Peri- and postmenopausal women (102)	Placebo vs DES 0.25 mg t.i.d. *vs* DES 0.25 mg/MT 5 mg t.i.d. *vs* MT 5 mg t.i.d.	10 mo	↑libido	Crossover

E = estrogen; CEE = conjugated equine estrogen; DES = diethylstilbestrol; E2 = estradiol; T = testosterone; MT = methyltestosterone; MPA = medroxyprogesterone acetate; i.m. = intramuscular; t.i.d. = three times daily; ↑ = increased/improved; ↓ = decreased; SMP = surgical menopause; NMP = natural menopause; nl = physiological; >nl = supraphysiological; FAI = free androgen index; mo = months; yr = years.
*: Both CEE and CEE/MT had equal benefit.
*1: With 300 μg dose only.
*2: Compared to placebo and E only; significant in first 3 weeks of injection, but not in week 4.
*3: In T group *vs* both placebo and E alone.

one spray are now undergoing clinical trials in women. Benefits of these delivery systems are that they provide consistent and stable testosterone levels, and are easy to administer. Topical 2% testosterone cream or gel made by compounding pharmacies are popular therapies. However, there are no published data on pharmacokinetic parameters, safety or efficacy of these compounded preparations.

Adverse effects of testosterone

Concern about the potential adverse effects of testosterone has stemmed from effects observed from the use of very high doses of androgens in men and the misuse of anabolic steroids to enhance athletic performance in women, and the use of pharmacological doses to treat medical conditions such as breast cancer.[48] The side effects observed from these studies include hirsutism, acne, deepening of the voice, alopecia, hepatic injury, polycythemia, sleep apnea and weight gain. However, in controlled trials of up to 2 y duration of testosterone therapy, women who receive substantially lower doses of androgens for replacement therapy, whether testosterone was administered as a pill, cream, implant or patch, tolerated androgen administration well and demonstrated none of the serious side effects noted above. The most common adverse reactions were minor androgenic skin effects such as acne and hirsutism, which women could use to monitor therapy.[33,35,37–39,49,50]

Virilization of a female fetus is a theoretical risk if used in reproductive age women, although the placental aromatase system should aromatize the testosterone to estrogens. However, if a nonaromatizable androgen is used, premenopausal women need to be on effective contraception.

Effects on lipids, BMI and other CVD risk factors

One of the potential side effects of testosterone therapy is the potential to lower HDL levels through an effect on the liver. Trials with oral MT have shown a reduction in HDL, with a reduction or no change in LDL levels.[35,49,50] However, the HDL reduction has not been observed with nonoral forms of T administration including T pellets, intramus-

cular or transdermal testosterone.[38,39,41] Long-term cardiovascular effects of testosterone therapy are not known, although studies in women have shown a decline in plasma viscosity, no alterations in coagulation factors, and enhanced endothelial-dependent and -independent vasodilation.[51,52]

Effects on breast tissue

Given the recent controversy of the effects of postmenopausal hormone therapy on the risks of breast cancer, brought to light by the publication of the Women's Health Initiative, one of the main concerns is the potential effects of androgen therapy on breast cancer risk. Epidemiological studies of androgen levels in breast cancer patients have produced conflicting results, with some demonstrating an increased risk of breast cancer in those with low androgen levels and other trials demonstrating an increased risk of breast cancer in those with high androgen (as well as high estrogen) levels.[53]

Although none of the trials on androgen therapy in women with sexual dysfunction were of long enough duration or sufficiently powered to evaluate risk of breast cancer, data from retrospective studies and animal and laboratory data suggest that androgens actually may have a protective effect on breast tissue.[54]

Indeed, androgens such as testosterone propionate, fluoxymesterone and calusterone were used in the past as adjuvant therapy for breast cancer, and had comparable efficacy to other types of endocrine manipulation. Furthermore, a higher response rate and longer time to disease progression was observed when androgens were added to antiestrogen therapies such as tamoxifen.[54] About 20–50% of pre- and postmenopausal women with breast cancer develop tumor regression with androgen therapy. Breast cancer cells have androgen receptors and androgenic stimulation of these receptors in several cell lines suppresses estrogen receptor content and inhibits breast cancer cell growth. Thus, naturally occurring androgens might constitute a direct inhibitory control of mammary cancer cell growth.[55]

Other data supporting this theory include data showing that suppression of androgens in men is associated with breast growth, and mutations of androgen receptor in men are associated with breast cancer development.[56] Furthermore, female athletes and transsexuals taking high-dose androgen supplements show atrophy of mammary gland epithelial tissue. Animal data demonstrate that androgen blockade results in increase in mammary epithelial proliferation, and that treatment with physiological doses of testosterone in addition to standard estrogen therapy in oophorectomized monkeys completely attenuates the estrogen-induced increases in mammary epithelial proliferation.[56]

A recent systematic review of 508 patients treated with estrogen/progestin/testosterone (EPT) therapy in one clinician's practice in South Australia between 1987 and 1999 found that the rates of breast cancer in this population were lower than that found in the three largest trials on EPT and comparable to national averages of women who did not take hormones.[57]

However, as there are no randomized controlled trials (RCT) and as testosterone potentially can be aromatized to estrogen in target tissues, the use of testosterone in women with a history of estrogen-sensitive breast cancer should be discouraged at this time.

Endometrial cancer

Clinical studies on the effects of testosterone therapy on the endometrium are lacking. *In vitro* studies suggest that androgens have an inhibitory or neutral effect on endometrial growth. A study by Tuckerman *et al* of endometrial epithelial cells from normal cycling women treated with four different types of androgens (testosterone, dihydrotestosterone, A, and DHEA) demonstrated that there are androgen receptors on endometrial cells. Furthermore, they demonstrated that A exerts an inhibitory effect on the growth of endometrial cells *in vitro*, and that this inhibitory effect was blocked with the addition of an antiandrogen. They also found that there was no change to endometrial cell proliferation *in vitro* with the addition of either testosterone, dihydrotestosterone or DHEA.[58] Additionally, a study of 32 women undergoing gender reassignment treated with large doses of androgen therapy for a period of 1 y or more demonstrated marked atrophy of cervical epithelium, which could mimic dysplasia, and variable degrees of endometrial atrophy, which were detected at hysterectomy.[59]

Monitoring therapy

Monitoring women using androgen therapy should include assessment of efficacy and of side effects. Efficacy end points include changes to sexual response and satisfaction. Side effects of particular interest are hirsutism, acne, hemoglobin and, for oral preparations, lipids and liver function tests. These should initially be evaluated at 3 months. Subsequent monitoring depends on the androgen used, dose and route of administration. The need for monitoring testosterone levels is controversial. Given the widespread off-label use of the androgens on the market formulated for treating hypogonadism in men and the proliferation of products made by compounding pharmacies, as well as the lack of

quality control for some of the products used, it would be prudent to monitor testosterone levels if these preparations are used in order to minimize adverse effects with the goal of maintaining testosterone levels within the normal range, or just slightly above the normal range for women of reproductive age. If testosterone levels are measured, they should be done by a method that is validated for the levels found in women that is reliable and precise, such as an immunoassay following steroid extraction from the serum or gas chromatography and mass spectroscopy.

Quality of studies/shortcomings of studies

The caliber of studies on testosterone therapy varies widely. In recent years, there have been an increasing number of RCT in surgically or naturally menopausal women, which has given us greater insight into the benefits of testosterone therapy. Some of the RCT have compared testosterone therapy to placebo in women also receiving estrogen and others to testosterone plus estrogen *vs* estrogen alone. It is unknown whether testosterone would be effective in women who were not on estrogen therapy.[35]

Other shortcomings of many of the studies are that they lack sensitive, standardized and validated instruments for assessing sexual function. Furthermore how each investigator defines various aspects of sexuality is not consistent between studies, making it difficult to make comparisons between the studies. Many studies also do not correlate interventions and response rates to testosterone levels in order to provide a physiologic framework for understanding how endocrine status influences sexual functioning. In trials in which such information has been reported, measurements have been inconsistent because different assays have been used.[35]

Future studies should consider a discussion of clinical significance in addition to statistical significance. Although a result may be of statistical significance, those improvements may be so small that they do not provide a meaningful improvement. This could be measured in terms of the percentage of patients that are satisfied with a particular result and how many elect to remain on the therapy.[60]

Many of the studies did not report power calculations, and several may have had sample sizes that were inadequate for analyzing the effects of therapy. Therefore, the potential effects of testosterone therapy may not have been found in these studies. Studies with higher power may show more profound effects on sexual functioning.[60]

Lastly, investigators have used different types of testosterone and different routes of administration. Equivalent doses of different types of testosterone have not been established and we do not have any clinical trials comparing efficacy and safety profiles of different types of testosterone.

Summary and conclusions

Although there have been an increasing number of studies on the impact of androgen therapy in various aspects of women's general and sexual health, there are still a number of areas where more research is needed in the field of androgen therapy. This includes the efficacy, risks and benefits of androgen therapy in:

a. premenopausal and perimenopausal women;
b. women not taking concomitant estrogen therapy (as all the studies thus far have been on women that have been adequately estrogenized);
c. women taking oral contraceptives with Women's Sexual Interest/Desire Disorder and/or androgen insufficiency;
d. women on antidepressant medications with low libido;
e. effects of testosterone therapy on mood, cognition and memory;
f. whether testosterone therapy is sufficient to protect the endometrium from estrogen without concomitant progestin therapy;
g. need for testosterone therapy in surgical menopausal women to maintain bone mineral density; and
h. most effective formulation for testosterone replacement and minimum effective dose have not yet been determined, as well as dose comparison of the various types of testosterone (ie what dose of testosterone undecanoate is equivalent to dosage of MT, transdermal testosterone or intramuscular testosterone esters).

Conclusions

The results of these trials suggest that testosterone therapy in the low-dose regimens is efficacious for the treatment of low libido in postmenopausal women who are adequately estrogenized. Clinical studies support the idea that androgens stimulate sexual desire and satisfaction and demonstrate improved sexual enjoyment and well being in women who switched from estrogen alone to estrogen–androgen therapy.

Women who elect to receive androgen therapy must be fully informed of the risks and benefits of therapy and that they are engaging in off-label use of this medication. Based on the results of short-term clinical trials, the use of low-dose testosterone therapy in women, particularly with the use of

nonoral forms of therapy, appears to be safe. With over 40 y of use of this therapy, there are no published reports of serious hepatic or cardiovascular events with postmenopausal estrogen–androgen therapy. However, long-term placebo-controlled clinical trials or a robust pharmacosurveillance system are needed to evaluate the long-term effects of androgen therapy. Before beginning therapy, it is important to evaluate for other causes that could mimic symptoms of androgen deficiency.

Female sexual dysfunction is a complex problem with multiple overlapping etiologies. Based on the evidence of current studies, it is reasonable to consider testosterone therapy for a symptomatic androgen-deficient woman with Women's Sexual Interest and Desire Disorder who fulfills the clinical criteria for androgen insufficiency.

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