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MODERN TRENDS

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Androgen replacement therapy in women

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Objective: Review of literature with regard to androgen replacement therapy in women.

Design: Review of the MEDLINE database and references from articles.

Conclusions: Androgens affect sexual function, bone health, muscle mass, body composition, mood, energy, and the sense of well-being. Androgen insufficiency clearly has been demonstrated in patients with hypopituitarism, adrenalectomy, oophorectomy, and in some women placed on oral estrogen therapy which increases sex hormone-binding globulin (SHBG) levels and lowers the free and bioavailable forms of T. Symptoms of androgen insufficiency in women may include a diminished sense of well-being, low mood, fatigue, and hypoactive sexual desire disorder with decreased libido, or decreased sexual receptivity and pleasure that causes a great deal of personal distress. The preponderance of evidence from clinical trials supports the correlation of decreased endogenous androgen levels with these symptoms and alleviation of many of the symptoms with the administration of T or, in some cases, DHEA. There are no Food and Drug Administration-approved androgen preparations on the market for treating androgen insufficiency in women. The safety profile of androgens in doses used for the treatment of hypoactive sexual desire disorder has been excellent with only mild acne and hirsutism being noted in a minority of patients. (Fertil Steril® 2004;82:273–89. © 2004 by American Society for Reproductive Medicine.)

Key Words: Androgen replacement therapy, androgen insufficiency syndrome, testosterone replacement, oophorectomy, female sexual dysfunction, hypoactive sexual desire disorder, libido

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Female sexual dysfunction has been classified as four distinct disorders—sexual desire disorders (includes hypoactive and aversion disorders), sexual arousal disorder, orgasmic disorder, and sexual pain disorders (dyspareunia, vaginismus, and other causes) (1, 2). For some women, androgen insufficiency may result in hypoactive sexual desire disorder (HSDD), which is defined as a change in sexual function such as a persistent or recurring deficiency (or absence) of sexual fantasies or thoughts and desire for or receptivity to sexual activity that causes personal distress (1–3). For seven decades (4–11), androgens have been used to treat menopausal symptoms including low libido and other manifestations of HSDD, but only recently have careful clinical trials established the beneficial effects of androgens in women with androgen insufficiency (12–15). This review focuses on the clinical constellation of symptoms that have been associated with androgen insufficiency, the relationship of androgens to female sexuality, and the efficacy and safety of androgen therapy in women.

ANDROGENS IN WOMEN

The biological activity of an androgen depends on its ability to bind to androgen receptors in target tissues and regulate gene transcriptional activity (i.e., its potency), the production rate, metabolic clearance rate, which includes various metabolic conversions and excretion, and the quantitative amount that is available to the target tissues. The metabolic clearance rate and amount of androgen that is bioavailable in the blood to be transported into cells is dependent to a great extent on the degree of binding to the low capacity and high affinity β-globulin, sex hormone-binding globulin (SHBG), and the high capacity but low affinity albumin (16–21). The quantity of androgen in the blood that is not bound to serum proteins or weakly bound to albumin is considered to be bioavailable. Table 1 summarizes the relative potency, serum concentrations, and protein binding of the major androgens or precursors that are present in blood (16–21).

Taking into account the potency, concentration, and clinical correlations with hyper- and

TABLE 1

Relative potency; mean serum concentrations, and protein binding of major androgens or androgen precursors in women.

Androgen	Premenopausal serum concentrations (ng/dL)	Postmenopausal serum concentrations (ng/dL)	Relative potency	% Unbound	% Bound to albumin	% Bound to SHBG
DHT	20	11	5	0.5	21	78
T	32	22	1	1.4	30.4	66
A	140	77	0.1	7.5	84.5	6.6
DHEA	415	186	0.01	3.9	88.1	7.9
DHEAS	188,500	106,000	0.001	5.0	95.0	—

Note: DHT = dihydrotestosterone; A = androstenedione; DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate.
Adapted from 16–21.

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hypoandrogenic states in women, T is a reasonable measure of the androgen status of women. The total T level is markedly influenced by the SHBG concentration. Sex hormone-binding globulin levels are decreased in obesity, hyperinsulinism, glucocorticoid or growth hormone excess, hypothyroidism, and hyperandrogenic states (17, 22). The levels are increased with oral estrogen therapy, hyperthyroidism, cirrhosis, and some antiepileptic medications (17, 22). Therefore, the free or bioavailable T level more accurately reflects androgen status than does the total T concentration. Free T is best measured by equilibrium dialysis and not by the various direct or analogue assays on the market (22, 23). The Free T Index (also called the Free Androgen Index) closely correlates with the free T measurement, and can be calculated from measurements of total T and SHBG (24).

Androgens are directly secreted into the circulation by the ovaries and adrenals (25). In addition, various peripheral tissues, such as adipose tissue, muscle, and fat, convert androgens and androgen precursors from the ovaries and adrenals into androgens that then enter the circulation as part of the androgen pool. The relative contributions of these sources to androgen production in pre- and postmenopausal women are summarized in Table 2 (17, 26–29).

The circulating concentrations of the androgens may not reflect androgen action at a specific target tissue. For instance, the expression of the levels of 5α-reductase, the enzyme that catalyzes the conversion of T to dihydrotestosterone (DHT), varies in different target organs and at different sites. Indeed, the term 'intracrinology' has been used to describe hormone production, metabolism, and effect occurring in the same local target tissue (30). This process allows androgens to be biologically available for physiologic effects, but unavailable for direct biologic measurement in serum. An indirect measurement of androgen status of peripheral tissues may be assessed by biological assay of DHT metabolites: androsterone-glucoronide (ADT-G), andro-

TABLE 2

Relative contributions of ovarian, adrenal, or peripheral tissues in androgen production in premenopausal and postmenopausal women.

	Ovarian production (%)		Adrenal production (%)		Peripheral production (%)	
	Premenopause	Postmenopause	Premenopause	Postmenopause	Premenopause	Postmenopause
DHT	Very small	None	Small	Small	Almost entirely from T	Almost entirely from T
T	25%	↑ 50%	25%	↓ 10%	50% from A	↓ 40% from A
A	40%	↓ 20%	50%	↑ 70%	10% from D	10% from D
DHEA	10%	10%	50%	50%	40% from DS	40% from DS
DHEAS	0%	0%	90%	90%	10% from D	10% from D

Note: D = DHEA; DS = DHEAS; other abbreviations as in Table 1.
Adapted from 17, 26–29.
Changes from the premenopausal to postmenopausal status are highlighted with arrows.

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stane-3α, 17β-diol-glucoronide (3α-diol-G), androstane-3β, 17β-diol-glucoronide (3β-diol-G), and ADT-sulfate (31).

Androgen production and serum levels decrease with age. Both T and androstenedione (A) levels decrease before menopause. One study in a small number of women noted that the mean serum T concentration at age 21 years was approximately twice that at age 40 years (32), whereas an approximate 25% decrease was noted between ages 42 and 50 years in the Study of Women's Health Across the Nation (SWAN) (33).

There is conflicting data, however, as to whether T levels decrease further during the menopause transition. Some studies suggest that an approximately 15% decline occurs (16, 34–36). In contrast, the large longitudinal Melbourne Women's Midlife Health Project, which studied women through the menopausal transition, did not demonstrate a decline in total serum T; indeed, a decrease in SHBG levels resulted in an increase in the calculated free androgen index (37). Similarly, the SWAN study did not find a reduction in T concentrations during the menopausal transition (33).

There is no controversy surrounding the observations that production of the major androgen precursor from the adrenals, DHEA, and its sulfate peak during the third decade and then sharply decline between ages 30 and 60 years (37–41). Between the ages of 20 and 80 years, serum DHT levels steadily decrease an average of 44% in association with a decrease between 48% and 72% of various conjugated metabolites (38). Thus, the relatively low androgen levels found in women after the menopause in comparison to women in their 20s and 30s reflects an age-related decrease, rather than a specific menopausal effect.

ANDROGENS AND SEXUALITY

The individual and combined effect of estrogens and androgens on female sexual function is controversial. Estrogens clearly decrease the vasomotor symptoms that can lead to sleep disturbances, which can affect mood, energy, and quality of life. Estrogens also improve vaginal mucus production, thereby reducing dyspareunia and the avoidance of sexual intercourse because of pain. These estrogen-mediated improvements may improve sexual receptivity, but they do not improve libido (42). The role of androgens has been difficult to discern. Libido, arousability, and frequency of sexual activity have been correlated with the mid-menstrual cycle increase in T (43–47). Women with high normal T levels across the menstrual cycle are less depressed and experience more sexual gratification than do women with low normal T concentrations (44).

In addition, several cross-sectional studies performed on women at various ages across the adult lifespan have shown positive correlations with T and sexual desire, arousal, initiation, responsiveness to sexual activity, and frequency of sexual gratification and intercourse (44, 48–50). A longitudinal study (50), which followed women from approximately 2 years before until 2 years after the final menses, demonstrated a decline in coital frequency and sexual thoughts or fantasies, an increase in dyspareunia, and an increased dissatisfaction with their partners as lovers. In this study, E_2 and T levels both showed significant ($P<.002$) declines, whereas T demonstrated closer correlation with coital frequency.

In contrast, several studies (51–58) have not found a correlation of androgen levels to sexual function. The variables that are most problematic in attempts to correlate androgen levels to sexual function include insufficiently sensitive androgen assays, insufficient study power, and the lack of validated measures to assess sexual function (59). Even in the studies showing a positive association between androgens and parameters of sexual function, the correlations generally have not been very robust, indicating that in addition to androgens other factors such as relationship issues, attitudes, and general health as well as medication use by the patient and partner contribute to sexual function.

ANDROGEN INSUFFICIENCY SYNDROME

Androgen insufficiency has been well documented in four conditions: hypopituitarism, adrenalectomy/adrenal insufficiency, oophorectomy/premature ovarian failure, and after institution of oral estrogen replacement therapy (ERT) (10, 12, 19, 60–65). In a study of 55 estrogenized and nonestrogenized women with hypopituitarism (66), characterized by hypogonadism or hypoadrenalism, and 92 controls, serum total T, free T, A, and DHEAS were significantly decreased in the women with hypopituitarism as compared to the control group. The investigators reported that the severity of androgen insufficiency in these women was probably underestimated due to the limitations of androgen assays.

In an early study (10), an abrupt loss of libido was observed in women after adrenalectomy with concomitant or prior oophorectomy as treatment for breast cancer. In this study, 17 of 29 women with a mean age of 51 years reported some sexual desire before surgery. Of the 17 women who were sexually active before surgery, all reported reduced frequency of intercourse, with almost half reporting cessation of sexual intercourse ($P\leq.05$) and 14 reported a decrease in desire of which 10 reported a total loss of desire ($P = .01$). Of the 12 women who were responsive in intercourse before surgery, 11 women experienced a decrease of which 9 reported a total loss of responsiveness ($P = .01$) after surgery. More recent studies have confirmed that women with adrenal insufficiency have reduced concentrations of a variety of serum androgens (10, 60, 61, 66, 67). Similarly, chronic administration of glucocorticoids may decrease androgen levels through suppression of DHEA production by the adrenals (68).

Longitudinal hormone measurements after bilateral oophorectomy have shown an approximate 50% reduction in T

TABLE 3

Components of female androgen insufficiency syndrome.

Symptoms
Low libido with global decrease in sexual desire, fantasy, or arousability
Persistent, unexplained fatigue
Decreased sense of well-being
Blunted motivation
Flattened mood
Signs
Thinning or loss of public hair
Decreased lean body mass
Osteopenia or osteoporosis
Other indications
Onset after an event associated with decreased androgen production
Other causes of symptoms have been evaluated and ruled out
Symptoms persist despite having normal estrogen production if premenopausal or being on adequate estrogen replacement if hypogonadal

Note: From 72.

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levels and a 40%–50% reduction in A levels (62, 63, 69). The cross-sectional Rancho Bernardo study found that elderly postmenopausal women without ovaries had total and bioavailable T levels that were 40% lower and A levels that were 10% lower compared to postmenopausal women with intact ovaries (70).

There is general agreement that ERT, especially by the oral route, may result in elevations of SHBG, which binds much of the circulating T, thereby reducing the free or biologically active fraction (19, 71). In women who are prone to exhibit low androgen levels because of oophorectomy, adrenal insufficiency, or hypopituitarism, estrogen administration may precipitate symptomatic androgen insufficiency.

The symptom complex, which constitutes the androgen insufficiency syndrome, has been empirically derived from observations of patients who developed symptoms after an event, such as oophorectomy, that can precipitate a decrease in T (Table 3) (72). The frequently described symptoms are fatigue, low energy, decreased or absent sexual motivation, and desire, as well as a generalized decrease in the sense of well-being (3). These symptoms, which are consistent with the diagnosis of HSDD, often result in considerable personal distress in some women (1–3). Signs of androgen insufficiency, such as thinning or sparsity of pubic hair and decreased muscle mass may be seen (3, 73). Reduction of bone mineral density may be present on bone densitometry testing (74).

In women who have hypopituitarism, hypoadrenalism, or who have undergone oophorectomy and present with symptoms of androgen insufficiency, free T levels and the free T index are low. According to a recent consensus conference, it is reasonable to consider a menopausal woman to have androgen insufficiency if she exhibits typical symptoms and has a free T or free T index level in the lowest quartile of the normal range or below the normal range for reproductive age women (3).

In evaluating a woman suspected of having androgen insufficiency, it is important to eliminate other causes of the symptoms such as depression, iron deficiency, hypothyroidism, anemia, and medication use (especially glucocorticoids and selective serotonin reuptake inhibitors) from consideration (3). It is important to make sure that the woman is adequately estrogenized to eliminate dyspareunia with secondary avoidance of sexual activity. However, as noted, ERT can precipitate symptoms of androgen insufficiency by increasing the production and serum concentrations of SHBG, thereby reducing the concentration of free and bioavailable androgens. This is most commonly found with oral estrogen therapy, which directly stimulates the liver through a first pass effect. Therefore, before attempting androgen replacement therapy, the woman should be switched to a transdermal estrogen preparation, which results in lower SHBG concentrations (71). If these conditions are met, then a therapeutic trial of androgen replacement should be considered.

EFFECTS OF ANDROGEN REPLACEMENT

Testosterone Trials

Many, but not all, studies have demonstrated that exogenous androgen administration improves various sexual function parameters (coital frequency, desire and libido, arousal, pleasure, orgasm, thoughts or fantasy), and mood or the sense of well-being, as well as bone health, body composition, and muscle mass in women with symptomatic androgen insufficiency. There are a myriad of variables that make direct comparison between studies difficult. These include differences in study design (e.g., type of blinding, placebo, or estrogen control), duration of exposure to the androgen, whether the androgen level attained was physiologic or supraphysiologic, type of menopause (natural or surgical), selection criteria for inclusion of patients (no sexual dysfunction, low libido, mixture of menopausal symptoms), type of instrument for assessing sexual function and whether it has been psychometrically validated, type of sexual activity measured (with partner, self stimulation, intercourse only, or total sexual activity), and number of subjects in the study. These considerations are especially important as there may be a substantial placebo effect in these types of studies (12).

Nevertheless, as summarized in Table 4 and discussed in detail in the following paragraphs, the randomized, double blind, placebo, or estrogen-controlled trials in women with low libido after menopause that used well-validated tools to

TABLE 4

Testosterone replacement clinical trials in women that measured sexual function and other psychological parameters.

Trial	Therapy	N/avg. age	Sexual function parameter improvement	Other psychological parameter improvement	Population/ prestudy sexual dysfunction	Rx duration	Study design	Dose effect on T (reproductive age range)	Sexual function tool
Randomized, double-blind, placebo-controlled trials									
Greenblatt et al. (9)	Oral E, T, or E + T [5 mg MT q d]	102[c]/44 yr	↑ Libido[b,d]	↑ Well-being[b,d]	~72 NMP ~30 SMP/ "menopausal symptoms"	1 mo	Cross-over	unk	Interview
Sherwin et al. (75,76)	IM E, T, or E + T [150 mg TE + E, or, 200 mg TE q mo]	43/46 yr	↑ Desire[a] ↑ Fantasy[a] ↑ Arousal[a]	↑ Energy[a] ↑ Well-being[a] ↓ Psychological symptoms[a]	SMP only/unk	3 mo	Cross-over	Initially supraphysiologic	DMRS
Myers et al. (77)	Oral E, E, + MPA, or E + MT [5 mg MT q d]	40/~58 yr	↑ Pleasure from masturbation[a]	No improvement	37 NMP 3 SMP/no	2 mo	Parallel	Initially supraphysiologic	Daily logs
Shifren et al. (12)	E + Transdermal T [150 μg q d; 300 μg q d]	65/47 yr	Effect of 300 μg dose ↑ Frequency[a] ↑ Pleasure–orgasm[a]	Effect of 300 μg dose: ↑ Well-being[a] ↑ Mood[a]	SMP only/yes	3 mo	Cross-over	Physiologic free T, supraphysiologic total T	BISF-W
Braunstein et al. (15)	E + Transdermal T [150 μg q d; 300 μg q d; 450 μg q d]	447/49–50 yr	↑ Desire[a] ↑ Satisfying activity[a]	NR	SMP only/yes	6 mo	Parallel	Physiologic free T (for 300 μg group)	SAL, PFSF
Goldstat et al. (14)	T 1% cream [10 mg q d]	31/40 yr	↑ Interest[a] ↑ Activity[a] ↑ Satisfaction[a] ↑ Pleasure[a] ↑ Fantasy[a] ↑ Orgasm[a]	↑ Positive well-being[a] ↓ Anxiety[a] ↑ Self-confidence[a] ↑ Vitality	Pre-MP/yes	3 mo	Cross-over	Physiologic total-T, supraphysiologic FAI	SSSRS
Randomized, double-blind, estrogen only comparison trials									
Sarrel et al. (42)	Oral E or E + T [2.5 mg MT q d]	20/52 yr	↑ Frequency (at 4 wks)[b] ↑ Sensation[b] ↑ Desire[b]	Not tested	12 NMP 8 SMP/dissatisfied with E alone Rx	2 mo	Placebo lead-in	NR	SALS
Lobo et al. (13)	Oral E or E + T [1.25 mg MT q d]	218/53 yr	↑ Interest or desire[a] ↑ Responsiveness[a]	Not tested	150 NMP 68 SMP/yes	4 mo	parallel	Supraphysiologic	SIQ, BISF-W
Randomized, single-blind, estrogen only comparison trials									
Dow and Hart (80)	SC E or E + T [100 mg]	40/47 yr	↑ Orgasm at 2 months[b] (low dyspareunia patients only)	↑ "Psychological factor" at 4 months[b] (low dyspareunia patients only)	6 NMP 34 SMP/yes	4 mo	Parallel	unk	7 pt. scale

TABLE 4 Continued

Trial	Therapy	N/avg. age	Sexual function parameter improvement	Other psychological parameter improvement	Population prestudy sexual dysfunction	Rx duration	Study design	Dose effect on T (reproductive age range)	Sexual function tool
Burger et al. (78)	SC E or E + T [50 mg]	20/43 yr (E + T)	↑ Libido[b] ↑ Enjoyment[b]	Not tested	14 NMP 6 SMP/yes	6 wk	Parallel	Supraphysiologic	AS
Davis et al. (79)	SC E or E + T [50 mg q 3 mo]	32/57 yr (E + T)	↑ Activity[a] ↑ Satisfaction[a] ↑ Orgasm[a] ↑ Pleasure[a] ↑ Relevancy[a]	Not tested	30 NMP 2 SMP/no	2 yr	Parallel	Supraphysiologic	SSSRS
				Other trials					
Kupperman et al. (11)	Oral, IM, SC E + T [5 mg MT q d; 10 mg MT q d; 100 mg T cyclopentyl-propionate q 2 wks; E + 150 mg T SC]	 114 54 28 unk	↑ Libido[b]	↑ Physical vigor[b] ↑ "Joie de vivre"[b] ↓ Anxiety[b] ↓ Nervousness[b] ↑ Well-being[b]	MP	unk	Not randomized, controlled, or blinded	unk	Self-report
Burger et al. (81)	SC E or E + T [100 mg]	17/42 yr	↑ Libido[b] ↑ Enjoyment[b] ↑ Climax[b] ↑ Initiation[b]	↓ Tiredness[b] ↑ Concentration[b]	6 NMP 11 SMP/yes	6 mo	Pilot study	Supraphysiologic	AS
Sherwin et al. (83)	IM E or E + TE [150 mg q mo]	44/47 yr (E + T)	↑ Desire[a] ↑ Arousal[a] ↑ Fantasies[a] ↑ Frequency[a,e] ↑ Orgasm[a,e]	↑ Mood[a] ↑ Elation[a] ↑ Composure[a] ↑ Energy[a] ↓ Depression[b] ↓ Tiredness[b] ↓ Anxiety[b]	SMP only/unk	2 yr	2 yr follow-up	Supraphysiologic	DMRS, MAS

Note: E = estrogen; T = testosterone; MT = methyltestosterone; ↑ = increased/improved; ↓ = decreased/improved; NMP = naturally menopausal; SMP = surgically menopausal; unk = unknown; TE = T enanthate; DMRS = Daily Menopausal Rating Scale; MPA = medroxyprogesterone acetate; BISF-W = Brief Index of Sexual Functioning for Women; NR = not reported; SAL = Sexual Activity Log; PFSF = Profile for Female Sexual Function; Pre-MP = premenopausal; FAI = free androgen index; SSSRS = Sabbatsberg Sexual Self-Rating Scale; SALS = Sexual Activity and Libido Scale; SIQ = Sexual Interest Questionnaire; AS = analog scale; MP = menopausal; NA = not applicable; MAS = marital adjustment scale.

[a] Significant change between groups.

[b] Significant change from baseline within group; or, self-report (11) of increase or improvement.

[c] Only 22 participants crossed-over to all four treatment groups; 7 were surgically menopausal.

[d] Data not provided in statistical terms; 67% preferred E + T compared to E alone due to increased sense of well-being and libido. 23.5% of E + T users reported an increase in libido; 42% of T alone users reported an increased libido.

[e] Between-group significance during first 2 weeks after injection only.

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measure sexual function have generally shown increased libido, satisfaction, and sexual activity with T therapy in comparison to the response seen with placebo or estrogen alone.

In 1950, Greenblatt et al. (9) reported results of a randomized, double-blind, placebo-controlled clinical trial of oral 0.25 mg diethylstilbestrol (DES) daily alone, 5 mg methyltestosterone (MT) daily alone, combined DES and MT, and placebo in 102 women with postmenopausal symptoms after natural or surgical menopause. Each treatment was administered for 1 month in a cross-over fashion, and the effect of therapy was determined by vaginal smears and monthly interviews with regard to changes in bleeding, breast turgidity, pelvic congestion, acne, libido, hot flashes, insomnia, lubrication, and nervousness. The average age of participants was 44 years (range, 23 to 63 years). The investigators noted a carry-over effect of the prior treatment on the baseline assessment of the subsequent treatment, as well as a placebo effect. Of the 102 study participants, only 22 received all four treatments. Complete relief of menopausal symptoms was experienced by 90% of the women in the estrogen alone and combined treatment groups, but 67% of women preferred the combined therapy due to an increase in the sense of well-being. After 1 month of treatment, increased libido was reported by 2% in the placebo group, 12% in the estrogen alone group, 23% in the combined therapy group, and 42% in the MT alone group.

Sherwin and Gelfand (75) and Sherwin et al. (76) studied a group of 43 premenopausal women with benign gynecological diseases and who subsequently underwent bilateral oophorectomy with total abdominal hysterectomy. The women were randomized in an 8-month cross-over study undergoing IM injections at 28-day intervals of estrogen plus androgen (n = 12; 150 mg of T enanthate, 7.5 mg of E_2 dienanthate, and 1 mg of E_2 benzoate), estrogen alone (n = 11; 10 mg of E_2 valerate), androgen alone (n = 10; 200 mg of T enanthate), or placebo (n = 10) given in a double-blind fashion. Ten women who underwent hysterectomy without oophorectomy served as a second control group. There were four time periods—1 month of baseline monitoring, 3 months of the first hormone treatment, 1 month of placebo treatment, followed by a crossover to 3 months of the second hormone treatment. Serum T levels were significantly increased in the estrogen plus T or T alone treatment groups compared to the hysterectomy control group, estrogen alone group, and placebo group.

In the same studies, Sherwin and colleagues found a significant ($P<.01$) correlation between the increased T levels of the estrogen plus T and T alone groups with improved energy level and well-being compared to the estrogen alone and placebo groups. This study measured sexual function on a daily basis with a questionnaire using a rating scale that included the domains of sexual desire, sexual arousal, sexual thoughts or fantasies, frequency of sexual encounters with the partner, and orgasm. Significant increases were demonstrated in sexual desire ($P<.01$), sexual fantasy ($P<.01$), and sexual arousal ($P<.01$) in the two T treatment groups as compared to the estrogen alone and placebo groups. Importantly, the investigators noted that sexual function of both the androgen groups did not differ from the ovary-sparing, hysterectomy-only control group. The investigators suggested that the lack of response with regard to coital frequency and orgasm may be due to partner variability or that androgens in women affect sexual motivation but not frequency and orgasm.

Myers et al. (77) did not find an improvement in sexual function with androgen therapy in a randomized, double-blind, placebo-controlled study of 40 predominantly naturally menopausal women (surgical menopause n = 3, natural menopause n = 37). The participants had not taken any hormones 3 months before receiving study treatment with either 0.625 mg of conjugated equine estrogens (CEE), 0.625 mg of CEE plus 5 mg of medroxyprogesterone acetate (MPA), 0.625 mg of CEE plus 5 mg of MT, or placebo for 8 weeks in parallel groups. There was a significant difference of total T levels in the combined estrogen and androgen group, but initially supraphysiologic levels decreased after several weeks of treatment to levels similar to the placebo group for the remainder of the 8-week treatment period.

Myers and colleagues used daily logs for quantitative assessment of menopausal symptoms, mood state, sexual desire, sexual thoughts, and sexual activity. A seven-point Likert scale was used to assess mood states including anxiety, depression, energy level, irritability, and euphoria. Vaginal photoplethysmography provided assessment of physiologic sexual arousal. Perceived arousal to films and self-fantasy was assessed with a 10-point Likert scale. The investigators found no significant difference between groups for mood or sexual behavior. A significant improvement was found for pleasure from masturbation, but only a trend toward significance was found for frequency of masturbation and mean number of orgasms from masturbation.

Shifren et al. (12) studied the effect of a transdermal T patch in 65 oophorectomized women who were on a stable dose of estrogen therapy of at least 0.625 mg of CEE daily for at least 2 months before study entry. In this double-blind, cross-over study, the women were randomized to three treatment groups for 12 weeks each of CEE plus 150 μg per day of T, CEE plus 300 μg of T, and CEE plus placebo. Serum total T levels were above the normal range, but the free and bioavailable T concentrations were within the normal range for young women, reflecting the fact that the majority of women receiving oral CEE had markedly elevated levels of SHBG.

Shifren and associates measured sexual function at baseline and at the end of each 12-week treatment period, which included testing in the domains of sexual thoughts and desires, arousal, frequency of sexual activity, receptivity and

initiation, pleasure and orgasm, relationship satisfaction, and problems affecting sexual function. The investigators reported that the CEE plus 300 μg of T group demonstrated increased frequency of sexual activity ($P = .03$) and pleasure–orgasm ($P = .03$). A dose-dependent effect was demonstrated as there was an increased percentage of women with increased frequency of sexual fantasies, masturbation, and sexual intercourse in the CEE plus 300-μg of T group as compared to the 150-μg of T group. The sense of well-being ($P = .04$) and mood ($P = .03$) improved significantly in the 300-μg of T group in comparison to the placebo group. There was a strong placebo response that was greater in the younger women. Women under the median study age of 48 years showed an increased composite score on the Brief Index of Sexual Function for Women during placebo treatment and no further improvement during T treatment.

A recent trial conducted by Goldstat and colleagues (14), which investigated the use of T cream in premenopausal women, mean age of approximately 40 years, with low libido, demonstrated not only an improvement in sexual function, but also mood and well-being. Thirty-one women provided complete data using 10 mg of 1% T cream applied daily to the thigh. The study participants were randomized in a double-blind fashion to treatment or placebo for 12 weeks then crossed-over, after a 4-week wash-out time period, for another 12 weeks of treatment or placebo. The mean baseline serum T levels was near the lowest quartile of the normal range for reproductive age women. Serum total T levels increased with T treatment to the upper limit of the normal range, whereas the Free Androgen Index (total T/SHBG × 100) increased above the upper limit of normal. Of note, there was no change in serum E_2 levels.

Goldstat et al. found a significant improvement from baseline with T treatment as compared to placebo in the composite score ($P = .001$) on the Sabbatsberg Sexual Self-Rating Scale as well as significant improvement of individual sexual function domains of sexual interest ($P = .001$), sexual activity ($P = .006$), satisfaction of sexual life ($P = .004$), sexual pleasure ($P = .004$), sexual fantasy ($P<.001$), and orgasm ($P = .005$). That is, all sexual function domains on the Sabbatsberg Sexual Self-Rating Scale were significantly improved from baseline with T cream compared to placebo, except for the domain described as "importance of sex" ($P = .108$). In addition, T treatment demonstrated a significant improvement in the composite score on the Psychological General Well-Being Index ($P = .004$), which measures anxiety ($P = .009$), depressed mood ($P = .053$), positive well-being ($P = .009$), self confidence ($P = .024$), general health ($P = .014$), and vitality ($P = .010$). There was a beneficial decrease in the composite score on the Beck Depression Inventory, which did not reach significance ($P = .062$). Interestingly, this study did not demonstrate a placebo effect as did the trial conducted by Shifren and colleagues (12) involving surgically menopausal women. Hirsutism scores using the Ferriman-Gallway Scale did not change and none of the participants developed acne.

More recently, Braunstein et al. (15) reported in abstract form the results of a phase IIb, 6-month double-blind, placebo-controlled trial using varying doses of transdermal T delivered by a matrix delivery system patch in parallel groups of randomized surgically menopausal women (n = 447) receiving estrogen therapy with complaints of lowered libido after their oophorectomy. A 300-μg daily transdermal dose was found to be optimal in this trial, which tested daily doses of 150 μg (n = 107), 300 μg (n = 110), and 450 μg (n = 111). Again, transdermal T demonstrated significant improvement in sexual desire with minimal side effects. There was a 30% increase ($P<.05$) in total satisfying sexual activity after 6 months of treatment with 300 μg of transdermal T compared to placebo and an 81% increase ($P<.05$) from baseline using a weekly Sexual Activity Log. The sexual desire score was also significantly increased 18% ($P<.05$) with T as measured by the Profile of Female Sexual Function. There was no difference in reports of adverse effects between the placebo and T groups.

There are several controlled trials evaluating estrogen alone vs. estrogen plus T that support the benefits of androgen replacement. Sarrel et al. (42) studied a group of 20 naturally (n = 12) and surgically (n = 8) menopausal women, who were dissatisfied with their conventional hormone therapy, and were randomized to daily administration of oral estrogen, 1.25 mg of oral esterified estrogen (EE), alone (n = 11), or estrogen plus androgen, 1.25 mg of oral EE plus 2.5 mg of MT (n = 9) in a double-blind fashion. This study incorporated a 2-week, single-blind, placebo lead-in time period before an 8-week double-blind treatment time period. Sexual function was assessed weekly with the Sexual Activity and Libido Scale, which included items on vaginal moisture, level of sexual desire, frequency of sexual intercourse, pain with intercourse, clitoral sensation, clitoral sensitivity, orgasm, sexual fantasy, and sexual response.

Sarrel and colleagues found that the EE plus MT group showed a significant improvement in the combined rating for sexual sensation and desire ($P<.01$ compared to previous estrogen therapy and previous hormone therapy; $P<.01$ compared to placebo) after 4 and 8 weeks of treatment. Frequency of sexual intercourse increased significantly after 4 weeks of the combined EE plus MT therapy compared to placebo, but was not significant at other assessment time periods. Serum levels of E_2 and estrone (E_1) increased in all groups in comparison to post-placebo levels. As expected, SHBG levels increased in the estrogen alone group and decreased in the estrogen plus androgen group. Although androgens were not measured in this study, the investigators concluded that the administration of estrogen plus androgen significantly improved sexual sensation and desire either as a direct result of the androgen or as an indirect result of decrease in SHBG levels, which increased the bioavailability

of T. Of interest, 13 study participants elected to continue with estrogen (0.625 mg EE daily) plus androgen (1.25 mg. MT daily) therapy after the trial was completed.

Lobo et al. (13) performed a randomized, double-blind study with 218 postmenopausal women using a combined oral estrogen–androgen preparation (0.625 mg EE plus 1.25 mg MT; n = 107) and estrogen alone (0.625 mg EE; n = 111) during 4 months. Sexual function measurement was performed at 1, 2, 3, and 4 months of treatment, and both groups demonstrated increases in sexual interest after 1 month of treatment, with the increase in sexual interest or desire being greater for the combined therapy group. Combined therapy also effected greater sexual responsiveness ($P = .002$). There was no difference as to response related to age, race, or type of menopause. This study correlated the increases in sexual function parameters to significant increases ($P<.01$) in mean serum concentration of bioavailable T in association with significant decreases ($P<.01$) in SHBG levels in the combined treatment group compared to the control group. In the group of women with baseline SHBG in the normal range, there was a highly significant correlation between the change in bioavailable T to change in interest, responsiveness, and total Sexual Interest Questionnaire (SIQ) score.

Burger et al. (78) studied the effect of implanted pellets containing estrogen alone (40 mg of E_2) or estrogen (40 mg of E_2) plus androgen (50 mg of T) on 20 postmenopausal women with "severe" loss of libido unresolved by conventional hormone therapy in a randomized, single-blind fashion. Supraphysiologic levels of T were noted in this study. After 6 weeks, the combined therapy group demonstrated improvement in libido ($P<.01$) and sexual enjoyment, whereas the estrogen alone treatment group did not demonstrate an increase in libido or sexual enjoyment.

Also using implanted pellets, Davis et al. (79) performed a randomized, single-blind study involving 32 postmenopausal women. Unique to this study was the exclusion of women with low libido. The women received implants of either 50 mg of T combined with 50 mg of E_2 or 50 mg of E_2 alone every 3 months during 2 years. Supraphysiologic levels of T were also attained in this study. Sexual function including the domains of libido, activity, satisfaction, pleasure, fantasy, orgasm, and relevancy, were measured at baseline and at each 6-month period throughout the 2-year study. The results of this prospective study revealed that the women who received the combined therapy (E_2 plus T) had a significantly greater improvement in sexual activity ($P<.03$), satisfaction ($P<.03$), orgasm ($P<.035$), relevancy ($P<.05$), and pleasure ($P<.01$) compared to the estrogen alone group. This study also measured bone mineral density (BMD) and body composition. The estrogen plus T treatment group showed a significantly greater improvement in total body, vertebral (L1–L4), and trochanter BMD.

In contrast to the generally positive results found in these studies, Dow and Hart (80) reported a lack of a difference in restoration of sexual function in postmenopausal women (n = 40 [natural menopause n =6; surgical menopause n = 34]) with a decline in sexual interest given 100 mg of T and 50 mg of E_2 implants as compared to E_2 implants alone. Participants self-rated using a seven-point scale for frequency of sexual interest, general satisfaction with the sexual relationship, general satisfaction with the marital relationship, frequency of orgasm, ease of responding to sexual stimulation, and frequency of dyspareunia before treatment and at 2 and 6 months after treatment in this randomized, single-blind trial. Although there was a significant improvement in all sexual function domains in each group compared to baseline, there was no significant difference found between groups. Therefore, the investigators stratified the two groups with regard to baseline measurement of dyspareunia. A significant increase in orgasm was noted only in the combined pellet group at 2 months in the patients with low dyspareunia.

Several other studies bear noting, although they are of lower scientific quality than those summarized previously, because they are neither randomized, blinded, nor adequately controlled.

In 1959, Kupperman and colleagues (11) gave 5 or 10 mg of oral MT or 100 mg of T cyclopentylpropionate intramuscularly along with estrogen to postmenopausal women and reported improvement in libido, "physical vigor," and "*joie de vivre*," as well as decreased anxiety and decreased nervousness. Also, these early investigators reported improved libido and well-being using implanted E_2 and T.

Burger et al. (81) conducted a pilot study with 17 postmenopausal women who were complaining of low libido, which was unresponsive to estrogen alone, using implanted pellets containing 40 mg of E_2 and 100 mg of T. This study did not include estrogen alone or placebo control groups. Participants were assessed monthly with an analogue scale for libido and enjoyment of sex, and initiation of sexual activity and frequency of orgasm was assessed by interview and diary. Serum total and free T levels peaked after 1 month of treatment and remained at supraphysiologic levels at 6 months. Significant improvement in libido ($P<.01$) and enjoyment of sex ($P<.01$) was demonstrated compared to baseline assessments. The improvement in libido and enjoyment was cumulative and peaked after 3 months of therapy (n = 14). Improvement was maintained up to 6 months. Tiredness, ability to concentrate, change in hot flashes, sweats, and depression were assessed, but only tiredness ($P<.01$) and concentration ($P<.05$) showed significant improvements from baseline.

Sherwin (82) and Sherwin and Gelfand (83) studied 44 women, who had undergone oophorectomy 2 years earlier, using monthly IM injections of estrogen and androgen (150 mg of T enanthate, 7.5 mg of E_2 dienanthate, and 1 mg of E_2

benzoate) or estrogen alone (10 mg of E_2 valerate). A placebo group was not a part of the study design; however, a third group of women in this study who had been untreated since the time of surgery was used for control purposes. Supraphysiologic levels of T were achieved and maintained for 84 days in this study. Sexual function was measured daily by a rating scale in the domains of desire, number of fantasies, level of arousal during intercourse, orgasm, and frequency of intercourse. The estrogen plus androgen group showed significant improvement in comparison to the estrogen alone and control groups in the first 3 weeks (of 4 weeks) of therapy in the domains of sexual desire ($P<.01$), number of sexual fantasies ($P<.01$), and sexual arousal ($P<.01$). In the first 2 weeks of therapy, frequency of intercourse and orgasm was significantly better ($P<.01$) in the cotherapy group as compared to the monotherapy and untreated groups. However, by week 3 the frequency of intercourse and orgasm of the cotherapy group exceeded only the control group.

These studies examined the effects of T treatment in menopausal or premenopausal women, whereas Tuiten et al. (84) studied eight women with hypothalamic amenorrhea and eight healthy menstruating women. The first phase of their investigation established that amenorrheic women had significantly decreased frequency of sexual thoughts, frequency of sexual desire, frequency of sexual activity, and low serum T levels. In the second phase of the study, these eight amenorrheic women were treated with 40 mg of T undecanoate for 8 weeks followed by a 28-day wash-out period and then a cross-over to placebo treatment for 8 weeks. Supraphysiologic serum levels of T were achieved. Only genital vasocongestion showed a significant difference between groups, being increased on T, whereas there were no significant mood or subjective sexual behavior effects noted between T and placebo treatment.

DHEA Trials

Because DHEA is converted into A and then T, several studies have examined the effects of DHEA administration on sexual function in women (Table 5). Morales and coworkers (85) conducted a 6-month, randomized, placebo-controlled, cross-over study using 50 mg of DHEA in 17 women, aged 40 to 70 years. Within 2 weeks of treatment, serum DHEA and DHEAS levels were within the normal range for reproductive age women and there was a twofold increase in A, T, and DHT. Although 84% of the women reported an improvement in well-being, there was no improvement in libido. It should be noted that 15 of the 17 women were menopausal and that only 7 were on conventional hormone therapy. Thus, it is possible that dyspareunia was present in some of the participants, which remained unaltered, as there were no changes in the serum levels of E_1, E_2, or SHBG with DHEA administration.

Barnhart et al. (86) conducted a study with 60 symptomatic perimenopausal women with an average age of 48 years. This randomized, double-blind, placebo-controlled, parallel group study used 50 mg of oral DHEA given daily for 3 months. There was no improvement in sexual or psychological domains over placebo. However, libido was assessed with only one question from the Hamilton Depression Rating Scale, which is insufficient to examine sexual function.

Baulieu and colleagues (87) conducted a trial with 50 mg of daily, oral DHEA during 1 year in 140 women aged 60 to 79 years in a double-blind, randomized, placebo-controlled fashion. Serum androgens reached supraphysiogic levels after 6 months of therapy, but decreased to physiologic levels after 12 months of therapy. Estradiol levels increased significantly ($P<.001$), but did not exceed early follicular phase levels, after 6 months of treatment and were maintained through 12 months of treatment. Sexual attitudes, libido, activity (intercourse or masturbation), and satisfaction were measured with a questionnaire at baseline, 6 months, and 12 months.

Baulieu and associates found that there was a significant improvement in sexual parameters in the women more than 70 years of age, but not less than 70 years of age. In the former, there was an increase in libidinal interest after 6 months of therapy that reached significance after 12 months of therapy. Of note, libido increased from baseline before the significant increases demonstrated in intercourse or masturbation ($P<.03$) and sexual satisfaction (quantitative and qualitative) ($P<.01$) after 12 months of therapy. As well, bone turnover improved in women who were more than 70 years old.

Because the adrenals are a significant source of androgens in women, low serum androgen levels are found in patients with adrenal insufficiency. Arlt et al. (61) studied treatment with 50 mg of oral DHEA daily during 4 months in 24 women with adrenal insufficiency of whom 14 had primary adrenal insufficiency (11 had autoimmune adrenalitis and 3 had bilateral adrenalectomy) and 10 had secondary adrenal insufficiency (6 had pituitary surgery, 3 had Sheehan's syndrome, and 1 had autoimmune hypophysitis). This study was randomized, double-blind, and placebo-controlled. Participants were randomized to treatment or placebo for 4 months with an intervening month for wash-out purposes in a cross-over fashion. After 4 months, the DHEA treatment group demonstrated significant increases in serum levels of DHEA, DHEAS, A, T, and DHT compared to the placebo group. Of note, SHBG concentrations significantly decreased after 4 months of treatment compared to placebo. Serum concentrations of E_1 and E_2 did not change significantly between groups.

In addition to the finding of significantly increased serum androgen levels between groups after 4 months of treatment, Arlt and colleagues noted an improvement in sexual function (increased frequency of sexual thoughts or fantasies, degree of sexual interest, and sexual satisfaction) and mood that correlated to the change in androgen levels. The improve-

TABLE 5

Oral DHEA replacement clinical trials in women that measured sexual function and other psychological parameters.

Trial	Therapy	N/average age (y)	Sexual function parameter improvement	Other psychological parameter improvement	Population/prestudy sexual dysfunction	Rx Duration	Study design	Dose effect on T (reproductive age female range)	Sexual function tool
Randomized, double-blind, placebo-controlled trials									
Morales et al.[c] (85)	50 mg q d	17/54 yr	No improvement	↑ Well-being	2 Pre-MP, 15 MP; 7 no HT/unknown	3 mo	Cross-over	Physiologic	VAS
Arlt et al. (61)	50 mg q d	24/42 yr	↑ Frequency of thoughts/ fantasies[a] ↑ Interest[a] ↑ Satisfaction[a]	↑ Mood[a] ↓ Exhaustion[a] ↓ Depression[a] ↓ Anxiety[a] ↓ Hostility[a] ↓ Obsessive–compulsive traits[a]	AI/unknown	4 mo	Cross-over	Physiologic	VAS
Barnhart et al. (86)	50 mg q d	60/48 yr	No improvement	No improvement	Peri-MP only/yes	3 mo	Parallel	Physiologic	1 question from Ham-D
Baulieu et al.[c] (87)	50 mg q d	140/60–79 yr	> 70 yrs only: ↑ libido[b] ↑ Intercourse–masturbation[b] ↑ Satisfaction[b]	Not tested	MP/unknown	1 yr	Parallel	Initially supraphysiologic	Questionnaire
Hunt et al.[c] (66)	50 mg q d	24/26–69 yr	No improvement	↑ Self-esteem[a] ↑ Evening mood[a] ↓ Evening fatigue[a]	AI/unknown	3 mo	Cross-over	Physiologic	GRISS
Johannsson et al. (88)	30 mg if <45 yr, 20 mg if > 45 yr	38/51 yr (DHEA group)	No improvement	No improvement	Hypopituitarism/ unknown	6 mo + 6 mo open phase	Parallel	Subnormal	Self-report
Lovas et al. (67)	25 mg q d	39/46 yr (DHEA group)	No improvement	No improvement	AI/unknown	9 mo	Parallel	Physiologic	MSQ (AS)

Note: ↑ = increased/improved; ↓ = decreased/improved; Pre-MP = premenopausal; MP = menopausal; HRT = hormone replacement therapy; VAS = visual analog scale; AI = adrenal insufficiency; AS = analogue scale; Peri-MP = peri-menopausal; Ham-D = Hamilton Depression Rating Scale; GRISS = Golombok Rust Inventory of Sexual Satisfaction; DHEA = dehydroepiandrosterone; MSQ = McCoy's sexuality questionnaire.

[a] Significant change between groups.

[b] Significant change from baseline within group.

[c] Data reflects only female participants in the study.

Cameron. Androgen replacement therapy in women. Fertil Steril 2004.

ment in sexual satisfaction (mental satisfaction [$P = .009$]; physical satisfaction [$P = .02$]) in the treatment group compared to the placebo group did not occur until 4 months of treatment, whereas the increases in the degree of sexual interest ($P = .06$) and frequency of sexual thoughts or fantasies ($P = .07$) was demonstrated after 1 month of treatment. Timing of effects coincided with the evaluation schedule as psychological assessments were performed after 1 and 4 months of treatment with both the placebo and DHEA treatments and 1 month after the completion of the second treatment in this cross-over trial. In addition, it should be noted that there was a significant carry-over effect with treatment in association with sexual interest effect ($P = .05$). The improvement in the sense of well-being occurred after 4 months of treatment. After 4 months, the DHEA treatment group demonstrated a significant decrease in depression ($P = .05$) and obsessive–compulsive traits ($P = .03$) compared to the placebo group. Anxiety ($P = .01$) and hostility ($P = .03$) decreased significantly in the DHEA treatment group compared to the absolute change from baseline in the placebo group. Mood (degree of unpleasantness, $P = .008$; degree of alertness, $P = .03$; and degree of restlessness, $P = .01$) improved significantly in the DHEA treatment group compared to the placebo group after 4 months of treatment.

In contrast to these results, Hunt and co-workers (66) found no improvement in sexual function in 24 women, aged 26 to 69 years with adrenal insufficiency who received 50 mg of oral DHEA daily for 12 weeks in comparison to the response to 12 weeks of placebo in a randomized, double-blind study. This cross-over study used a 1-month wash-out period between drug and placebo treatment periods. There was a significant increase in serum total T ($P = .003$) and a significant decrease in serum SHBG ($P<.001$) levels in the treatment group as compared to the placebo group. There were no differences in sexual interest or arousal, frequency of intercourse, or lubrication between the DHEA and placebo groups, but there was a significant improvement in self-esteem, evening mood, and a decrease in evening fatigue in the DHEA treatment group.

Similar negative results were found by Lovas et al. (67) who conducted a randomized, placebo-controlled study using 25 mg of oral DHEA daily for 9 months in 39 women with adrenal insufficiency. The serum T levels significantly increased from baseline to reach premenopausal levels. However, there was no effect on sexual function parameters.

The effect of oral DHEA administration to women who were androgen deficient from hypopituitarism was studied by Johannsson and colleagues (88) who used an age-adjusted, dosing scheme of DHEA administration in 38 women, with 30 mg being given if the woman was less than 45 years of age and 20 mg if she was 45 years or older. The study was double-blinded, randomized, and placebo-controlled for a 6-month period followed by a 6-month open phase. The mean ages of the placebo and DHEA groups were 50 and 51 years, respectively. Although levels of DHEAS, A, and T increased in the treatment group, the serum androgen levels remained subnormal at the completion of the study, and at 6 months there was no statistically significant differences in androgen levels compared to the placebo group.

Johannsson and associates used patient reports at 6 and 12 months to measure changes in sexual interest and activity in three categories: reduced, unchanged, or increased. Quality of life was measured by the Psychological General Well-Being Index. A 12-item questionnaire was completed by the patients' partners to assess mood and behavior changes. Of interest, there were no significant changes in sexual function as self-reported during the placebo-controlled phase of the study, although the patients' partners reported an increase in sexual relations during this period. During the open phase of the study, increased sexual activity and interest was reported by 100% of the women with partners on 30 mg of DHEA and 41% of the women with partners on the 20-mg dose. There were no significant changes in the quality of life noted during either phase.

Tibolone Trials

Tibolone is a steroid hormone that possesses estrogenic, progestational, and androgenic properties. Although not available in the United States, it has had several decades of use in Europe and Asia. There are four randomized, placebo-controlled, single or double-blind trials using 2.5 mg of tibolone given orally each day.

Kicovic and colleagues (89) studied 82 postmenopausal women for 16 weeks in each arm of a cross-over trial and noted that there was a 26% improvement in libido with tibolone compared to placebo. Nevinny-Stickel (90) also performed a cross-over trial for 16 weeks on active drug or placebo in 35 postmenopausal women and found no significant difference in effect on libido, which was the only sexual function domain examined.

A single-blind, placebo-controlled trial was conducted by Palacios et al. (91) with 28 postmenopausal women using a questionnaire that measured several parameters of sexual function. At 12 months there was a significant improvement with tibolone compared to baseline and control in all parameters that included desire, frequency of arousability, intensity and frequency of orgasmic response, and coital activity.

More recently, Laan and co-workers (92) studied 38 postmenopausal women for 12 weeks in a cross-over trial using sexual function questionnaires, daily diaries, and measurements of vaginal blood flow and lubrication. In comparison to placebo, tibolone significantly increased vaginal lubrication and blood flow, arousability, sexual fantasies, and sexual desire. There was no difference in the initiation of sexual activity, frequency of intercourse, or orgasm.

As reviewed elsewhere (93, 94), multiple other trials with tibolone have been carried out that have either not been blinded, not randomized, or not had a prospective placebo control or have compared tibolone to estrogens or estrogen/progesterone combinations. It is difficult to interpret the results because of the estrogenic and progestational activities of tibolone and the differences between the potency of tibolone and the comparators used in the studies. Also, because tibolone lowers SHBG, whereas estrogens increase this protein, differences in results may actually reflect alterations in the free endogenous androgen levels, rather than a direct androgenic activity of tibolone.

ANDROGEN PREPARATIONS

At the present time, there are no androgen preparations that have Food and Drug Administration approval for the treatment of HSDD. Many compounding pharmacies will prepare T pellets, creams, gels, drops, and lozenges by prescription. However, these generally have not been standardized with regard to absorption, duration of effect, or the range of serum levels achieved. There are numerous androgen products available for the treatment of male hypogonadism. However, normal serum T levels in men are 10–20 times higher than those found in women, and, therefore, off-label use in women requires breaking tablets, diluting injectables, cutting patches, or trying to squeeze out just the right amount of gel, which generally leads to the administration of too much or too little androgen.

The only T preparation produced by a pharmaceutical manufacturer that is made specifically for women is a combination product containing EE and MT (Estratest HS with 0.625 mg of EE plus 1.25 mg of MT or Estratest with 1.25 mg of EE and 2.5 mg of MT, both from Solvay Pharmaceuticals, Marietta, GA). The specific indication for these preparations are for the treatment of vasomotor menopausal symptoms not responsive to estrogens alone and not for the treatment of HSDD. However, as noted, the studies of Sarrel (42) and Lobo (13) and their co-workers have shown that this combination improves sexual function in women to a greater extent than that found with EE alone. Clinical trials are currently underway investigating T preparations that have been specifically designed to treat HSDD in women, but it is anticipated that it will still be several months to years before these complete the regulatory approval process and reach the market.

Dehydroepiandrosterone is administered orally and has been used for androgen replacement in women with primary and secondary adrenal insufficiency. Doses more than 30 mg/day are usually required to produce a beneficial effect on sexual function. Dehydroepiandrosterone is considered a dietary supplement by the Food and Drug Administration, and as such is available in health food stores and markets. An investigation into the actual DHEA content of multiple over-the-counter DHEA products demonstrated a wide range with some containing no measurable DHEA to levels that were as much as 149% of the expected amount (95).

Another preparation that theoretically could be used to provide androgen replacement therapy is androstenedione. Androstenedione, like DHEA, is considered a dietary supplement by the Food and Drug Administration. There have been two pharmacokinetic studies in women, which have not measured effect on sexual function parameters (96, 97).

Kicman et al. (96) studied A administration in 10 healthy, premenopausal women aged 20–32 years. Oral A in a single dose of 100 mg or placebo was administered in a double-blind, cross-over fashion. Serum A and T levels were supraphysiologic at the 100-mg dose of A. Serum A levels in the treatment group were significantly different from placebo after 15 minutes to 24 hours, whereas T levels were significantly different from 30 minutes to 8 hours. Serum A levels plateaued between 2 and 4 hours.

Leder et al. (97) studied oral A replacement in 30 postmenopausal women in single doses of 0 (n = 10), 50 (n = 10), and 100 (n = 10) mg, which resulted in significantly ($P<.0001$) increased serum T levels that were often supraphysiologic in the 50- and 100-mg treatment groups compared to the placebo group. There was considerable individual variability using this intermediate precursor of T.

Androgen replacement therapies potentially lead to increases in the estrogen concentrations due to aromatization. In this study E_1, but not E_2, levels were increased, whereas oral DHEA administration has been shown to increase E_2 levels. Because this study investigated the effect of a single oral dose, the adverse and beneficial effects, including sexual function parameters, with long-term administration of A is unknown in women.

SAFETY OF ANDROGENS IN WOMEN

The various studies that have investigated the administration of androgens in women have found that androgen replacement therapy is well tolerated and devoid of serious side effects. All may result in unwanted mild androgenic effects, such as acne and hirsutism, if supraphysiologic T concentrations are reached, but are rarely associated with more serious virilization.

Acne has been found in 3%–8% of patients with oral preparations of EE plus MT compared to 0%–7% in women receiving EE alone (13, 98–101). An increase in acne was not found with IM or SC E_2 plus T in comparison to the estrogen only control, or with transdermal T vs. placebo (12, 14, 15, 79, 82).

The reported hirsutism rates with oral EE plus MT varied from 4.2% to 6%, which is not significantly different from patients receiving EE alone (13, 98, 100, 101). Of interest, in a group of 100 women who had no facial hair at baseline, 14% developed facial hair with 0.625 mg of EE plus 1.25 mg

TABLE 6

Blood lipid effects (% change from baseline) of T or DHEA replacement clinical trials in women.

Trial	Therapy	N	Total cholesterol	HDL	LDL	Triglycerides	Dose effect on T	Rx Duration
			Oral					
Lobo et al. (13)	Oral MT 1.25 mg q d	106	−16.8	−12.4	NC	−31.1	Supraphysiologic	4 mo
	Oral EE low dose	110	2.4	3.2	1.0	−7.5		
Johannsson et al. (88)	Oral DHEA 30 or 20 mg q d	38	+5.7	+1.3	+3.7	+1.6	Subnormal	1 yr
Arlt et al. (61)	Oral DHEA 50 mg q d	24	−9.5[a]	−13.5[a]	−8.1	−1.75	Physiologic	4 mo
Barnhart et al. (86)	Oral DHEA 50 mg q d	60	−2.5	−3.1	NC	−1.5	Physiologic	3 mo
Barrett-Connor et al. (101)	Oral EE low dose	25	+0.7	+15.6	−11.3	+72.1	NR	2 yrs
	Oral EE high dose	25	+3.2	+23.2	−4.8	+56.1		
	Oral EE + MT 1.25 mg q d	26	−11.7	−19.5	−6.4	−16.2		
	Oral EE + MT 2.5 mg q d	23	−11.2	−18.6	−5.7	−7.3		
Raisz et al. (99)	Oral EE + MT 2.5 mg q d	13	−11.5[a]	−23.0[a]	−4.9	−32.4[a]	Physiologic	9 wks
	Oral EE	13	−6.5	+22.1[a]	−24.1[a]	+25.5[a]		
Watts et al. (103)	Oral EE + MT 1.25 mg q d	33	−9.1	−16.4[a]	+1.9	−30.0*	unk	2 yrs
	Oral EE	33	−5.2	6.7[a]	−11.9	+19.5		
Hickok et al. (102)	Oral EE + MT 1.25 mg. q d	13	−33.3	−14.5	−19.3[a]	+3.4	unk	6 mo
	Oral EE + MT 2.5 mg q d	13	−6.1	+2.1	−10.1	+8.1		
			Transdermal					
Shifren et al. (12)	E + Transdermal T 300 μg q d	67	+3.2	NC	+5.1	NR	Physiologic free T	3 mo
			Parenteral					
Davis et al. (79)	SC E + T 50 mg q 3 mo	16	−10.7	NC	−17.1	−10.5	Supraphysiologic	2 yrs
	SC E	17	−8.1	+6.7	−17.5	−5.5		
Burger et al.[b] (78)	SC E or E + T 50 mg × 1	20	NS	NS	NS	NS	Supraphysiologic	6 wks
Farish et al. (104)	SC E + T 100 mg × 1	17	−5.4*	+4.1	−7.6*	−14.2	Initially	6 mo
	SC E	14	−3.1	+6.5*	−6.4	−8.1	Supraphysiologic	
Burger et al. (81)	SC E + T 100 mg × 1	17	NC	NC	NS[a]	−0.2	Supraphysiologic	5 mo

Note: dosages are for T, low dose EE is 0.625 mg EE, high dose EE is 1.25 mg, dose effect on T comparison to normal reproductive age range.
HDL = high-density lipoprotein; LDL = low-density lipoprotein; NC = no change; E = estrogen; NR = not reported; EE = esterified estrogen; MT = methyltestosterone; NS = not significant; unk = unknown.

[a] Statistical significance.

[b] Values for lipid profile not provided, but reported as no significant change.

Cameron. Androgen replacement therapy in women. Fertil Steril 2004.

of MT and 22% developed facial hair with 1.25 mg of EE plus 2.5 mg of MT at 12 months, most of which was reported as light or medium growth. In comparison, both the high-dose and low-dose estrogen-only control groups had a 20% increase in facial hair growth (98). The hirsutism rates for IM or SC T administration, which results in supraphysiologic T levels, have been reported to vary between 0% and 20%, but has not been systematically compared to parental or SC estrogen-only therapy (82, 85). No difference in hirsutism incidence rates between transdermal placebo or T have been reported (12, 14, 15).

Due to the first pass effect on the liver after absorption from the gastrointestinal tract, oral androgen preparations generally exhibit a greater degree of lowering of SHBG and, therefore, greater increase in the free androgen levels than do parental or transdermal androgens. This liver effect also leads to a reduction of high-density lipoprotein (HDL) cholesterol levels, which is usually not found with androgens given in replacement doses by a nonoral route. Table 6 (12, 13, 61, 78, 79, 81, 86, 88, 99, 101–104) summarizes the effects on cholesterol found with the different androgen preparations that have been reported in the studies included in Tables 4 and 5. Fortunately, many of the adverse reactions listed in the product labels of the various androgen preparations and in the literature concerning androgen therapy for male hypogonadism, such as hepatic dysfunction, polycythemia, sleep apnea, and breast stimulation have not been found in women receiving replacement therapy.

SUMMARY

Clinical investigations attempting to correlate androgen levels and sexual function parameters are exceedingly difficult as sexual behavior is complex. Individual patterns of sexual expression do not have an exclusive determinant and are largely dependent on interrelational dynamics. Only small observational studies have attempted to correlate androgen levels with female sexual function and there are no

large studies that used validated questionnaires to confirm the correlation.

The physiologic mechanisms of female androgen insufficiency syndrome and subsequent symptoms are not entirely clear. The decline of androgen production is well documented and probably a consequence of the effects of advancing age on the adrenals and the ovaries rather than menopause. It is clear that women with hypopituitarism, adrenal insufficiency, or oophorectomy are often androgen insufficient. Why some women become symptomatic, and others not, has yet to be determined. That some symptomatic women respond to androgen replacement is clear.

Although androgen therapy has been used in the treatment of menopausal symptoms since the 1930s, the understanding of the importance of endogenous androgens as well as the benefits and risks of exogenous androgen replacement therapy in women is incomplete. Androgen therapy may be most beneficial to women with androgen insufficiency due to hypopituitarism, adrenal insufficiency, or subsequent to bilateral oophorectomy. However, as most women now live approximately one-third of their lives after menopause, the consideration of androgen therapy for symptomatic, naturally menopausal women has gained increasing support and attention in the lay and medical communities. In addition, because womens' partners now have longer life expectancies and have therapies to address their sexual function, the quality of life of women increasingly includes the ability to enjoy a meaningful, intimate sexual relationship.

Related to the consideration of androgen therapy in symptomatic postmenopausal women are issues of inadequate and excessive estrogen therapy. Loss of libido may be simply due to underestrogenization and therefore, aversion due to dyspareunia, or overestrogenization with resultant increase in SHBG and binding of T. The role of ET for menopausal women is currently undergoing reassessment in the wake of the Women's Health Initiative and Heart and Estrogen/Progestin Replacement Study studies. Because the studies dealing with androgen replacement in women have been carried out on a background of estrogen replacement, it is unknown what the effect of androgen replacement will be on women who are not receiving estrogens. To be sure, more large-scale, long-term, placebo-controlled clinical evaluations of androgen replacement therapy in women with both surgical and natural menopause, with and without systemic ET, which accurately measure serum androgens and sexual function with validated tools are urgently needed.

References

1. American Psychiatric Association. DSM-IV. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, D.C.: American Psychiatric Press, 1994.
2. Basson R, Berman J, Burnett A, Derogatis L, Ferguson D, Fourcroy J, et al. Report of the international consensus development conference of female sexual dysfunction: definitions and classifications. J Urol 2000; 163:888–93.
3. Bachmann G, Bancroft J, Braunstein GD, Burger H, Davis S, Dennerstein L, et al. Female androgen insufficiency: the Princeton Consensus Statement on definition, classification, and assessment. Fertil Steril 2002;77:660–5.
4. Nathanson IT, Towne LE. The urinary excretion of estrogens, androgens and FSH following the administration of testosterone to human female castrates. Endocrinology 1939;25:754–8.
5. Geist SH, Salmon UJ. Androgen therapy in gynecology. JAMA 1941; 117:2207–13.
6. Kurzrok L, Rothbart H. Treatment of female menopause with methyltestosterone and stilbestrol. Am J Surg 1942;LVI:636–9.
7. Greenblatt RB. Androgenic therapy in women. Endocrinology 1942; 2:665–6.
8. Salmon UJ, Geist SH. Effects of androgens upon libido in women. J Clin Endocrinol Metab 1943;3:235–8.
9. Greenblatt RB, Warfield WE, Garner JF, Calk GL, Harrod JP. Evaluation of estrogen, androgen, and estrogen–androgen combination and a placebo in the treatment of menopause. J Clin Endocrinol Metab 1950;10:1547–58.
10. Waxenberg SE, Drelich MG, Sutherland AM. The role of hormones in human behavior: changes in female sexuality after adrenalectomy. J Clin Endocrinol Metab 1959;19:193–202.
11. Kupperman HS, Wetchler BB, Blatt MHG. Contemporary therapy of the menopausal syndrome. JAMA 1959;171:103/1627–113/1637.
12. Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, et al. Transdermal testosterone treatment in women with impaired sexual function after oopherectomy. N Engl J Med 2000; 343:682–8.
13. Lobo RA, Rosen RC, Yang HM, Block B, van der Hoop RG. Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. Fertil Steril 2003;79:1341–52.
14. Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. Menopause 2003;10:390–8.
15. Braunstein GD, Shifren J, Simon J, Lucas J, Rodenberg C, Watts N. Testosterone patches for the treatment of low sexual desire in surgically menopausal women. [abstract no. 60]. In: Program and abstracts of the 14th annual meeting of The North American Menopause Society. Miami Beach: The North American Menopause Society, 2003.
16. Longcope C. Androgen metabolism and the menopause. Sem Reprod Endocrinol 1998;16:111–5.
17. Vermeulen A. Plasma androgens in women. J Reprod Med 1998;43: 725–33.
18. Plouffe LJ. Ovaries, androgens and the menopause: practical application. Sem Reprod Endocrinol 1998;16:117–20.
19. Simon JA. Estrogen replacement therapy: effects on endogenous androgen milieu. Fertil Steril 2002;77:S77–S82.
20. Dunn JF, Nisula BC, Rodbard D. Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab 1981;53:58–68.
21. Simpson ER. Aromatization of androgens in women: current concepts and findings. Fertil Steril 2002;77:S6–S10.
22. Guay AT. Screening for androgen deficiency in women: methodological and interpretive issues. Fertil Steril 2002;77:S83–S88.
23. Boots LR, Potter S, Potter D, Azziz R. Measurement of total serum testosterone levels using commercially available kits: high degree of between kit variability. Fertil Steril 1998;69:286–92.
24. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999;84:3666–72.
25. Longcope C. Adrenal and gonadal androgen secretion in normal females. Clin Endocrinol Metab 1986;15:213–28.
26. Longcope C, Hunter R, Franz C. Steroid secretion by the postmenopausal ovary. Am J Obstet Gynecol 1980;138:564–8.
27. Serio M, Mannelli M, Calabresi E, Orlando C, Giannotti P. Ovarian and adrenal secretion of androgens. In: Molinatti GM, Martini L, James VHT, eds. Androgenization in women. New York: Raven Press, 1983:15–24.
28. Adashi EY. The climacteric ovary as a functional gonadotropin-driven androgen-producing gland. Fertil Steril 1994;62:20–7.
29. Judd HL, Fournet N. Changes of ovarian hormonal function with aging. Experiment Gerontol 1994;29:285–98.
30. Labrie F, Luu-the V, Labrie C, Belanger A, Simard J, Lin S, et al. Endocrine and intracrine sources of androgens in women: inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. Endocr Rev 2003;24:152–82.
31. Labrie F, Belanger A, Cusan L, Candas B. Physiological changes in dehydroepiandrosterone are not reflected by serum levels of active androgens and estrogens but their metabolites: intracrinology. J Clin Endocrinol Metab 1997;82:2403–9.

32. Zumoff B, Strain GW, Miller LK, Rosner W. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. J Clin Endocrinol Metab 1995;80:1429–30.
33. Lasley BL, Santoro N, Randolf JF, Gold EB, Crawford S, Weiss G, et al. The relationship of circulating dehydroepiandtrosterone, testosterone, and estradiol to stages of the menopausal transition and ethnicity. J Clin Endorcrinol Metab 2002;87:3760–7.
34. Vermeulen A, Verdonck L. Plasma androgen levels during the menstrual cycle. Am J Obstet Gynecol 1976;125:491–4.
35. Rannevik G, Jeppsson S, Johnell O, Bjerre B, Laurell-Borulf Y, Svanberg L. A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG and bone mineral density. Maturitas 1995;21:103–13.
36. Bancroft J, Cawood EHH. Androgens and the menopause: a study of 40–60 year-old women. Clin Endocrinol 1996;45:577–87.
37. Burger HG, Dudley EC, Cui J, Dennerstein L, Hopper JL. A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin levels through the menopause transition. J Clin Endocrinol Metab 2000;85:2832–8.
38. Labrie F, Belanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C_{19} sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab 1997;82:2396–402.
39. Hornsby PJ. Biosynthesis of DHEAS by the human adrenal cortex and its age-related decline. Ann NY Acad Sci 1995;774:29–46.
40. Orentreich N, Brind JL, Rizer RL, Vogelman JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. J Clin Endocrinol Metab 1984;59:551–5.
41. Ravaglia G, Forti P, Maioli F, Boschi F, Bernardi M, Pratelli L, et al. The relationship of dehydroepiandrosterone sulfate (DHEAS) to endocrine-metabolic parameters and functional status in the oldest-old. Results from an Italian study on healthy free-living over-ninety-year-olds. J Clin Endocrinol Metab 1996;81:1173–8.
42. Sarrel P, Dobay B, Wiita B. Estrogen and estrogen-androgen replacement in postmenopausal women dissatisfied with estrogen-only therapy. J Reprod Med 1998;43:847–56.
43. Bancroft J, Sanders D, Davidson D, Warner P. Mood, sexuality, hormones, and the menstrual cycle. III. Sexuality and the role of androgens. Psychosom Med 1983;45:509–16.
44. Persky H, Lief AI, Strauss D, Miller WR, O'Brien CP. Plasma testosterone levels and sexual behavior of couple. Arch Sex Behav 1987;7:157–73.
45. Morris NM, Udry JD, Khan-Dawood F, Dawood MY. Marital sexual frequency and midcycle female testosterone. Arch Sex Behav 1987; 16:27–38.
46. Van Goozen SHM, Wiegant VM, Endert E, Helmond FA, Van de Poll NE. Psychoendocrinological assessment of the menstrual cycle: the relationship between hormones, sexuality, and mood. Arch Sex Behav 1997;26:359–82.
47. Riley A, Riley E. Controlled studies on women presenting with sexual drive disorder. I. Endocrine status. J Sex Marital Ther 2000;26:269–83.
48. Floter A, Nathorst-Boos J, Carlstrom BK, von Schoultz B. Androgen status and sexual life in perimenopausal women. Menopause 1997;4: 95–100.
49. Persky H, Dreisbach L, Miller WR, O'Brien CP, Khan MA, Lief HI, et al. The relation of plasma androgen levels to sexual behaviors and attitudes of women. Psychosom Med 1982;44:305–19.
50. McCoy NL, Davidson JM. A longitudinal study of the effects of menopause on sexuality. Maturitas 1985;7:203–10.
51. Dennerstein L, Randolph J, Taffe J, Dudley E, Burger H. Hormones, mood, sexuality, and the menopausal transition. Fertil Steril 2002;77: S42–S48.
52. Bachmann GA, Leiblum SR, Kemmann E, Colburn DW, Swartzman L, Shelden R. Sexual expression and its determinants in the postmenopausal woman. Maturitas 1984;6:19–29.
53. Cutler WB, Garcia CR, Huggins GR, Preti G. Sexual behavior and steroid levels among gynecologically premature premenopausal women. Fertil Steril 1986;48:496–502.
54. Schreiner-Engel P, Schiavi RC, White D, Ghizzani A. Low sexual desire in women: the role of reproductive hormones. Horm Behav 1989;23:221–34.
55. Bancroft J, Sherwin B, Alexander GM, Davidson DW, Walker A. Oral contraceptives, androgens, and the sexuality of young women. II. The role of androgens. Arch Sex Behav 1991;20:121–35.
56. Cawood EHH, Bancroft J. Steroid hormones, the menopause, sexuality and well-being of women. Psycholog Med 1996;26:925–36.
57. Studd JWW, Collins WP, Chakravarti S, Newton JR, Oram D, Parsons A. Oestradiol and testosterone implants in the treatment of psychosexual problems in the postmenopausal woman. Br J Obstet Gynaecol 1977;84:314–5.
58. Dennerstein L, Dudley EC, Hopper JL, Burger H. Sexuality, hormones and the menopausal transition. Maturitas 1997;26:83–93.
59. Rosen RC. Assessment of female sexual dysfunction: review of validated methods. Fertil Steril 2002;77:S89–S93.
60. Miller KK, Sesmilo G, Schiller A, Schoenfeld D, Burton S, Klibanski A. Androgen deficiency in women with hypopituitarism. J Clin Endocrinol Metab 2001;86:51–7.
61. Arlt W, Callies F, van Vlijmen JC, Koehler I, Reincke M, Bidlingmaier M, et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med 1999;341:1013–20.
62. Hughes CL, Wall LL, Creasman WT. Reproductive hormone levels in gynecologic oncology patients undergoing surgical castration after spontaneous menopause. Gynecol Oncol 1991;40:42–5.
63. Judd HL, Lucas WE, Yen SS. Effect of oophorectomy on circulating testosterone and androstenedione levels in patients with endometrial cancer. Am J Obstet Gynecol 1974;118:793–8.
64. Gravholt CH, Svenstrup B, Bennett P, Christiansen JS. Reduced androgen levels in adult Turner syndrome: influence of female sex steroids and growth hormone status. Clin Endocrinol 1999;50:791–800.
65. Hartmann BW, Kirchengast S, Albrecht A, Laml T, Soregi G, Huber JC. Androgen serum levels in women with premature ovarian failure compared to fertile and menopausal controls. Gynecolog Obstet Invest 1997;44:127–31.
66. Hunt PJ, Gurnell EM, Huppert FA, Richards C, Prevost AT, Wass JAH, et al. Improvement in mood and fatigue after dehydroepiandrosterone treatment in Addison's disease in a randomized double-blind trial. JCEM 2000;85:4650–6.
67. Lovas K, Gabre-Medhin G, Trovik TS, Fougner KJ, Uhlving S, Nedrebo BG, et al. Replacement of dehydroepiandrosterone in adrenal failure: no benefit for subjective health status and sexuality in a 9-month, randomized, parallel group clinical trial. J Clin Endocrinol Metab 2003;88:1112–8.
68. Abraham GE. Ovarian and adrenal contribution to peripheral androgens during the menstrual cycle. J Clin Endocrinol Metab 1974;39: 340–6.
69. Heinonen PK, Koivula T, Rajaniemi H, Pystynen P. Peripheral and ovarian venous concentrations of steroid and gonadotropin hormones in postmenopausal women with epithelial ovarian tumors. Gynecol Oncol 1986;25:1–10.
70. Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, von Muhlen D. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. J Clin Endocrinol Metab 2000;85:645–51.
71. Vehkavaara S, Hakala-Ala-Pietilä T, Virkamaki A, Bergholm R, Ehnholm C, Hovatta O, et al. Differential effects of oral and transdermal estrogen replacement therapy on endothelial function in postmenopausal women. Circulation 2000;102:2687–93.
72. Braunstein GD. Androgen insufficiency in women. In: Carr B, Blackwell R, Azziz R, eds. Essential reproductive medicine. New York: McGraw-Hill. In press.
73. Braunstein GD. Androgen insufficiency in women: summary of critical issues. Fertil Steril 2002;77:S94–S9.
74. Notelovitz M. Androgen effects on bone and muscle. Fertil Steril 2002;77:S34–S41.
75. Sherwin BB, Gelfand MM. Differential symptoms response to parenteral estrogen and/or androgen administration in the surgical menopause. Am J Obstet Gynecol 1985;1512:153–9.
76. Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females: a prospective, crossover study of sexual steroid administration in the surgical menopause. Psychosom Med 1985;47: 339–51.
77. Myers LS, Dixen J, Morrissette D, Carmichael M, Davidson JM. Effects of estrogen, androgen, and progestin on sexual psychophysiology and behavior in postmenopausal women. J Clin Endocrinol Metab 1990;70:1124–31.
78. Burger H, Hailes J, Nelson J. Effect of combined implants of oestradiol and testosterone on libido in post-menopausal women. Br Med J 1987;294:936–7.
79. Davis SR, McCloud P, Strauss BJG, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas 1995;21:227–36.
80. Dow MGT, Hart DM. Hormonal treatments of sexual unresponsiveness in postmenopausal women: a comparative study. Br J Obstet Gynaecol 1983;90:361–6.
81. Burger HG, Hailes J, Menelaus M, Nelson J, Hudson B, Balazs N. The management of persistent menopausal symptoms with oestradiol-testosterone implants: clinical, lipid and hormonal results. Maturitas 1984;6:351–8.
82. Sherwin BB. Affective changes with oestrogen and androgen replacement therapy in surgically menopausal women. J Affect Dis 1988;14: 177–87.

83. Sherwin BB, Gelfand M. The role of androgen in the maintenance of sexual functioning in ovarectomized women. Psychosom Med 1987; 49:397–409.
84. Tuiten A, Laan E, Panhuysen G, Everaerd W, Haan ED, Koppeschaar H, et al. Discrepancies between genital responses and subjective sexual function during testosterone substitution in women with hypothalamic amenorrhea. Psychsom Med 1996;58:234–41.
85. Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SS. The effect of six months treatment with a 100 mg daily dose of dehydropepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. Clin Endocrinol (Oxf) 1998;49:421–32.
86. Barnhart KT, Freeman E, Grisso JA, Rader DJ, Sammel M, Kapoor S, et al. The effect of dehydroepiandrosterone supplementation to symptomatic perimenopausal women on serum endocrine profiles, lipid parameters, and helath-related quality of life. J Clin Endocrinol Metab 1999;84:3896–902.
87. Baulieu E, Thomas G, Legrain S, Lahlou N, Roger N, Debuire B. Dehydroepiandrosterone (DHEA), DHEA sulphate, and aging: contribution of the DHEAge study to a sociobiomedical issue. Proc Natl Acad Sci USA 2000;97:4279–84.
88. Johannsson G, Burman P, Wiren L, Engstrom BE, Nilsson AG, Ottosson M, et al. Low dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women: a placebo-controlled trial. J Clin Endocrinol Metab 2002;87:2046–52.
89. Kicovic PM, Cortes-Prieto J, Luisit M, Milojevic S, Franchi F. Placebo-controlled cross-over study of effects of Org OD 14 in menopausal women. Reproduction 1981;6:81–91.
90. Nevinny-Stickel J. Double-blind cross-over study with Org OD 14 and placebo in postmenopausal patients. Arch Gynecol 1983;234:27–31.
91. Palacios S, Menendez C, Jurado AR, Castano R, Vargas JC. Changes in sex behaviour after menopause: effects of tibolone. Maturitas 1995; 22:155–61.
92. Laan E, van Lunsen RH, Everaerd W. The effects of tibolone on vaginal blood flow, sexual desire and arousability in postmenopausal women. Climacteric 2001;4:28–41.
93. Moore RA. Livial: a review of clinical studies. Brit J Obstet Gynaecol 1999;106(Suppl 19):1–21.
94. Davis SR. The effects of tibolone on mood and libido. Menopause 2002;9:162–70.
95. Parasrampuria J, Schwartz K, Petesch R. Quality control of dehydroepiandrosterone dietary supplement products. JAMA 1998;280:1565.
96. Kicman AT, Bassindale T, Cowan DA, Dale S, Hutt AJ, Leeds AR. Effect of androstenedione ingestion on plasma testosterone in young women; a dietary supplement with potential health risks. Clin Chem 2003;49:167–9.
97. Leder BZ, Leblanc KM, Longcope C, Lee H, Catlin DH, Finkelstein JS. Effects of oral androstenedione administration on serum testosterone and estradiol levels in postmenopausal women. J Clin Endocrinol Metab 2002;87:5449–54.
98. Barrett-Connor E, Timmons C, Young R, Wiita B, and the Estratest Working Group. Interim Safety Analysis of a two-year study comparing oral estrogen-androgen and conjugated estrogens in surgically menopausal women. J Womens Health 1996;5:593–602.
99. Raisz LG, Wiita B, Artis A, Bowen A, Schwartz S, Trahiotis M, et al. Comparison of the effects of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women. J Clin Endocrinol Metab 1996;81:37–43.
100. Phillips E, Bauman C. Safety surveillance of esterified estrogens–methyltestosterone (Estratest and Estratest HS) replacement therapy in the United States. Clin Therap 1997;19:1070–84.
101. Barrett-Connor E, Young R, Notelovitz M, Sullivan J, Wiita B, Yang H, Nolan J. A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. J Reprod Med 1999;44:1012–20.
102. Hickok LR, Toomey C, Speroff L. A comparison of esterified estrogens with and without methyltestosterone: effects on endometrial histology and serum lipoproteins in postmenopausal women. Obstet Gynecol 1993;82:919–24.
103. Watts NB, Notelovitz M, Timmons MC, Addison WA, Wiita B, Downey LJ. Comparison of oral estrogens and estrogens plus androgen on bone mineral density, menopausal symptoms, and lipid-lipoprotein profiles in surgical menopause. Obstet Gynecol 1995;85: 529–37.
104. Farish E, Fletcher CD, Hart DM, Al Azzawi F, Abdalla HI, Gray CE. The effects of hormone implants on serum lipoproteins and steroid hormones in bilaterally oophorectomised women. Acta Endocrinol 1984;106:116–20.