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POSITION STATEMENT

The role of testosterone therapy in postmenopausal women: position statement of The North American Menopause Society

ABSTRACT

Objective: To create an evidence-based position statement regarding the role of exogenous testosterone in postmenopausal women.

Design: The North American Menopause Society (NAMS) enlisted a panel of clinicians and researchers acknowledged to be experts in the field of testosterone therapy to review the evidence obtained from the medical literature, compile supporting statements and conclusions, and reach consensus on recommendations. The document was reviewed and approved by the NAMS Board of Trustees.

Results: Endogenous testosterone levels have not been clearly linked to sexual function in postmenopausal women. Published evidence from randomized controlled trials, although limited, indicates that exogenous testosterone, both oral and nonoral formulations, has a positive effect on sexual function, primarily desire, arousal, and orgasmic response, in women after spontaneous or surgically induced menopause. Data are inadequate to support recommending testosterone use for any other indication, including preserving or increasing bone mineral density, reducing hot flashes, increasing lean body mass, or improving well-being. Hirsutism and acne have been associated with testosterone therapy, but the actual risks are not well defined. It is not known whether testosterone therapy increases the risk of breast cancer, cardiovascular disease, or thromboembolic events. There are few data regarding the safety and efficacy of testosterone therapy in women not using concomitant estrogen therapy or for the use of testosterone therapy for longer than 6 months. Clinically available laboratory assays do not accurately detect testosterone concentrations at the values typically found in women, and no testosterone level has been clearly linked to a clinical syndrome of hypoandrogenism or testosterone insufficiency.

Conclusions: Postmenopausal women with decreased sexual desire associated with personal distress and with no other identifiable cause may be candidates for testosterone therapy. Testosterone treatment without concomitant estrogen therapy cannot be recommended because of a lack of evidence. When evaluating a woman for testosterone therapy, recommendations are to rule out causes not related to testosterone levels (eg, physical and psychosocial factors, medications) and to ensure that there is a physiologic cause for reduced testosterone levels (eg, bilateral oophorectomy). Laboratory testing of testosterone levels should be used only to monitor for supraphysiologic levels before and during therapy, not to diagnose testosterone insufficiency. Monitoring should also include subjective assessments of sexual response, desire, and satisfaction as well as evaluation for potential adverse effects. Transdermal patches and topical gels or creams are preferred over oral products because of first-pass hepatic effects documented with oral

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The North American Menopause Society (NAMS) developed this manuscript with assistance from an Editorial Board composed of Jan L. Shifren, MD (Chair); Susan R. Davis, MBBS, FRACP, PhD; Lorraine Dennerstein, AO, MBBS, DPM, PhD, FRANZCP; Julia R. Heiman, PhD; Rogerio A. Lobo, MD; and James A. Simon, MD.

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formulations. Custom-compounded products should be used with caution because the dosing may be more inconsistent than it is with government-approved products. Testosterone products formulated specifically for men have a risk of excessive dosing, although some clinicians use lower doses of these products in women. Testosterone therapy is contraindicated in women with breast or uterine cancer or in those with cardiovascular or liver disease. It should be administered at the lowest dose for the shortest time that meets treatment goals. Counseling regarding the potential risks and benefits should be provided before initiating therapy.

Key Words: Menopause – Testosterone – Androgen – Estrogen – Postmenopausal sexual function – Sexual desire disorder – Testosterone testing.

In response to the need to define standards of clinical practice in North America as they relate to menopause-associated health conditions, The North American Menopause Society (NAMS) has created this evidence-based position statement on the role of testosterone therapy in postmenopausal women.

An Editorial Board composed of experts from both clinical practice and research was enlisted to review the published data, compile supporting statements and conclusions, and make recommendations. If the evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was established. (Practice parameter standards related to NAMS position statements have been described in an editorial.[1]) The NAMS Board of Trustees was responsible for the final review and approval of this document. Updates to this position statement will be considered annually to review for developments in scientific research that substantially alter the conclusions.

For this position statement, a MEDLINE search of the medical literature was conducted to identify studies presenting data on the efficacy of testosterone therapy to treat postmenopausal women. Priority was given to evidence from randomized, controlled trials as well as to systematic reviews and meta-analyses of such trials, using criteria described elsewhere for evaluating evidence.[2-4] Recommendations from other evidence-based guidelines as well as data from meeting abstracts, US Food and Drug Administration (FDA) committee reviews, and unpublished sources were also reviewed.

The overall objective of this position statement is to provide a review of clinical data relating to efficacy and safety of testosterone therapy and to make recommendations regarding its role in the clinical management of postmenopausal women. In narrowing the focus, several qualifying statements were established:

- Therapeutic recommendations are limited to postmenopausal women. Safety and efficacy data from adequately sized randomized controlled trials in premenopausal and perimenopausal women are lacking.
- Recommendations pertain to women who have experienced either spontaneous or surgically induced menopause. Although surgically induced menopause may cause physiologic symptoms different from those of spontaneous menopause, it is reasonable to assume that the therapeutic results will be similar. However, there have been no adequately powered clinical trials comparing these populations. No data are available for women who experienced induced menopause for reasons other than surgery.
- Clinical evidence presented in this position statement is limited to prescription testosterone products. Custom-compounded testosterone formulations are sometimes used; however, the quality and dosing consistency of these formulations can vary greatly.
- Although the treatment recommendations are relevant internationally, the discussion is limited to prescription therapies available for clinical practice in the United States and Canada.
- A general evaluation of all androgens, including over-the-counter products such as dehydroepiandrosterone (DHEA), is beyond the scope of this position statement. Although some efficacy data on DHEA in women with adrenal insufficiency are encouraging, data in healthy postmenopausal women are not adequate to establish the efficacy of this agent in this population.
- Clinical evidence and management strategies focus primarily on sexual concerns that occur around the time of menopause, as this was the primary end point of most clinical trials. A general discussion of other causes of, and treatments for, sexual health problems is beyond the scope of this position statement.

PHYSIOLOGY

In women, circulating androgens are normally produced in the ovaries and the adrenal glands, and through

peripheral conversion of circulating androstenedione and DHEA to testosterone. Five androgens and androgen precursors are clinically important: testosterone, dihydrotestosterone, androstenedione, DHEA, and dehydroepiandrosterone sulfate (DHEAS). This section focuses primarily on testosterone production and factors affecting serum levels.

Testosterone production and metabolism

Approximately one third of circulating testosterone comes directly from the ovaries, and two thirds comes from peripheral conversion of precursors derived from the ovary and the adrenal gland. Although the adrenal gland does not produce testosterone directly, a large percentage of circulating testosterone is derived from adrenal precursors.

Because the ovaries account, either directly or indirectly, for approximately 50% of the testosterone in circulation, bilateral oophorectomy—even after menopause—significantly decreases testosterone levels.[5] However, spontaneous menopause per se is not associated with a significant change in circulating levels of testosterone. Postmenopausal women have lower levels of testosterone than premenopausal women, but the decrease is very gradual and likely results from declining ovarian and adrenal function with aging.[6] Although not all studies are in agreement, the postmenopausal ovary appears to produce testosterone throughout life.[7]

No significant changes in the metabolic clearance rates of androgen occur at menopause or with advancing age. The pathways of metabolism are also not altered at menopause, but the capacity of adipose tissue for aromatization of androstenedione and testosterone to estrone and estradiol increases with age.[8]

Serum testosterone levels

Circulating levels of testosterone are a reflection of both production and clearance rates. Only 1% to 2% of testosterone in the circulation is free or unbound. The remainder is bound either tightly to sex hormone-binding globulin (SHBG) or loosely to albumin (approximately 66% and 33%, respectively).[9] Variables that increase SHBG levels, such as oral estrogen therapy, can lower the levels of unbound testosterone. Factors that lower SHBG levels, such as obesity and hypothyroidism, can increase free testosterone levels.

Most studies indicate that free testosterone concentrations remain the same or increase slightly during the menopause transition, possibly because SHBG levels decrease with the cessation of ovarian estrogen production. In a small cross-sectional study of premenopausal women,[10] total testosterone levels did not differ significantly in any cycle stage between older women (43-47 years old) and younger women (19-37 years old), although the midcycle rise in free testosterone levels and androstenedione characteristic of younger women was absent in the older women. In a cross-sectional study of healthy premenopausal women aged 21 to 51 years,[11] 24-hour mean levels of testosterone declined significantly with age, such that a woman in her 40s had approximately half the circulating testosterone levels of a woman in her early 20s. A prospective longitudinal study from Norway[12] reported a 15% decrease in testosterone after menopause, but this was dependent on the woman's age, not her menopause status. In the Melbourne Women's Midlife Health Project,[13] a prospective longitudinal study of Australian women aged 45 to 55 years, mean testosterone levels did not vary in the years before and after menopause. More recently, in a cross-sectional study of Australian women aged 18 to 75 years, total and free testosterone levels were found to significantly decline with age, starting in the early reproductive years.[14]

Circulating testosterone levels are also affected by medical therapies and diseases. Both endogenous and exogenous estrogens, especially oral therapy, decrease free testosterone levels, primarily through increased SHBG binding.[15-17] Markedly lower levels of testosterone have been found in women with hypopituitarism[18] and in women infected with the human immunodeficiency virus who had significant weight loss.[19]

Table 1 provides a summary of factors that may lower testosterone levels.

TABLE 1. *Conditions that decrease testosterone levels in women*

- *Bilateral oophorectomy.* Surgical removal of both ovaries decreases testosterone levels by as much as 50%.
- *Age.* Advancing age is associated with reduced levels of testosterone and its precursors DHEA and androstenedione. This likely is caused by natural aging of the ovaries and adrenal glands.
- *Hypothalamic/pituitary/adrenal insufficiency.* Low testosterone levels are associated with hypopituitarism of any cause, including Sheehan's syndrome, and with adrenal disease, including Addison's disease.
- *Systemic glucocorticoid or oral estrogen therapy.* Decreased testosterone levels are associated with the suppression of adrenocorticotropic hormone levels with glucocorticoid use and luteinizing hormone levels with oral estrogen therapy. Oral estrogen users have significantly lower levels of free testosterone, due to increased levels of SHBG.
- *Hyperthyroidism.* Both hyperthyroidism and excessive thyroid medication increase SHBG levels, leading to lower levels of free testosterone.
- *Chronic illness*. Low testosterone concentrations are found in women with anorexia nervosa, clinical depression, advanced cancer, and burn trauma, although the precipitating mechanism is not known.

Conclusions

The postmenopausal ovary continues to produce testosterone. Although postmenopausal women generally have lower testosterone levels than premenopausal women, the levels decline as a function of aging rather than menopause. In most studies, free testosterone levels remained relatively unchanged during the menopause transition. Bilateral oophorectomy results in a significant decrease in testosterone production. Oral estrogen therapy, in general, reduces circulating free testosterone levels.

CLINICAL EVIDENCE

Testosterone therapy has been studied for various end points in women; however, most evidence from randomized controlled trials relates to therapeutic management of sexual function, particularly, disorders of sexual desire. (See Female sexual function terminology in Table 2.) Although data on other effects of testosterone therapy are presented, the primary focus is on sexual function.

Only randomized, placebo-controlled, blinded (either single- or double-blind) trials of postmenopausal women published in peer-reviewed journals are included in this section. Trials were excluded for reliance on a nonvalidated sexual function instrument, inadequately powered sample size, or inclusion of premenopausal women. In the text, use of the word *significant* refers to findings that are statistically significant.

As most testosterone treatment phases lasted 6 months or less, an evaluation of long-term safety and efficacy is not possible.

TABLE 2. *Female sexual function terminology*

Hypoactive sexual desire disorder. The persistent or recurrent deficiency or absence of sexual fantasies, thoughts, and/or desire for sexual activity, which causes personal distress.
Sexual arousal disorder. The persistent or recurrent inability to attain or maintain sufficient sexual excitement, which causes personal distress. It may be expressed as a lack of subjective excitement, genital lubrication, swelling, or other somatic responses.
Orgasmic disorder. The persistent or recurrent difficulty of, delay in, or absence of attaining orgasm after sufficient sexual stimulation and arousal, which causes personal distress.
Dyspareunia. Recurrent or persistent genital pain associated with sexual intercourse.
Vaginismus. Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration and causes personal distress.

Adapted from DSM-IV-TR.[20]

Sexual function

The effects of endogenous and exogenous testosterone on a woman's sexual function are discussed in this section.

Endogenous testosterone

The relationship between endogenous testosterone levels and sexual function in women has not been clearly established. Observational studies have found varying results.[11,13,21-28] This may be attributable to factors such as inclusion of small numbers of women of limited age ranges[11,21] and/or of limited reproductive status,[22] insensitivity of most assays of total and free testosterone at the lower end of the range for reproductive-aged women,[13,23] reliance on total testosterone rather than free testosterone measures,[24-26] and failure of some studies to take into account the diurnal and cyclical variations in testosterone levels for blood sampling. In addition, few of the studies used a well-validated instrument to assess female sexual function.

The two largest and most rigorously controlled studies[27,28] did not find a link. A randomly selected cross-sectional study of 1,423 women aged 18 to 75 years who were not seeking health care found no relationship between low sexual function and testosterone levels, based on measurements of either free or total testosterone.[27] This supported an earlier longitudinal study of 438 women that found low testosterone levels were not associated with declines in sexual function during the menopause transition.[28]

Because no clear association can be made between sexual function and testosterone concentrations, it is not possible to establish total or free testosterone values that would indicate a clinical testosterone deficiency state.

Exogenous testosterone

In randomized controlled trials of exogenous testosterone in postmenopausal women, evidence has shown improved sexual desire, sexual responsiveness, and frequency of sexual activity (see Table 3).

With the exception of a testosterone-alone arm in one study[29] that provided no data on adverse events, all trials combined testosterone with either estrogen therapy or, for women with a uterus, estrogen-progestogen therapy. Thus, the efficacy and safety of testosterone therapy without concomitant estrogen therapy in postmenopausal women have not been established.

In an early study, Dow and colleagues[30] evaluated the addition of testosterone implant therapy (100 mg) to estradiol implant therapy (50 mg) in postmenopausal women (mean age, 46.9 years), both spontaneous and surgically induced, who were experiencing a decline in

TABLE 3. *Randomized controlled trials of testosterone for sexual desire disorders in postmenopausal women*

Year	Author	Intervention (dose/d)	Menopause type	N	Duration (mo)	Design	Result
1983	Dow[30]	Implants: E (50 mg) ± T (100 mg)	I,N	40	4	SB, PG	NS
1985	Sherwin[29]	Inj: T enan (200 mg); T enan (150 mg) + E dien (7.5 mg) + E benz (1 mg); E val (10 mg)	I	53	3	DB, CO	S
1987	Burger[31]	Implants: E (40 mg) ± T (100 mg)	I,N	20	6	SB, PG	S
1995	Davis[32]	Implants: E (50 mg) ± T (50 mg)	I,N	34	24	SB, PG	S
1998	Sarrel[33]	Oral: EE (1.25 mg) ± mT (2.5 mg)	I,N	20	2	DB, PG	S
2000	Shifren[36]	Oral CEE (0.625 mg) ± T patch (150 or 300 μg)	I	75	3	DB, CO	S
2002	Floter[35]	Oral: E val (2 mg) ± T und (40 mg)	I	50	6	DB, CO	S
2003	Lobo[34]	Oral: EE (0.625 mg) ± mT (1.25 mg)	I,N	218	4	DB, PG	S
2005	Braunstein[37]	Oral estrogen ± T patch (150, 300, or 450 μg)	I	447	6	DB, PG	S
2005	Buster[38]	Oral/transdermal estrogen ± T patch (300 μg)	I	533	6	DB, PG	S

CEE, conjugated equine estrogens; CO, crossover; DB, double blind; E, estradiol; E benz, estradiol benzoate; E dien, estradiol dienanthate; EE, esterified estrogens; E val, estradiol valerate; I, surgically induced menopause; Inj, injection; mT, methyltestosterone; N, natural (spontaneous) menopause; NS, nonsignificant results; PG, parallel-group; S, significant results; SB, single blind; T, testosterone; T enan, testosterone enanthate; T und, testosterone undecanoate.

sexual interest. No significant differences were found between the groups in sexual interest and responsiveness.

Sherwin and colleagues[29] undertook the only clinical trial that used a testosterone-alone arm to evaluate sexual functioning in women after surgical menopause. Women were randomized at the time of surgery to one of five groups: 150 mg testosterone enanthate plus estrogen (7.5 mg estradiol dienanthate and 1.0 estradiol benzoate), 10 mg estradiol valerate alone, 200 mg testosterone enanthate alone, placebo, or a control group. All drug treatments and placebo were intramuscular injections. The crossover design had 3-month active-treatment phases plus a 1-month placebo washout between the phases. In the treatment phases, adding testosterone significantly enhanced intensity of sexual desire, sexual arousal, and frequency of sexual fantasies compared with estrogen alone or placebo. The testosterone levels achieved with this formulation of intramuscular testosterone were often supraphysiologic for women.

Burger and colleagues[31] compared the efficacy of implants combining 100 mg testosterone and 40 mg estradiol against those containing 40 mg estradiol alone in postmenopausal women (either spontaneous or surgically induced) with psychosexual complaints while taking oral estrogen therapy. The mean ages of women in the combined-implant and estradiol-alone groups were 43.5 and 48.2 years, respectively. At 6 weeks, significant improvements in libido and sexual enjoyment were noted in testosterone-treated women, and these improvements persisted throughout the 24-week trial.

In a 2-year trial, Davis and colleagues[32] evaluated the effect of adding subcutaneous 50-mg testosterone implants to estradiol implants (50 mg) in women who experienced spontaneous or surgically induced menopause (mean age range, 51-57 years). Testosterone recipients had significantly greater improvements in sexual activity, satisfaction, pleasure, and frequency of orgasm compared with women receiving estradiol alone.

Sarrel and colleagues[33] randomized women who experienced spontaneous or surgically induced menopause (mean age, 52 years) to either oral esterified estrogens (1.25 mg) or esterified estrogens plus oral methyltestosterone therapy (2.5 mg). All women were using estrogen therapy at baseline. At 8 weeks, methyltestosterone recipients had significantly improved sexual desire and satisfaction compared with baseline; the esterified estrogen-alone group did not have a significant improvement from baseline.

Lobo and colleagues[34] investigated the effect of adding oral methyltestosterone (1.25 mg) to oral esterified estrogens (0.625 mg) for postmenopausal women aged 40 to 65 years (mean age range, 53-54 years) with hypoactive sexual desire disorder. Both spontaneous and surgically induced postmenopausal women were included. Testosterone recipients had significantly increased levels and frequency of sexual interest or desire compared with those receiving estrogen alone; however, other sexual function scores did not improve.

In a placebo-controlled, crossover trial, Floter and colleagues[35] added oral testosterone undecanoate (40 mg/day) to oral estradiol valerate (2 mg/day) therapy for surgically induced postmenopausal women aged 45 to 60 years (mean age, 54 years). Crossover occurred after 24 weeks of therapy and continued for another

24 weeks. Compared with estrogen-alone recipients, testosterone-estrogen recipients had significantly improved overall sexual function, which included greater interest in and enjoyment of sexual activity. Testosterone levels obtained with testosterone undecanoate in this study were supraphysiologic.

Three published randomized controlled trials have evaluated the effect of transdermal testosterone patches on women experiencing impaired sexual function after surgically induced menopause.[36-38] Shifren and colleagues[36] evaluated the effect of testosterone patches with release rates of 150 or 300 μg/day in surgically induced postmenopausal women aged 31 to 56 years (mean age, 47 years) with self-reported impaired sexual function since menopause. All participants were taking at least 0.625 mg/day oral conjugated equine estrogens. Compared with those receiving placebo, women using the higher-dose patches, but not the lower-dose ones, had significantly better scores on several sexual function measures, including sexual activity and orgasm.

In a 24-week trial, Braunstein and colleagues[37] evaluated the efficacy and safety of transdermal patches delivering testosterone doses of 150, 300, or 450 μg/day in postmenopausal women (aged 24 to 70 years) with low sexual desire causing personal distress. All women were also taking oral estrogen therapy, at various doses. Compared with placebo, only the 300-μg/day dose significantly increased sexual desire and frequency of satisfying sexual activity. Results with the 150- and 450-μg/day doses were not significantly different from placebo. Adverse events occurred at similar rates in all groups.

In another 24-week trial, Buster and colleagues[38] reported that testosterone patches delivering a dose of 300 μg/day significantly increased the number of satisfying sexual activities versus baseline in postmenopausal women (mean age range, 48-50 years) with hypoactive sexual desire disorder. Testosterone recipients had a mean increase of 1.56 events per 4 weeks over baseline (3.1 events); placebo recipients had an increase of 0.73 events. The between-group difference was also statistically significant ($P < 0.001$). Testosterone also significantly improved sexual desire and decreased personal distress. The overall safety profile was similar for both groups. All women received concomitant estrogen therapy, either oral or transdermal.

Other effects

In addition to sexual function, testosterone therapy has been evaluated for its effect on several other end points.

Bone mineral density

Several small randomized controlled trials have suggested that adding testosterone to estrogen therapy has a favorable effect on bone, either by improving bone mineral density[32,39,40] or by reducing bone turnover markers (see Table 4).[41] No randomized controlled trial has reported the effects of testosterone therapy on fracture risk in postmenopausal women. Two other trials[42,43] provided data that were inadequate to evaluate their findings.

Well-being

In four randomized controlled trials, testosterone in either an oral or injectable formulation has not been shown to have a beneficial effect on psychological well-being significantly greater than that of placebo (see Table 5).[35,44-46] However, significant improvements in well-being scores were reported in a well-designed, crossover study using a testosterone patch (300 μg/day but not 150 μg/day) plus oral CEE in surgically induced postmenopausal women.[36]

Menopause symptoms

In a trial by Dow et al,[30] testosterone implants had no beneficial effect on menopause symptoms (see Table 5), defined on the Greene Climacteric Scale[47] as psychological, somatic, and vasomotor symptoms. Similarly, Regestein et al,[45] using the Menopause-Specific Quality of Life Questionnaire,[48] found oral testosterone had no significant effect on somatic, psychological, and total scores. Two other trials evaluated the efficacy of

TABLE 4. *Randomized controlled trials of testosterone effects on bone in postmenopausal women*

Year	Lead author	Intervention (dose/d)	N	Duration (mo)	End point	Design
1992	Garnett[42]	Implants: E (75 mg) ± T (100 mg)	50	12	Bone markers	DB, PG
1995	Davis[32]	Implants: E (50 mg) ± T (50 mg)	34	24	BMD	SB, PG
1995	Watts[40]	Oral: EE (1.25 mg) ± mT (2.5 mg)	66	24	BMD	DB, PG
1995	Raisz[41]	Oral: CEE (1.25 mg) vs EE (1.25 mg) + mT (2.5 mg)	28	2.25	Bone markers	Open-label, PG
1999	Barrett-Connor[43]	Oral: CEE (0.625/1.25 mg) ± mT (1.25/2.5 mg)	311	24	BMD	DB, PG
2000	Miller[39]	Sublingual: mic E (0.5 mg) ± mic T (1.25 mg)	56	6	BMD, bone markers	DB, PG

BMD, bone mineral density; CEE, conjugated equine estrogens; DB, double blind; E, estradiol; EE, esterified estrogens; mT, methyltestosterone; mic, micronized; PG, parallel group; SB, single blind; T, testosterone.

TABLE 5. *Randomized controlled trials of testosterone therapy on various end points in postmenopausal women*

Year	Lead author	Intervention dose/d	N	Mo	End point	Design
1983	Dow[30]	Implants: E (50 mg) ± T (100 mg)	40	4	Menopausal symptoms	SB, PG
1984	Farish[51]	Implants: E (50 mg) ± T (100 mg)	31	6	Lipids	DB
1985	Sherwin[46]	Inj: E dien (7.5 mg) + E benz (1 mg) + T enan (150 mg); E val (10 mg); T enan (200 mg)	53	3	Well-being	DB, CO
1987	Montgomery[44]	Implants: E (50 mg) ± T (100 mg)	84	4	Well-being	DB, PG
1993	Hickok[52]	Oral: EE (0.625 mg) ± mT (1.25 mg)	26	6	Lipids, coagulation	DB, PG
1995	Watts[40]	Oral: EE (1.25 mg) ± mT (2.5 mg)	66	24	Menopausal symptoms, lipids	DB, PG
1999	Barrett-Connor[43]	Oral: CEE (0.625/1.25 mg/day) ± mT (1.25/2.5 mg/d)	311	24	Lipids, hirsutism	DB, PG
1999	Simon[16]	Oral: EE (0.625/1.25 mg) ± mT (1.25/2.5 mg)	93	3	Menopausal symptoms	DB, PG
2000	Davis[53]	Implants: E (50 mg) ± T (50 mg)	34	24	Body composition, lipids	SB, PG
2000	Shifren[36]	Oral E (0.625 mg) ± T patch (150 or 300 μg)	75	3	Well-being, coagulation, hirsutism/acne	DB, CO
2001	Regestein[45]	Oral: EE (0.625 mg) ± mT (1.25 mg)	42	4	Well-being, menopausal symptoms, cognition	DB, CO
2002	Basaria[49]	Oral: EE (1.25 mg) ± mT (2.5 mg)	40	4	Coagulation, lipids	DB, PG
2002	Dobs[50]	Oral: EE (1.25 mg) ± mT (2.5 mg)	40	4	Lipids, body composition	DB, PG
2002	Floter[35]	Oral: E val (2 mg) ± T und (40 mg)	50	6	Well-being, coagulation, hirsutism/acne	DB, CO
2002	Wisniewski[54]	Oral: EE (1.25 mg) ± mT (2.5 mg)	26	4	Cognition	DB, PG
2003	Lobo[34]	Oral: EE (0.625 mg) ± mT (1.25 mg)	218	4	Lipids, hirsutism/acne	DB, PG
2005	Buster[38]	Oral/transdermal estrogen ± T patch (300 μg)	533	6	Lipids, coagulation, cardiovascular, hirsutism/acne	DB, PG
2005	Braunstein[37]	Oral estrogen ± T patch (150, 300, or 405 μg)	447	6	Lipids, hirsutism/acne	DB, PG

CEE, conjugated equine estrogens; CO, crossover; DB, double blind; E, estrogen; E benz, estradiol benzoate; E dien, estradiol dienanthate; EE, esterified estrogens; E val, estrogen valerate; inj, injection; mT, methyltestosterone; PG, parallel group; SB, single blind; T, testosterone; T enan, testosterone enanthate; T und, testosterone undecanoate.

testosterone on this end point,[16,40] but study design limitations have raised questions regarding their findings.

Lipids

Clinical trials indicate that oral testosterone therapy is associated with a reduction in high-density lipoprotein (HDL) cholesterol and triglycerides in postmenopausal women receiving concomitant oral estrogen therapy (see Table 5),[34,40,43,49-52] an effect that is not apparent with nonoral testosterone therapy.[36,53] Two 6-month trials of transdermal testosterone therapy found no significant effect on lipids.[37,38]

Coagulation

Trials in postmenopausal women evaluating the effect of testosterone therapy on hematocrit have reported inconsistent results. A 6-month randomized controlled trial[52] reported a statistically significant increase in hematocrit with testosterone therapy, although the levels remained within the normal range. Other trials,[35,36] however, have not shown any differences (see Table 5). Testosterone therapy has not been associated with increased plasma viscosity.[37,38,49]

Cardiovascular disease

There are no data from randomized controlled trials of adequate size and duration to evaluate the effect of testosterone therapy on cardiovascular outcomes in postmenopausal women, including myocardial infarction, stroke, or venous thromboembolic events.

Cognition

Two small trials have looked at the effects of testosterone on cognitive functioning in postmenopausal women (see Table 5). Wisniewski et al[54] reported maintenance of scores on building memory tasks in women treated with oral estrogen-methyltestosterone versus a decline in women treated with estrogen alone. Regestein et al[45] reported faster mean reaction time for the switching-attention test for women treated with estrogen-methyltestosterone compared with those receiving estrogen alone or no treatment.

Weight, body composition

Most clinical trials that evaluated these end points reported a tendency toward greater weight gain with testosterone therapy, although the increases did not reach statistical significance (see Table 5). Two trials[50,53] found significantly increased lean body mass (reported by Davis et al[53] as total body fat-free mass) with testosterone therapy.

Hirsutism and acne

Of the published randomized clinical trials in postmenopausal women, few have prospectively and systematically evaluated the effects of testosterone

therapy on facial hair growth and skin (see Table 5). Furthermore, some of the trials may have been too short to accurately assess hirsutism. Crossover studies with no washout periods reported no adverse effect on hirsutism or acne from either testosterone undecanoate (a 6-month trial)[35] or transdermal testosterone (a 3-month trial),[36,38] although the transdermal patch recipients did have a statistically significant, but not clinically significant, increase in depilation frequency. In a 4-month parallel-group trial, Lobo et al[34] reported no differences in hirsutism or mean scores for acne between groups treated with oral methyltestosterone plus estrogen or oral estrogen alone. A 24-month parallel-group trial[43] using oral methyltestosterone found hirsutism was uncommon, and rates were similar in all groups regardless of testosterone use or dose. More recently, a 24-week parallel-group trial[37] using transdermal testosterone patches with doses of 150, 300, or 450 μg/day had similar incidences of hirsutism, acne, and other androgenic adverse events in all treatment groups.

Breast cancer

No randomized controlled trials have been of sufficient size or duration to evaluate the effect of testosterone on breast cancer. A review of published studies assessing exogenous testosterone effects on the risk of breast cancer in both animal and human models[55,56] did not find an adverse effect from estrogen-testosterone therapy. A retrospective, observational study (mean follow-up 5.8 years) comparing breast cancer rates in 508 postmenopausal women using estrogen alone, estrogen-testosterone, or no postmenopausal hormone therapy also found no increased risk from testosterone.[57] Any potential effect of testosterone on breast cancer, however, would require evaluation in a randomized clinical trial of long duration.

Testosterone enanthate for injection (Delatestryl) is government-approved in both the United States and Canada to treat metastatic breast cancer. However, this drug was approved in the 1950s, and it is rarely used for this indication in clinical practice.

Conclusions

Endogenous testosterone levels have not been clearly linked to specific clinical syndromes related to disorders of sexual desire in postmenopausal women.

Although data are limited, there is consistent evidence that in postmenopausal women with sexual concerns, adding either oral or nonoral testosterone to estrogen therapy results in a positive effect on sexual function, primarily an increase in sexual desire. Data are inadequate to support the therapeutic use of testosterone for any other indication, including bone preservation, menopause symptoms, well-being, body composition, or cognition.

Hair growth and acne may occur with therapy, but the actual risks have not been quantified. The frequency of these symptoms is low when testosterone levels are maintained within the normal range for women. Oral testosterone formulations are associated with a reduction in HDL cholesterol that is not observed with nonoral formulations. Whether testosterone therapy increases the risks for breast cancer, cardiovascular disease, or thromboembolic events is not known.

There are insufficient data for any conclusions to be made regarding the efficacy and safety of testosterone therapy in postmenopausal women not receiving concomitant estrogen therapy or for therapeutic use exceeding 6 months.

CLINICAL EVALUATION

In selecting postmenopausal women for testosterone therapy, clinical factors are generally of much greater importance than serum hormone levels, especially given the relative unreliability of most clinically available testosterone assays for women and the multiple causes of sexual desire disorders.

Postmenopausal women presenting with complaints of decreased sexual desire, arousal, or response may be appropriate candidates to evaluate for testosterone therapy. In the clinical evaluation, the primary goal is to rule out alternative causes of the woman's sexual concerns.

Potential candidates for testosterone therapy should have a comprehensive clinical evaluation. This includes a psychosexual and psychosocial history, a complete medical history including medications that may have an impact on sexual functioning, and a physical examination.

Laboratory tests should be ordered as indicated. Tests may include thyroid-stimulating hormone levels, complete blood cell count, prolactin levels, or a pelvic ultrasonogram.

The impact of physical, psychological, emotional, and relationship factors on sexual function must be considered. The Melbourne Women's Midlife Health Project[58] found that the most important factors affecting a middle-aged woman's sexual interest, arousal, and enjoyment were her prior level of sexual function, change in partner status, feelings toward partner, and estradiol levels (see Table 6). Although declining

TABLE 6. *Potential contributors to decreased sexual function in postmenopausal women*

Psychosocial issues
Previous attitudes toward sex
Social customs and religious beliefs regarding sex
Poor partner relationship
Feelings toward partner
Length of relationship
Partner's decreased capacity for sexual activity
Partner's loss of interest in sex
No available partner
Life stressors from work, family, relationships
Negative body image
Psychological disorders
Depression
Anxiety
Other psychiatric illness
Medical conditions
Menopause (lower levels of endogenous estrogen, testosterone)
Vaginal atrophy
Vasomotor symptoms
Age-related decline in sexual drive
Fatigue
Incontinence
Chronic illness, including cardiovascular disease, diabetes mellitus, arthritis, renal failure
Cancer, particularly gynecologic or breast cancer
Pharmacologic agents
Psychotropics: selective serotonin-reuptake inhibitors, tricyclic antidepressants, benzodiazepines, barbiturates, anxiolytics, sedatives
Cardiovascular: beta-blockers, clonidine, methyldopa, spironolactone (which has antiandrogenic properties)
Hormones: gonadotropin-releasing hormone agonists and antagonists, corticosteroids, antiandrogens
Recreational drugs: alcohol, marijuana, cocaine, heroin, methadone

estradiol levels at menopause are associated with declining domains of sexual function and physiologic conditions linked to sexual concerns (eg, vaginal atrophy, dyspareunia), the impact is not as great as these psychological factors.

Testosterone testing

The accuracy of commercially available testosterone assays has caused some concern, particularly with regard to sensitivity at the low levels typical for postmenopausal women. Most commercially available assays were designed to measure testosterone levels in men, which are approximately 10 times higher than in women.

In general, testosterone levels should not be used to diagnose testosterone insufficiency or to monitor the efficacy of therapy in postmenopausal women. Testosterone levels may be helpful as a safety measure to ensure that the testosterone levels are not elevated before or during testosterone therapy. Neither the normal physiologic range for testosterone levels nor an absolute threshold for testosterone insufficiency in postmenopausal women has been established. The reference range provided by the testing laboratory is commonly used.

Blood samples for laboratory analysis should be drawn in the morning, typically before 10 am. A diurnal variation in testosterone secretion has been noted, with peak levels found in the early morning.[59]

The following is a list of laboratory tests used for evaluating testosterone levels.

Total testosterone. This is the total amount of testosterone in the circulation. Many though not all commercial laboratories provide accurate measurements for total testosterone. As these assays were developed to measure testosterone in men, they may be insensitive to the low testosterone levels typical for postmenopausal women. All measures of free testosterone are dependent on an accurate total testosterone measurement.

Free testosterone. This is a direct measurement of the level of testosterone that is not bound to SHBG or albumin in the circulation. Equilibrium dialysis is generally considered the most accurate test of free testosterone, as long as it is undertaken in conjunction with a highly sensitive method for measuring total testosterone. However, this test is labor intensive, lengthy, and costly, and it is not available in most hospital and commercial laboratories. Direct analogue immunoassays of free testosterone, the assay type available in most clinical laboratories, is not recommended because it is unreliable and lacks precision at the low levels found in women.[18]

Rather than directly measuring free testosterone concentrations, the level of free testosterone can be calculated using a ratio of total testosterone to SHBG, called the free testosterone index (or free androgen index). Results have been shown to accurately correlate with free testosterone levels measured by equilibrium dialysis.[18,60,61] Figure 1 provides a formula for calculating the free testosterone index.

The free testosterone concentration can also be calculated with an equation created by Sodergard et al[62] that uses total testosterone, albumin, and SHBG. This equation provides values that are as accurate as free testosterone measured by equilibrium dialysis,[18,60,61] and it is the most accurate calculated free testosterone value available. However, the calculation is complex, which limits its use in clinical practice. Some laboratories are able to provide this calculated value.

Bioavailable testosterone. This measures testosterone not bound to SHBG plus the portion of total serum testosterone loosely bound to albumin, typically about

$$\frac{\text{Total T (ng/dL)}}{\text{SHBG (nmol/L)}} \times 3.47 = \text{free T index}$$

or

$$\frac{\text{Total T (nmol/L)}}{\text{SHBG (nmol/L)}} \times 100 = \text{free T index}$$

Note: Most laboratories report total T as ng/dL and SHBG as nmol/L. Multiplying by 3.47 (the conversion factor for testosterone between ng/dL and nmol/L) corrects for the units.

FIG. 1. Free testosterone index calculation.

20% of total testosterone. Because the portion bound to albumin is easily displaced, thereby becoming "free," some clinicians prefer to use bioavailable testosterone as a measure of free testosterone.

Salivary measurements. This provides a measurement of testosterone levels in saliva. These assays have questionable reliability and accuracy, especially in the low ranges seen in women. Furthermore, salivary concentrations of testosterone represent only a small fraction of the amount in circulation, and accurate measurement is limited by the imprecision of available assays. Their use in clinical practice is not recommended.

Estrogen testing

It is not necessary to measure endogenous estrogen levels. Postmenopausal women not using estrogen therapy can be assumed to have low estrogen levels. Women receiving standard doses of postmenopausal estrogen therapy typically have estrogen levels similar to those of reproductive-aged women.

A trial of estrogen therapy should be considered before initiating testosterone therapy in a woman experiencing bothersome menopause-related symptoms, including hot flashes, vaginal dryness, or dyspareunia.

Conclusions

Although not all total testosterone assays are reliable measures of the low concentrations typical for postmenopausal women, the test is clinically useful to rule out a testosterone excess state (either endogenous or secondary to testosterone treatment) rather than to identify testosterone insufficiency. Clinical practice standards for low testosterone levels in postmenopausal women have not been established. In general, clinicians should use the reference range provided by the testing laboratory. Measuring estrogen levels in postmenopausal women is unlikely to provide additional useful information.

TESTOSTERONE THERAPIES

No testosterone product is government-approved in the United States for treating symptoms of sexual dysfunction in women; an IM testosterone enanthate product (Delatestryl) available in Canada was approved nearly 50 years ago for "frigidity." However, a few prescription testosterone-containing products are government-approved for use by women and men, some of which are used off-label to treat sexual desire disorders in postmenopausal women.

Custom-compounded formulations containing testosterone are also available through prescription, but these formulations are not subject to the stringent quality-control standards of government-approved products. As a result, they may have inconsistent quality and dosing. Also, clinical trials have not evaluated either their safety or efficacy for any indication, including improvement of sexual function in women.

The following section profiles the available testosterone formulations and routes of administration.

Oral testosterone

When taken orally, micronized testosterone is generally not well absorbed and does not result in measurable blood levels. Thus, a chemical process (eg, methylation) is used to create testosterone derivatives that can provide adequate bioavailability and acceptable dosing consistency when administered orally.

The only testosterone-containing product with FDA approval to treat menopause-related symptoms is an oral tablet that combines esterified estrogens and methyltestosterone (Estratest, with 1.25 mg esterified estrogens plus 2.5 mg methyltestosterone; Estratest HS, with 0.625 mg esterified estrogens plus 1.25 mg methyltestosterone). This product is indicated for the treatment of moderate to severe vasomotor symptoms unresponsive to estrogen. However, it is often used off-label to treat symptoms of sexual desire disorders in postmenopausal women.

In Canada, one oral testosterone derivative—testosterone undecanoate (Andriol)—is used in postmenopausal women to treat symptoms of sexual desire disorders, but it is government-approved only for male androgen deficiency. For women, it is commonly dosed at 40 mg/day, but the optimal dose is not known. Testosterone undecanoate is rapidly absorbed, resulting in substantially increased blood levels within 2 to 4 hours.[63] In addition, it has some of the same metabolic effects as methyltestosterone.

All oral testosterone formulations undergo first-pass hepatic metabolism, increasing the risk of adverse

effects on lipids and liver function. Prolonged use of high doses of oral testosterone has been associated with liver dysfunction in women, including hepatomas and hepatocellular carcinomas. Oral formulations also reduce HDL cholesterol levels and triglycerides in estrogen-treated women.[34,40,43,49-52]

Transdermal testosterone gels, creams, and ointments

Testosterone is well absorbed through the skin.[64,65] Two testosterone transdermal gels (AndroGel and Testim) have been government-approved in the United States (AndroGel is approved in Canada) for use in men. These products deliver high doses of testosterone, which can cause masculinizing side effects in women. However, some clinicians modify the dose for off-label use in women by reducing the amount applied, although it is difficult to accurately regulate the amount of testosterone delivered.

Despite the lack of clinical trials and quality-control standards, custom-compounded testosterone gels, creams, and ointments are popular formulations for improving women's sexual desire. For women, an appropriate dose of compounded 1% testosterone gel, cream, or ointment is 0.5 g/day, which should deliver 5 mg of testosterone daily, one tenth the generally prescribed dose for men. The product can be applied directly to any skin surface (but commonly the clitoris, labia, thigh, arm, or abdomen) several times weekly. Genital application has the potential to increase sensitivity in the genital tissues, but it is often associated with local irritation.

Absorption and response may be erratic or unpredictable, requiring close clinical monitoring. Supraphysiologic levels are likely if large doses are applied. There is also a risk of drug transfer to another person through skin contact, although the likelihood of side effects in others is low, even after intense skin contact.[66] In addition, some women find these formulations messy.

Transdermal testosterone patches

Although transdermal patch administration is a well-accepted method of testosterone delivery in men, there are no available testosterone patches with appropriate doses for women. Androderm and Testoderm, two testosterone patches government-approved in the United States (Androderm is approved in Canada) for use in men, deliver high doses of testosterone that can cause masculinizing side effects in women. These patches, either whole or in part, should not be used by women.

Patches delivering lower testosterone doses (150-300 μg/day) are being investigated for use in women. Clinical trial reports indicate that a 300-μg/day dose for 3 to 6 months is generally safe and effective for the treatment of sexual desire disorder in surgically induced postmenopausal women receiving concomitant estrogen therapy.[36-38]

Subcutaneous testosterone pellets

There is no government-approved testosterone pellet available in the United States or Canada. However, custom-compounded testosterone pellets are available. Although tests have found that some of these formulations deliver stable levels of testosterone, there is a risk of achieving supraphysiologic levels in women.[32] Other risks include the surgical procedure required for insertion and removal, discomfort at the insertion site, and infection.

Intramuscular testosterone

In the United States, all testosterone products administered by IM injection are approved for use only in men. Recommended doses are inappropriate for women, although a smaller dose may be used in women.

In Canada, testosterone enanthate for injection (Delatestryl) is government-approved for the treatment of "frigidity" in women at an IM dose of 100 mg every 4 weeks. A combination of 150 mg/mL testosterone enanthate, 7.5 mg/mL estradiol dienanthate, and 1 mg/mL estradiol benzoate (Climacteron), administered 0.5 to 1.0 mL IM every 4 to 6 weeks, is approved for use in postmenopausal women, either spontaneous or surgically induced, to treat menopause symptoms and estrogen-induced osteoporosis. This drug is sometimes used off-label for treating symptoms of sexual desire disorders.

Testosterone administered by IM injection often results in supraphysiologic levels immediately after administration, followed by low levels over time. Peaks may result in both side effects and tachyphylaxis, leading to increased dosing requirements to obtain the same therapeutic effect. Resulting testosterone levels can be modified by adjusting the dose and the injection frequency. Injection may be uncomfortable for some women and proper injection technique is required to reduce the risk of infection or nerve injury.

Sublingual and buccal testosterone

These routes result in rapid absorption and turnover, requiring increased doses for an effect. There are no FDA-approved formulations of testosterone that have a sublingual route of administration. However, a buccal formulation (Striant) is FDA-approved for use in hypogonadal men; no buccal product is approved in

Canada. Custom-compounded sublingual and buccal preparations are available. Clinical trials have not determined the appropriate doses for women. Some recipients complain that sublingual preparations have an unpleasant taste.

Testosterone products in development

Several testosterone-containing products appropriately dosed for women are being investigated for the treatment of sexual desire disorders in postmenopausal women (see Table 7).

Adverse effects

The potential risks associated with testosterone therapy in postmenopausal women are not well defined. Commonly reported adverse effects are acne and excess facial hair. High testosterone doses causing supraphysiologic levels could result in lowering of the voice (which could be permanent), clitoral enlargement, excess body hair, edema, erythrocytosis, and liver dysfunction. Psychological changes (eg, increased anger or aggression) also are potential risks.

Adverse changes in lipids and liver function tests have been observed with testosterone, but primarily only with oral formulations. Studies have found that the risk of masculinizing side effects is generally low and dose dependent. With topical testosterone, hair growth or skin irritation may occur at the application site. In general, adverse effects can be minimized if testosterone levels are maintained within appropriate physiologic ranges.

Contraindications are focused primarily on those associated with postmenopausal estrogen therapy, because most data were collected in women receiving concomitant estrogen therapy. Nevertheless, testosterone is generally not recommended for use in women with breast or uterine cancer or with cardiovascular or liver disease.

Adverse effects of testosterone therapy in postmenopausal women not receiving concomitant estrogen therapy have not been determined.

Monitoring

During testosterone therapy, monitoring should include a subjective assessment of sexual desire, response, and satisfaction. Women also should be evaluated for potential adverse effects, such as acne and hirsutism, as these may be signs of excess dosing. Establishing baseline levels for lipids and liver function tests may be prudent before initiating testosterone therapy, particularly with oral testosterone. The tests may be performed 3 months after initiating therapy, and if levels are stable, annually thereafter. Testosterone treatment should be reduced or stopped if adverse events occur.

The free testosterone index may be used to determine whether testosterone levels exceed the appropriate physiologic range, to help reduce the risk of adverse events associated with supraphysiologic testosterone levels. This index is appropriate for monitoring all testosterone formulations except oral methyltestosterone, which cannot be detected by standard testosterone assays.

The free testosterone index should be checked after 2 or 3 months of therapy. If levels do not exceed the desired range, additional testing may be delayed for 6 to 12 months.

If improvements in sexual function do not result after approximately 3 months of treatment, testosterone doses may be increased until testosterone levels reach the upper limit of the normal range for reproductive-aged women. If therapy remains ineffective, it should be stopped.

Counseling

Any recommendation for testosterone therapy should be accompanied by a full explanation of the potential benefits and risks of therapy. Women must be informed that none of the commonly used testosterone therapies are government-approved for the treatment of symptoms related to female sexual function, and therefore, therapeutic use will be off-label. In addition, they should understand that potential risks are associated with a therapy for which safety and efficacy data are limited, including data on long-term use or use without concomitant estrogen therapy. Documentation of this discussion should be recorded in the medical record.

TABLE 7. *Testosterone products in development for female sexual desire disorders*

Formulation	Product name, developer	Trial status
Oral methyltestosterone (plus esterified estrogens)	Estratest, Solvay Pharmaceuticals, Inc.	Phase 2/3
Testosterone cream	Androsorb, Novavax, Inc.	Phase 2
Testosterone gel	Tostrelle, Cellegy Pharmaceuticals, Inc.	Phase 2/3
Testosterone gel (plus estrogen)	LibiGel, BioSante Pharmaceuticals	Phase 2/3
Testosterone patch	Intrinsa, Procter & Gamble Pharmaceuticals	Phase 3
Testosterone spray (metered-dose transdermal system)	Testosterone MDTS, Vivus, Inc.	Phase 2
Vaginal ring	[No product name], Warner Chilcott	Phase 2

RECOMMENDATIONS

Based on the evidence, The North American Menopause Society supports the following recommendations regarding testosterone use in postmenopausal women.

- Postmenopausal women may be candidates for testosterone therapy if they present with symptoms of decreased sexual desire associated with personal distress and have no other identifiable cause for their sexual concerns.
- Testosterone therapy without concomitant estrogen therapy cannot be recommended, because there are no data on the safety and efficacy of testosterone therapy in women not using concomitant estrogen.
- Laboratory testing of testosterone levels should be used only to monitor for supraphysiologic testosterone levels before and during therapy, not to diagnose testosterone insufficiency. Laboratory assays are not accurate for detecting testosterone concentrations at the low values typically found in postmenopausal women, and no testosterone level has been clearly linked to a clinical syndrome of hypoandrogenism or testosterone insufficiency. Oral methyltestosterone cannot be measured by standard assays.
- Testosterone values vary from laboratory to laboratory. In assessing results of testosterone testing, clinicians should use the reference ranges provided by the testing laboratory.
- The simplest and most readily available clinical estimate of free testosterone is the free testosterone index, calculated from total testosterone and SHBG.
- The Sodergard equation for free testosterone uses total testosterone, SHBG, and albumin. Although it is a more complex formula, it provides a more accurate calculation than the free testosterone index. It is an option to consider if the testing laboratory can provide the calculation.
- Salivary testing is not considered to be a reliable measure of testosterone levels.
- Before initiating testosterone treatment, baseline profiles for serum lipids and liver function tests should be established and retesting at 3 months considered. If stable, annual testing is advised.
- Testosterone therapy should be administered at the lowest dose for the shortest time that meets treatment goals.
- Transdermal patches and topical gels or creams may be preferred over oral products based on their avoidance of first-pass hepatic effects documented with oral formulations. However, only oral and IM testosterone products for women are currently government-approved.
- Pellet and IM formulations have a risk of excessive dosing. Also, administration may be uncomfortable.
- Products formulated specifically for men provide excessive doses for women and should not be used unless doses are reduced considerably and blood testosterone levels are monitored closely for supraphysiologic levels.
- Custom-compounded products should be used with caution because the dosing may be more inconsistent than it is with government-approved products.
- There are insufficient data for any conclusions to be made regarding the efficacy and safety of testosterone therapy exceeding 6 months.
- Therapeutic monitoring should include subjective assessments of sexual response, desire, and satisfaction as well as evaluation for potential adverse effects.
- If adverse events are observed, dose reductions are advised. If the adverse events do not diminish with lower doses, therapy should be discontinued.
- Contraindications are focused primarily on those associated with estrogen therapy. However, testosterone therapy should not be initiated in postmenopausal women with breast or uterine cancer or with cardiovascular or liver disease.
- Counseling regarding the potential risks and benefits of testosterone use and the limitations of formulations not government-approved should be provided before initiating therapy.

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