

## POSITION STATEMENT, PART 2

# The Role of Testosterone Therapy in Postmenopausal Women: Position Statement of The North American Menopause Society

With this article, *Menopause Management* continues its reprint of The North American Menopause Society's Position Statement addressing testosterone (reprinted with permission from *Menopause* 2005;12:497-511). Part 1 was reprinted in the November/December 2005 issue; this is the second and final part of the statement. The full report is available at [www.menopause.org/aboutmeno/consensus.html](http://www.menopause.org/aboutmeno/consensus.html).

– Wulf H. Utian, MD, PhD

## 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 com-

prehensive 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 ultrasound. The impact of physical, psychological, emotional, and relationship factors on sexual function must be considered. The Melbourne Women's Midlife Health Project<sup>58</sup> 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 estradiol levels at menopause are associated with declining domains of sexual function and physiologic conditions linked to sexual concerns (eg, vaginal atrophy,

## Erratum

*Menopause Management* regrets that errors were inadvertently introduced into the reprint of Part 1 of this statement. The errors concerned units of measure of testosterone; namely, milligram (mg) was used instead of microgram (µg). The corrected information is provided on page 26.

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.<sup>59</sup>

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

**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, methylodopa, spironolactone (which has antiandrogenic properties)
- Hormones: gonadotropin-releasing hormone agonists and antagonists, corticosteroids, antiandrogens
- Recreational drugs: alcohol, marijuana, cocaine, heroin, methadone

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 meas-

uring 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.<sup>18</sup>

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.<sup>18,60,61</sup> 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<sup>62</sup> that uses total testosterone, albumin, and SHBG. This equation provides values that are as accurate as free testosterone measured by equilibrium dialysis,<sup>18,60,61</sup> 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 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 pro-

## Postmenopausal women not using estrogen therapy can be assumed to have low estrogen levels.

vides 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 typi-

cally 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

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

or

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

**Figure 1. Free testosterone index calculation**

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.

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

## There are no available testosterone patches with appropriate doses for women.

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.<sup>63</sup> 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.<sup>34,40,43,49-52</sup>

### Transdermal testosterone gels, creams, and ointments

Testosterone is well absorbed through the skin.<sup>64,65</sup> 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.<sup>66</sup> 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.<sup>36-38</sup>

### 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.<sup>32</sup>

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

## The potential risks associated with testosterone therapy in postmenopausal women are not well defined.

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 pri-

**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

marily 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.

### 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.

# T

## estosterone therapy without concomitant estrogen therapy cannot be recommended.

- 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 suprathreshold 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 suprathreshold 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. ■

### Acknowledgments

NAMS appreciates the contributions of the following members of the Editorial Board: *Jan L. Shifren, MD (Chair)*, assistant professor of obstetrics, gynecology and reproductive biology, Harvard Medical School, and director, Menopause Program, Vincent Obstetrics and Gynecology Service, Massachusetts General Hospital, Boston, MA; *Susan R. Davis, MBBS, FRACP, PhD*, chair of women's health, Department of Medicine, Central and Eastern Clinical School, Monash University Medical School, Prahran, Victoria, Australia; *Lorraine Dennerstein, AO, MBBS, DPM, PhD, FRANZCP*, professor, and director, Office for Gender and Health, Department of Psychiatry, University of Melbourne, Parkville, Victoria, Australia; *Julia R. Heiman, PhD*, director, Kinsey Institute for Research in Sex, Gender and Reproduction, and professor of psychology and clinical psychiatry, Indiana University, Bloomington, IN; *Rogerio A. Lobo, MD*, professor of obstetrics and gynecology, Columbia University College of Physicians & Surgeons, New York, NY; and *James A. Simon, MD*, clinical professor of obstetrics and gynecology, George Washington University School of Medicine, Washington, DC.

Final review and approval was conducted by the 2004-2005 NAMS Board of Trustees: *Bruce Kessel, MD* (President), associate professor, Department of Obstetrics and Gynecology, and Women's Health, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI; *George I. Gorodeski, MD, PhD* (President-elect), professor of reproductive biology, Case Western Reserve University School of Medicine, University Hospitals of Cleveland, Department of Obstetrics and Gynecology, Cleveland, OH; *Marcie K. Richardson, MD* (Treasurer), assistant director of obstetrics and gynecology for clinical quality, Harvard Vanguard Medical Associates, The Copley Center, Boston, MA; *Marilyn L. Rotherth, PhD, RN, FAAN* (Secretary), dean and professor, College of Nursing, Michigan State University, East Lansing, MI; *Robert R. Freedman, PhD*, professor, Departments of Psychiatry and Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, MI; *J. Chris Gallagher, MD*, professor of medicine, Creighton University, Department of Metabolism, St. Joseph's Hospital, Omaha, NE; *Victor W. Henderson, MD, MS*, professor, Departments of Health Research & Policy and Neurology & Neurological Sciences, Stanford University School of Medicine, Stanford, CA; *JoAnn V. Pinkerton, MD*, associate professor, Department of Obstetrics and Gynecology, Medical Director, The Women's Place, Midlife Health Center, University of Virginia Health Sciences Center, Charlottesville, VA; *Nancy K. Reame, MSN, PhD, FAAN*, Rhettaugh Dumas Professor of Nursing and Research Scientist, University of Michigan, Reproductive Sciences Program, Department of Obstetrics and Gynecology, Ann Arbor, MI; *James A. Simon, MD*, clinical professor of obstetrics and gynecology, George Washington University School of Medicine, Washington, DC; *Leon Speroff, MD*, professor of obstetrics and gynecology, Oregon Health and Science University, Portland, OR; *Isaac Schiff, MD* (Ex officio), Joe Vincent Meigs Professor of Gynecology, Harvard Medical School, chief, Vincent Memorial Obstetrics and Gynecology Service, Massachusetts General Hospital, Women's Care Division, Boston, MA; and *Wulf H. Utian, MD, PhD* (Ex officio), Arthur H. Bill Professor Emeritus of Reproductive Biology, Case Western Reserve University School of Medicine, consultant in women's health, The Cleveland Clinic Foundation, executive director, The North American Menopause Society, Cleveland, OH.

The Society also acknowledges the valuable assistance of *Ian Graham, PhD*, senior social scientist and associate director, Clinical Epidemiology Program, Ottawa Health Research Institute, University of Ottawa, Ontario, Canada; as well as *Philip K. Lammers*, NAMS medical editor, and *Pamela P. Boggs, MBA*, NAMS director of education and development. The development of this position statement was supported by an unrestricted educational grant from Procter & Gamble Pharmaceuticals.

## Disclosure

NAMS is committed to ensuring balance, independence, and objectivity in all its educational activities. All those involved in the development of a CME activity are required to disclose financial relationships they or their spouse/partner have had during the last 12 months with a commercial interest whose products or services are discussed in the CME activity content, or with any commercial supporters of the activity, over which they have control. For the Editorial Board, Dr. Davis reports Lawley, Procter & Gamble (consultant); Dr. Dennerstein reports Procter & Gamble (consultant), research support, honoraria); Dr. Heiman reports Organon (consultant); Dr. Lobo reports no significant financial relationships; Dr. Shifren reports Procter & Gamble, Solvay, Watson, (research support), Procter & Gamble,

Solvay, Wyeth (consultant); Dr. Simon reports Abbott, Amgen, Aventis, Barr, Bayer, Berlex, Besins, BioSante, Bristol-Myers Squibb, Duramed, Eli Lilly, Galen, Merck, Novartis, Novavax, Organon/AKZO, Ortho-McNeil, Pfizer, Procter & Gamble, 3M, Solvay, TAP, Upsher-Smith, Watson, Vivus, Wyeth (research support), Abbott, Aventis, Berlex, Eli Lilly, Merck, Ortho, Pfizer, Solvay, Wyeth (speakers' bureau), Abbott, Barr, Berlex, BioSante, Duramed, Galen, Glaxo-SmithKline, Johnson & Johnson, Lipocine, Merck, Noven, Novavax, Pfizer, Procter & Gamble, Roche, Solvay, TAP, Vivus, Wyeth (consultant). The position statement was reviewed and approved by the NAMS 2004-2005 Board of Trustees.

## References (for Parts I & II)

- Boggs PP, Utian WH. The North American Menopause Society develops consensus opinions [editorial]. *Menopause* 1998;5:67-68.
- Scottish Intercollegiate Guidelines Network. SIGN 50: A Guideline Developers Handbook. 2001. Available at: <http://www.sign.ac.uk/guidelines>. Accessed April 25, 2005.
- Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ* 1999;318:593-596.
- Harbour R, Miller J, for the Scottish Intercollegiate Guidelines Network Grading Review Group. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001;323:334-336.
- 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;118:793-798.
- Longcope C. Hormone dynamics at the menopause. *Ann N Y Acad Sci* 1990;592:21-30.
- 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;85:645-651.
- Misso ML, Jang C, Adams J, et al. Adipose aromatase gene expression is greater in older women and is unaffected by postmenopausal estrogen therapy. *Menopause* 2005;12:210-215.
- 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.
- Mushayandebu T, Castracane VD, Gimpel T, Adel T, Santoro N. Evidence for diminished midcycle ovarian androgen production in older reproductive aged women. *Fertil Steril* 1996;65:721-723.
- 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;80:1429-1430.
- Overlie I, Moen MH, Morkrid L, Skjaeraasen JS, Holte A. The endocrine transition around menopause: a five-year prospective study with profiles of gonadotropins, estrogens, androgens and SHBG among healthy women. *Acta Obstet Gynecol Scand* 1999;78:642-647.
- 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; 85:2832-2838.
- Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. *J Clin Endocrinol Metab* 2005;90:3847-3853.
- Casson PR, Elkind-Hirsch KE, Buster JE, Hornsby PJ, Carson SA, Snabes MC. Effect of postmenopausal estrogen replacement on circulating androgens. *Obstet Gynecol* 1997;90:995-998.
- Simon J, Klaiber E, Wiita B, Bowen A, Yang HM. Differential effects of estrogen-androgen and estrogen-only therapy on vasomotor symptoms, gonadotropin secretion, and endogenous androgen bioavailability in postmenopausal women. *Menopause* 1999;6:138-146.
- Nachtigall LE, Raju U, Banerjee S, Wan L, Levitz M. Serum estradiol-binding profiles in postmenopausal women undergoing three common estrogen replacement therapies: associations with sex hormone-binding globulin, estradiol, and estrone levels. *Menopause* 2000;7:243-250.
- Miller KK, Rosner W, Lee H, et al. Measurement of free testosterone in normal women and women with androgen deficiency: comparison of methods. *J Clin Endocrinol Metab* 2004;89:525-533.
- Huang JS, Wilkie SJ, Dolan S, et al. Reduced testosterone levels in human immunodeficiency virus-infected women with weight loss and low weight. *Clin Infect Dis* 2003;36:499-506.
- American Psychiatric Association, Task Force on DSM-IV. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR*. 4th ed. Arlington, VA: American Psychiatric Association, 2000.
- Labrie F, Belanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. *J Clin Endocrinol Metab* 1997;82: 2396-2402.
- Randolph JF Jr, Sowers M, Gold EB, et al. Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. *J Clin Endocrinol Metab* 2003;88:1516-1522.
- Dennerstein L, Dudley EC, Hopper JL, Burger H. Sexuality, hormones and the menopausal transition. *Maturitas* 1997;26:83-93.
- McCoy NL, Davidson JM. A longitudinal study of the effects of menopause on sexuality. *Maturitas* 1985;7:203-210.
- Cawood EH, Bancroft J. Steroid hormone, the menopause, sexuality and well-being of women. *Psychol Med* 1996;26:925-936.
- Bachmann GA, Leiblum SR. Sexuality in sexagenarian women. *Maturitas* 1991;13:45-50.
- Davis SR, Davison SL, Donath S, Bell R. Relationships between circulating androgen levels and self-reported sexual function in women. *JAMA* 2005;294:91-96.
- Dennerstein L, Randolph J, Taffe J, Dudley E, Burger H. Hormones, mood, sexuality, and the menopausal transition. *Fertil Steril* 2002;77(suppl):S42-S48.
- Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females: a prospective, crossover study of sex steroid administration in surgical menopause. *Psychosom Med* 1985;47:339-351.
- Dow MG, Hart DM, Forrest CA. Hormonal treatments of sexual unresponsiveness in postmenopausal women: a comparative study. *Br J Obstet Gynaecol* 1983;90:361-366.
- Burger HG, Hailes J, Nelson J, Menelaus M. Effect of combined implants of estradiol and testosterone on libido in postmenopausal women. *BMJ* 1987;294:936-937.

## Erratum

*Menopause Management* regrets that errors were inadvertently introduced into the reprint of Part 1 of this statement. The errors concerned units of measure of testosterone; namely, milligram (mg) was used instead of microgram ( $\mu\text{g}$ ). The corrected information is provided below.

from Table 3, page 18:

### Randomized controlled trials of testosterone for sexual desire disorders in postmenopausal women

Year	Author	Intervention (dose/d)	Menopause type	N	Duration (mo)	Design	Result
2000	Shifren <sup>36</sup>	Oral CEE (0.625 mg) $\pm$ T patch (150 or 300 $\mu\text{g}$ )	I	75	3	DB, CO	S
2005	Braunstein <sup>37</sup>	Oral estrogen $\pm$ T patch (150, 300, or 450 $\mu\text{g}$ )	I	447	6	DB, PG	S
2005	Buster <sup>38</sup>	Oral/transdermal estrogen $\pm$ T patch (300 $\mu\text{g}$ )	I	533	6	DB, PG	S

CEE, conjugated equine estrogens; CO, crossover; DB, double blind; E, estradiol; E benz, estradiol benzoate; E dien, estradiol dianthate; 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.

from page 19:

#### Exogenous testosterone

Shifren and colleagues<sup>36</sup> evaluated the effect of testosterone patches with release rates of 150 or 300  $\mu\text{g}/\text{day}$  in surgically induced postmenopausal women aged 31 to 56 years (mean age, 47 years) with self-reported impaired sexual function since menopause.

In a 24-week trial, Braunstein and colleagues<sup>37</sup> evaluated the efficacy and safety of transdermal patches delivering testosterone doses of 150, 300, or 450  $\mu\text{g}/\text{day}$  in postmenopausal women (aged 24 to 70 years) with low sexual desire causing personal distress.

#### Well-being

However, significant improvements in well-being scores were reported in a well-designed, crossover study using a testosterone patch (300  $\mu\text{g}/\text{day}$  but not 150  $\mu\text{g}/\text{day}$ ) plus oral CEE in surgically induced postmenopausal women.<sup>36</sup>

from page 20:

#### Hirsutism and acne

More recently, a 24-week parallel-group trial<sup>37</sup> using transdermal testosterone patches with doses of 150, 300, or 450  $\mu\text{g}/\text{day}$  had similar incidences of hirsutism, acne, and other androgenic adverse events in all treatment groups.

from Table 5, page 22:

### Randomized controlled trials of testosterone therapy on various end points in postmenopausal women

Year	Lead author	Intervention dose/d	N	Mo	End point	Design
2000	Shifren <sup>38</sup>	Oral E (0.625 mg) $\pm$ T patch (150 or 300 $\mu\text{g}$ )	75	3	Well-being, coagulation, hirsutism/acne	DB, CO
2005	Buster <sup>38</sup>	Oral/transdermal estrogen $\pm$ T patch (300 $\mu\text{g}$ )	533	6	Lipids, coagulation, cardiovascular, hirsutism/acne	DB, PG

CEE, conjugated equine estrogens; CO, crossover; DB, double blind; E, estrogen; E benz, estradiol benzoate; E dien, estradiol dianthate; 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.

32. Davis SR, McCloud P, Strauss BJ, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas* 1995;21:227-236.

33. Sarrel P, Dobay B, Wiita B. Estrogen and estrogen-androgen replacement in postmenopausal women dissatisfied with estrogenonly therapy: sexual behaviour and neu-

roendocrine responses. *J Reprod Med* 1998;43:847-856.

34. Lobo RA, Rosen RC, Yang HM, Block B, van Der Hoop RG. Comparative effects of oral esterified estrogens with and without methyl testosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. *Fertil Steril* 2003;79:1341-1352.

35. Floter A, Nathorst-Boos J, Carlstrom K, von Schoultz B. Addition of testosterone to estrogen replacement therapy in oophorectomized women: effects on sexuality and well-being. *Climacteric* 2002;5:357-365.

(continued on page 32)

## TO COME

## Roche Laboratories

Boniva.....14-16

## Subscription Satisfaction

We want you to be completely satisfied with your subscription to *Menopause Management*. Please contact us if your address has changed or if there is any question about your subscription.

Write to:

**Menopause Management HealthCom Media**  
4259 W. Swamp Road,  
Suite 408  
Doylestown, PA 18901

Or fax to:  
215-489-7007

### The Role of Testosterone Therapy in Post-menopausal Women: Position Statement of The North American Menopause Society, Part II

(continued from page 26)

36. Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000;343:682-688.
37. Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med* 2005;165:1582-1589.
38. Buster JE, Kingsberg SA, Aguirre O, et al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol* 2005;105:944-952.
39. Miller B, De Souza M, Slade K, Lucciano AA. Sublingual administration of micronized estradiol and progesterone, with and without micronized testosterone: effect on biochemical markers of bone metabolism and bone mineral density. *Menopause* 2000;7:318-326.
40. 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;85:529-537.
41. Raisz LG, Wiita B, Artis A, 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* 1995;81:37-43.
42. Garnett T, Studd J, Watson N, Sawvas M, Leather A. The effects of plasma estradiol levels on increases in vertebral and femoral bone density following therapy with estradiol and estradiol with testosterone implants. *Obstet Gynecol* 1992;79:968-972.
43. Barrett-Connor E, Young R, Notelovitz M, et al. A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women: effects on bone mineral density, symptoms and lipid profiles. *J Reprod Med* 1999;44:1012-1020.
44. Montgomery J, Appleby L, Brincat M, et al. Effect of oestrogen and testosterone implants on psychological disorders in the climacteric. *Lancet* 1987;1:297-299.
45. Regestein Q, Friebely J, Shifren J, Schiff I. Neuropsychological effects of methyltestosterone in women using menopausal hormone replacement. *J Womens Health Gend Based Med* 2001;10:671-676.
46. Sherwin BB, Gelfand MM. Differential symptom response to parenteral estrogen and/or androgen administration in the surgical menopause. *Am J Obstet Gynecol* 1985;151:153-160.
47. Greene JG, Cooke D. Life stress and symptoms at the climacterium. *Br J Psychiatry* 1980;136:486-491.
48. Hilditch JR, Lewis J, Peter A, et al. A menopause-specific quality of life questionnaire: development and psychometric properties [published erratum appears in: *Maturitas* 1996;25:231]. *Maturitas* 1996;24:161-175.
49. Basaria S, Nguyen T, Rosenson RS, Dobs AS. Effect of methyl testosterone administration on plasma viscosity in postmenopausal women. *Clin Endocrinol (Oxf)* 2002;57:209-214.
50. Dobs AS, Nguyen T, Pace C, Roberts CP. Differential effects of oral estrogen versus estrogen-androgen replacement therapy on body composition in postmenopausal women. *J Clin Endocrinol Metab* 2002;87:1509-1516.
51. Farish E, Fletcher CD, Hart DM, Azzawi FA, Abdalla HI, Gray CE. The effects of hormone implants on serum lipoproteins and steroid hormones in bilaterally oophorectomized women. *Acta Endocrinol (Copenh)* 1984;106:116-120.
52. 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;82:919-924.
53. Davis SR, Walker KZ, Strauss BJ. Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. *Menopause* 2000;7:395-401.
54. Wisniewski A, Nguyen TT, Dobs AS. Evaluation of high-dose estrogen and high-dose estrogen plus methyltestosterone treatment on cognitive task performance in postmenopausal women. *Horm Res* 2002;58:150-155.
55. Somboonporn W, Davis S, for the National Health and Medical Research Council. Testosterone effects on the breast: implications for testosterone therapy for women. *Endocr Rev* 2004;25:374-388.
56. Key TJ, Appleby PN, Reeves GK, et al, for the Endogenous Hormones Breast Cancer Collaborative Group. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst* 2003;95:1218-1226.
57. Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. *Menopause* 2004;11:531-535.
58. Dennerstein L, Leher P, Burger H. The relative effects of hormones and relationship factors on sexual function of women through the natural menopausal transition. *Fertil Steril* 2005;84:174-180.
59. Vermeulen A. The hormonal activity of the postmenopausal ovary. *J Clin Endocrinol Metab* 1976;42:247-253.
60. 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;84:3666-3672.
61. Rinaldi S, Geay A, Dechaud H, et al. Validity of free testosterone and free estradiol determinations in serum samples from postmenopausal women by theoretical calculations. *Cancer Epidemiol Biomarkers Prev* 2002;11:1065-1071.
62. Södergard R, Backstrom T, Shanbhag V, Carstensen H. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. *J Steroid Biochem* 1982;16:801-810.
63. Floter A, Carlstrom K, von Schoultz B, Nalthorst-Boos J. Administration of testosterone undecanoate in postmenopausal women: effects on androgens, estradiol, and gonadotrophins. *Menopause* 2000;7:251-256.
64. Slater CC, Souter I, Zhang C, Guan C, Stanczyk FZ, Mishell DR. Pharmacokinetics of testosterone after percutaneous gel or buccal administration. *Fertil Steril* 2001;76:32-37.
65. Swerdloff RS, Wang C, Cunningham G, et al. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. *J Clin Endocrinol Metab* 2000;85:4500-4510.
66. Rolf C, Knie U, Lemmnitz G, Nieschlag E. Interpersonal testosterone transfer after topical application of a newly developed testosterone gel preparation. *Clin Endocrinol (Oxf)* 2002;56:637-641.