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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Sedentary Behavior, Physical Activity, and Nighttime Urinary Symptoms

By Chiara Ghetti, MD

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Dr. Ghetti reports no financial relationships relevant to this field of study.

SYNOPSIS: Sedentary behavior is associated with more severe symptoms of nocturia and nocturnal enuresis in women with urinary incontinence.

SOURCE: Chu CM, Khanijow KD, Schmitz KH, et al. Physical activity patterns and sedentary behavior in older women with urinary incontinence: An accelerometer-based study. *Female Pelvic Med Reconstr Surg* 2019;25:318-322.

The main objective of this study was to examine the relationship between physical activity, sedentary behavior, and the severity of urinary symptoms in community-dwelling women with urinary incontinence (UI). A secondary objective was to determine the feasibility of measuring physical activity using an accelerometer in this population and examining the correlation between objective accelerometer-based data and self-report measures.

This study is a secondary analysis of a cross-sectional, prospective study measuring the risk of falls in older women with UI. Subjects were recruited from three community centers and were included if they were 65 years of age or older, lived independently, were able to ambulate, and had moderate-to-severe UI (defined as a score of 6 or greater on the International Consultation on Incontinence Questionnaire [ICIQ]–UI Short Form), and were not actively seeking treatment. Subjects were excluded if they were receiving treatment for their urinary symptoms.

Subjects completed validated measures and physical functional testing in their home. Primary outcomes included: 1) incontinence severity measured by the ICIQ-UI score; 2) nighttime urinary symptoms as measured by the Nocturia, Nocturnal Enuresis and Sleep-interruption Questionnaire; 3) physical activity as measured by the Physical Activity Scale of the Elderly (PASE), a validated

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self-report questionnaire (scored 0-400, with a higher score indicating greater activity); and 4) physical activity as measured by waist-worn, tri-axial accelerometers for one week. The authors examined the relationship between physical activity/sedentary measures and urinary symptoms using univariable linear regression for continuous variables, and t-test and Wilcoxon rank sum test for categorical variables. They investigated the relationship between self-reported physical activity (PASE total score) and accelerometer-based activity data using Spearman correlation.

This analysis included data for the 35 of 37 subjects with accelerometer data. Subjects had a median age of 71 years, the majority were obese, they had severe UI based on ICIQ-UI score (median score, 12.8; range, 7-19), and they used incontinence products (71%). Half of the women reported mixed incontinence. Sixty-eight percent reported nocturia twice nightly, 97% reported it once nightly or more, and 50% reported nocturnal enuresis. Subjects wore the accelerometer for mean of eight days of the assigned seven days (range, 4–12 days). The total activity time measured by accelerometer was about three hours and constituted mainly low-intensity activity; self-reported activity also was predominantly low-intensity activity. As a corollary, accelerometer data indicated a median of 74% of time was spent in sedentary behavior.

The authors reported significant associations between low activity and lower urinary tract symptoms. In particular, low step counts were significantly associated with higher UI severity scores ($P = 0.02$). Low activity affected nighttime symptoms, with low step counts significantly associated with greater numbers of nocturia episodes ($P = 0.02$). Shorter duration of moderate to vigorous physical activity was significantly associated with greater numbers of episodes of nocturia ($P = 0.001$), severity of nocturnal enuresis ($P = 0.04$), and greater use of incontinence products ($P = 0.04$) consistent with worsened urinary incontinence.

■ COMMENTARY

The main finding of this study is that, in this sample of community-dwelling women with UI, sedentary behavior is very common, and low levels of physical activity are associated with worsened urinary symptoms.

By successfully implementing the use of accelerometers in this older population, the authors found that sedentary behavior is associated with worsened incontinence severity, nocturia, and nocturnal enuresis. As clinicians caring for elderly women, this study reminds us that physical activity may play an important role in affecting not only women's overall functional capacity, but possibly in reducing lower urinary tract symptoms. It is difficult to interpret the relationships between exercise and UI fully. Does exercise maintain pelvic floor strength in these older women? Perhaps sedentary women have bothersome urinary leakage and are less interested in activity. The small sample size and design of this study do not allow an answer to this question. However, there is a small and growing body of scientific literature regarding the relationship between physical exercise and pelvic floor function.

In 2004, Bo et al proposed two competing hypotheses[1]: that general exercise training strengthens the pelvic floor vs. general exercise training overloads and weakens the pelvic floor. The research has resulted in conflicting findings, with studies showing that physical exercise increases, decreases, or has no impact on pelvic floor strength. Nygaard et al found that mild to moderate physical activity decreases the odds of having or developing UI.[2] Since exercise unmasks UI, leaking during exercise is very common. Exercise may worsen leakage for women with incontinence. Pelvic organ prolapse also has been associated with a history of strenuous activity.

In their review, Nygaard et al concluded that the existing literature suggests that most physical activity does not harm the pelvic floor, and that mild to moderate activity may decrease the risk of urinary incontinence. In addition, exercise provides numerous other health benefits for women. The present study suggests that a sedentary lifestyle is associated with increased urinary incontinence and, in particular, increased nighttime urinary symptoms, both of which significantly affect quality of life in aging women.

It is important to encourage all our patients, older patients particularly, to stay physically active and to remind them about the health benefits of exercise. Activity provides many physical and mental health benefits and, as such, is a strong modifiable risk factor. Exercise contributes significantly to overall well-being and health-related quality of life in aging adults.[3] In 2018, the American Medical Association (AMA) published revised exercise recommendations, stating that adults should "get at least 150 minutes per week of moderate-intensity aerobic activity or 75 minutes per week of vigorous aerobic activity, or a combination of both, preferably spread

throughout the week." Further, the AMA recommends muscle strengthening activity at least twice per week, and states that adults can gain additional benefits by being active for at least 300 minutes.[4] The World Health Organization makes the same recommendations.[5] Nocturia and nocturnal enuresis are difficult conditions to treat, but women who stay active may be less likely to experience them. While there is still much research to be done to understand the relationship between physical activity and pelvic floor function, is it possible that the connection between physical activity and nocturia can provide an additional lifestyle benefit by improving both bothersome nighttime voiding and overall general health? ■

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ABSTRACT & COMMENTARY

Intrauterine Device Use and Ovarian Cancer Risk

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she receives grant/research support from Bayer and is a consultant for Merck.

SYNOPSIS: In this systematic review, the odds ratio of ever-use of an intrauterine device and incident ovarian cancer was 0.68 (95% CI 0.62-0.75).

SOURCE: Wheeler LJ, Desanto K, Teal SB, et al. Intrauterine device use and ovarian cancer risk: A systematic review and meta-analysis. *Obstet Gynecol* 2019; Sep. 10. doi: 10.1097/AOG.0000000000003463. [Epub ahead of print].

This was a systematic review and meta-analysis of existing studies that evaluated both the incidence ovarian cancer and ever-use of an intrauterine device (IUD). IUD use in the setting of menopausal hormone therapy was excluded; both case control and cohort studies were included. Data extracted from the studies included geographic location, years of data collection, year of publication, study size, and characteristics of the study population (age, menopausal status, gravidity, history of oral contraceptive use, body mass index, IUD type, method of ovarian cancer diagnosis, and family history of cancer).

After searching MEDLINE, Embase, Cochrane Library, Web of Science Core Collection, Google Scholar, and ClinicalTrials.gov, and reviewing the results for inclusion, researchers chose 11 trials (nine case-control and two cohort studies) for the analysis. The case-control studies contributed 4,484 cases of ovarian cancer and 9,107 controls, and the cohort studies contributed 649 ovarian cancer patients and 173,928 women without ovarian cancer. All studies took age, parity, and oral contraceptive use into consideration.

In the meta-analysis, the summary odds ratio between ever-use of an IUD and incidence ovarian cancer was 0.68 (95% confidence interval [CI], 0.62-0.75). This inverse association remained even when the meta-analysis was stratified to include studies that evaluated other confounding factors, such as body mass index, history of bilateral tubal ligation, menopausal status, and family history of cancer.

■ COMMENTARY

The National Cancer Institute estimates there will be 22,530 new cases of ovarian cancer and 13,980 deaths from ovarian cancer in the United States in 2019.[1] The five-year survival rate is 47.6%. Ovarian cancer is the second most common cause of gynecologic cancer in the United States, and the median age of diagnosis is 63 years. To date, attempts to develop screening programs for ovarian cancer have not been successful. Factors that are protective against the development of ovarian cancer are critical to elucidate. Other contraceptive methods known to reduce the risk of ovarian cancer include combined oral contraceptives (50% reduction with 10 or more years of use) and tubal ligation. Recently, the introduction of opportunistic salpingectomy at the time of hysterectomy or for permanent contraception has offered another possibility to reduce ovarian cancer risk.

The authors of this study sought to estimate the effect of IUD use on ovarian cancer incidence. They found that IUD use was protective (32% decreased risk) across multiple large, international, case-control and cohort studies, which increased the generalizability. Unfortunately, the investigators were not able to evaluate the risk by type of IUD; therefore, these data represent different copper, stainless steel, and levonorgestrel IUDs combined. The

theoretical mechanism of action for the copper IUD or stainless steel varieties used internationally could include alteration in the pH of the reproductive tract or a localized inflammatory response that would destroy malignant cells.[2] The levonorgestrel IUD has the additional effects of thickening cervical mucus, inhibition of endometrial proliferation, and also provides occasional ovulation suppression. Both copper and levonorgestrel IUDs are known to reduce the risk of endometrial cancer as well.[3]

The study is limited by the risk of biases in the individual studies included in the meta-analysis, which may include recall bias, selection bias, and lost-to-follow-up bias. The investigators also could not evaluate whether duration of IUD use affects risk, nor whether one type of IUD worked better than another. Nevertheless, these are promising data that indicate IUD use could have a future effect of reducing ovarian cancer rates as more women opt for this method of contraception. We can inform patients of this important potential non-contraceptive benefit of IUD use during contraceptive counseling. ■

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Editor's Note: Every month, the Associate Editors of **OB/GYN Clinical Alert** *and I pick a current manuscript of significance that we wish to report to readers. Occasionally, we pick the same topic. This month, Dr. Rebar and I both selected the recent consensus statement on use of testosterone in women. I feel the two pieces add complementary material, so decided to run both. Please enjoy these combined comments as a Special Feature.*

ABSTRACT & COMMENTARY

Consensus Position Statement on the Use of Testosterone in Women

By Jeffrey T. Jensen, MD, MPH, Editor

SYNOPSIS: A task force of representatives from leading international societies issued guidance for appropriate prescribing of testosterone in women.

SOURCE: Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. *Climacteric* 2019; Sep. 2. doi: 10.1080/13697137.2019.1637079. [Epub ahead of print].

Clinicians lack clearly established guidance and indications for testosterone therapy for women, which has led to considerable variation in practice patterns. The absence of clear indications and approved products for women has resulted in the use of compounded therapies or off-label prescription of testosterone formulations approved for men. To address concerns regarding current prescribing practice, representatives from the International Menopause Society, the European Menopause and Andropause Society, the International Society for Sexual Medicine, and the Endocrine Society established a task force to conduct a systematic review and meta-analysis of the risks and benefits of testosterone therapy in women. The task force met in Berlin in May 2019 and drafted a consensus position paper that was published simultaneously in the journals *Climacteric*, *Maturitas*, *Journal of Sexual Health*, and *Journal of Clinical Endocrinology and Metabolism*.

The task force developed this consensus position statement to inform healthcare professionals of the known benefits and potential risks of testosterone therapy with the aim of providing clear guidance for treatment, considering benefit and risk. They also addressed conditions for which evidence does not support prescribing testosterone. Wherever possible, the task force based recommendations on findings from blinded placebo/comparator randomized controlled trials (RCTs) of at least 12 weeks' duration. They reported findings with Levels of Evidence (e.g., Level I, experimental studies [RCTs]; Level II, quasi-experimental studies [prospective studies]; Level III, non-experimental studies [case-control]; Level IV, opinion of respected authorities [clinical practice guidelines, consensus panels]; Level V, experiential and non-research [literature reviews, case reports]) and Grades of Recommendations (A = high quality [Level I] to recommend; B = good quality [Level II]; C = weak evidence).

Here are the highlights of the recommendations: *Measurement of testosterone, female sexual dysfunction, and endogenous androgen levels.* The task force noted that testosterone concentrations decline during the reproductive years, but are maintained during menopause (Level IIB). They found direct assays highly unreliable (Level A) for diagnosis within the normal female range of values, but useful to exclude high baseline concentrations in the setting of suspected pathology or to rule out supra-

physiologic doses during treatment (expert opinion). The task force recommended the use of high accuracy liquid/gas chromatography and tandem mass spectrometry (LC/GC-MS/MS) assays for total testosterone.

Recommendations for the terminology for female sexual dysfunction (FSD). Grade B evidence supports the categorization of hypoactive sexual desire disorder/dysfunction (HSDD) and female sexual arousal disorder (FSAD) as distinct conditions. They have different etiologies, risk factors, clinical features, and responses to psychological and biological interventions, including androgen therapy. The task force recommended basing the diagnosis of HSDD in clinical practice on a thorough clinical assessment[1] guided by diagnostic criteria, such as those proposed by the International Society for the Study of Women's Sexual Health (expert opinion).[2-4]

Recommendations pertaining to the associations between endogenous androgen concentrations and female sexual function. The task force categorized the evidence for using androgen concentrations as a diagnostic test for sexual function as "insufficient," and found no cut-off blood level for any measured circulating androgen to differentiate women with and without sexual dysfunction (Grade C).

Recommendations regarding systemic testosterone therapy. The task force found insufficient evidence to make any recommendations regarding the use of testosterone in *premenopausal women* for treatment of sexual function or any other outcome. In contrast, high-quality (Level I, Grade A) evidence supports the beneficial effect of testosterone replacement at physiologic levels on sexual function in naturally or surgically *postmenopausal women with HSDD*. The benefit over placebo includes an average of one satisfying sexual event per month, and increases in the subdomains of sexual desire, arousal, orgasmic function, pleasure, and sexual responsiveness, along with a reduction in sexual concerns including sexual distress. The group of experts found insufficient evidence to support the use of testosterone to enhance cognitive performance or delay cognitive decline in postmenopausal women. They found high-quality evidence that testosterone does not improve bone density or increase lean body mass (Level I, Grade A). They also found systemic testosterone therapy in postmenopausal women at physiologic levels associated with mild side effects in some women (acne, increased body/facial hair) but not with alopecia, clitoromegaly, or voice change (Level I, Grade A).

With respect to cardiovascular health, oral testosterone therapy results in adverse changes in lipid profiles, but these effects are not seen with transdermal therapy (Level I, Grade A). Short-term transdermal testosterone therapy does not increase mammographic breast density or affect breast cancer risk (Level I, Grade A), but insufficient data exist to assess long-term breast cancer risk or to support safety in women with hormone-sensitive breast cancer (Expert Opinion). The experts found high-quality evidence supporting an absence of serious adverse events associated with physiologic testosterone replacement in postmenopausal women, but noted safety data do not exist beyond 24 months of treatment.

Considerations for clinical care of postmenopausal women with FSD. The task force noted that clinicians should consider the multiple biopsychosocial etiologies (neuroendocrine imbalance, health status, interpersonal difficulties, psychological distress, and sexually repressive cultural or religious values) that contribute to FSD (Grade C), and offer treatments that follow this biopsychosocial model, including pharmacologic options (hormone therapies and other pharmacologic agents), psychotherapy, or multimodal treatments that combine both (Grade B). The only evidence-based female indication for the use of testosterone is HSDD in postmenopausal women (Level I, Grade A). Use of supra-physiologic doses of testosterone is not recommended (Expert Opinion). To keep levels in the physiologic range, the task force recommended measurement of a baseline total testosterone prior to initiation of treatment, and a repeat level three to six weeks later (Level II, Grade C). They further recommended monitoring patients for signs of androgen excess, monitoring testosterone levels every six months to screen for overuse (Expert Opinion), and discontinuing treatment at six months in the absence of benefit. The group found high-quality evidence to recommend against the use of systemic DHEA for the treatment of HSDD (Level I, Grade A).

■ COMMENTARY

This statement by an international panel of experts provides useful guidance to clinicians considering the use of androgen therapy to treat FSD. The task force reviewed the available literature to determine the quality of evidence both for and against the use of testosterone. For many recommendations, little data exist, and for this reason, many recommendations are conservative and based on expert opinion only.

The take-home recommendation is that postmenopausal women with a diagnosis of HSDD benefit from testosterone (T) replacement in the physiologic range of normal premenopausal women. This recommendation is based on a meta-analysis of seven RCTs by Achilli and colleagues.[5] The testosterone-treated women reported significantly more satisfying sexual episodes, sexual activity, orgasms, and desire; a decrease in Personal Distress Scale score; and minor androgenic adverse events compared with the placebo group. Most of the studies used transdermal doses of T at 150-300 mcg per day.

As only postmenopausal women meeting the criteria of HSDD have been shown to benefit from T therapy, the task force cautioned clinicians not to generalize the findings to other groups. Another caveat is that more is not better, and, in fact, more T may be worse from the perspective of side effects. Measure T levels and keep these in the normal range of premenopausal women for your reference lab. Use a lab that measures T using state-of-the-art LC/GC-MS/MS methods if possible.

Another consideration is that RCTs of T therapy have excluded women at high risk for cardiovascular disease, and that most studies have included women taking concurrent estrogen therapy. Furthermore, all studies have been of relatively short duration. Therefore, we have much less information regarding risks and benefits of T therapy than we do with estrogen only or combined estrogen/progestogen treatment. Keeping up-to-date on this evolving literature remains important. ■

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ABSTRACT & COMMENTARY

Recommendations for the Use of Testosterone Therapy in Women: A Global Consensus Statement

By Robert W. Rebar, MD

Founding Chair Emeritus and Professor, Department of Obstetrics and Gynecology, Western Michigan Homer Stryker M.D. School of Medicine, Kalamazoo, MI

Dr. Rebar reports no financial relationships relevant to this field of study.

SYNOPSIS: Exogenous testosterone is currently indicated only for women with documented hypoactive sexual desire disorder/dysfunction.

SOURCE: Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. *J Clin Endocrinol Metab* 2019;104:4660-4666.

Although there are no definitive indications for the use of testosterone in women and there are no FDA-approved products containing testosterone for women, clinicians have used several different preparations of testosterone to alleviate a variety of symptoms despite uncertain benefits and risks. The need for clarity in the management of women asking or using exogenous testosterone led to the establishment of a task force of representatives from several leading international societies. The purpose of this task force was to make recommendations based on a systematic review and meta-analysis based only on findings from blinded placebo/comparator randomized controlled trials of at least 12 weeks' duration. The international panel produced several recommendations:

- The only evidence-based indication for testosterone therapy for women is for the treatment of hypoactive sexual desire disorder (HSDD), with available evidence suggesting a moderate therapeutic effect.
- The diagnosis of HSDD involves complete clinical assessment and does not involve the measurement of serum testosterone concentrations. Diagnosis should be guided by available diagnostic criteria such as the International Society for the Study of Women's Sexual Health[1,2] or the *International Classification of Diseases*, 11th edition.
- Doses that approximate physiological testosterone concentrations in premenopausal women should be used.
- Testosterone therapy exerts a beneficial effect on sexual function, including an increase of an average of one satisfying sexual event per month, as well as increases in sexual desire, arousal, orgasmic function, pleasure, and sexual responsiveness, together with a reduction in sexual concerns, including sexual distress.
- Meta-analyses of short-term data do not document severe adverse events with physiological testosterone administration, but the long-term safety of testosterone therapy has not been established.
- Systemic testosterone therapy for postmenopausal women in doses that approximate levels in premenopausal women is associated with mild increases in acne and body and facial hair growth in some women, but not with alopecia, clitoromegaly, or voice change; no such changes occur in premenopausal women.
- Non-oral testosterone therapies (percutaneous and injectable) may be preferred because there are no statistically significantly adverse effects on lipid profiles.
- Because randomized controlled trials of testosterone therapies have excluded women at high cardiometabolic disease risk, recommendations

regarding the effect of physiologic doses on cardiovascular health are not generalizable to more at-risk individuals or to long-term therapy.

- Because women with a prior diagnosis of breast cancer were excluded from the randomized trials for HSDD, caution is recommended for testosterone use in women with hormone-sensitive breast cancer.
- In the absence of any approved female product, formulations for males can be used at female doses with careful monitoring of serum testosterone concentrations.
- The use of compounded testosterone preparations is not recommended.
- Systemic dehydroepiandrosterone is not associated with significant improvement in libido or sexual function in postmenopausal women with normal adrenal function and cannot be recommended for women with HSDD.
- The panel cited the pressing need for additional research into the use of testosterone in women and highlighted the need for development and licensing of products indicated specifically for women.

■ COMMENTARY

Whether these recommendations will be observed remains to be determined. They were formulated by a distinguished panel and endorsed by several international societies. Still, I say this because clinicians have administered androgens to women for many reasons for decades; yet the analysis of the available data does not justify widespread use at this time. Perhaps the last recommendation of the panel is the most important: Additional research is badly needed to determine if there are other uses for physiologic doses of testosterone in women. If so, then the appropriate products need to be developed, tested, and approved for use.

Several years ago, one commercial FDA-approved product combined esterified estrogens (0.625 or 1.25 mg) with methyltestosterone (1.25 or 2.5 mg) (Estratest). It also was marketed in a form containing only esterified estrogens (Estratab). These products were approved because their effects were broadly equivalent to products containing conjugated estrogens. They are no longer produced, and it is unlikely that the same products containing methyltestosterone would be approved today without additional studies.

Randomized studies with the estrogen-only and the combined estrogen-methyltestosterone preparation indicated that those containing androgen produced nonsignificantly greater improvements in well-being and sexual interest.[3] Somatic symptom relief in the low-dose preparation containing methyltestosterone was the same as with those containing the higher dose of esterified estrogens.[4]

It is possible that the effects of the methyltestosterone added to the esterified estrogens may be due, at least in part, to higher doses of circulating estrogens. This is true because methyltestosterone is efficiently aromatized to estrogens. In fact, in a study supported by the manufacturer but never published because of the untimely death of the

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first author, the study showed that more than 90% of the effect of esterified estrogens plus methyltestosterone was due to the estrogen alone, making it possible that the entire effect on well-being and sexual satisfaction was merely due to estrogen.[5]

Women with primary ovarian insufficiency (POI) are documented to have lower levels of circulating androgens than do age-matched controls. Yet in a 12-month randomized, placebo-controlled, parallel-design investigation of the efficacy of testosterone augmentation of estrogen/progestin therapy in 128 women with POI, the addition of physiologic amounts of testosterone failed to have any significant effects on quality of life, self-esteem, and mood.[6]

The conclusion from studies published to date can be summarized succinctly: Until we have additional data, the long-term administration of testosterone in women should be discouraged except in the treatment of women with documented HSDD. ■

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CME/CE QUESTIONS

1. Based on the study by Chu et al, sedentary older women with incontinence:
a. are less likely to have urinary symptoms compared to active women.
b. are more likely to have nocturia and nocturnal enuresis compared to active women.
c. should begin exercising immediately to improve their leakage.
d. should limit physical activity in order to avoid aggravating urinary symptoms.

2. In the study by Wheeler et al, the percent decreased risk of ovarian cancer associated with ever-use of the IUD was:
a. 20%.
b. 32%.
c. 50%.
d. 60%.

3. Which of the following was recommended by the Global Consensus Position Statement on the Use of Testosterone Therapy Task Force?
a. Treatment with testosterone at physiologic levels in postmenopausal women diagnosed with hypoactive sexual desire disorder/dysfunction
b. Treatment with estrogen with testosterone at pharmacologic levels in premenopausal women with arousal disorder
c. Treatment with testosterone at pharmacologic levels to increase bone density in breast cancer survivors
d. Treatment with testosterone at pharmacologic levels in postmenopausal women diagnosed with hypoactive sexual desire disorder/dysfunction

4. Physiologic doses of testosterone are clearly indicated for all women with documented:
a. female sexual arousal disorder.
b. hypoactive sexual desire disorder/dysfunction.
c. bilateral oophorectomy.
d. primary ovarian insufficiency.

5. Which of the following is required for diagnosis of hypoactive sexual disorder/dysfunction?
a. Measurement of serum testosterone levels
b. Complete clinical assessment
c. Assessment by a registered nurse practitioner
d. Measurement of both serum testosterone and serum estradiol levels