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Are the Endocrine Society's Clinical Practice Guidelines on Androgen Therapy in Women Misguided? A Commentary

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Abstract

The Endocrine Society Clinical Guidelines on Androgen Therapy in Women (henceforth referred to as *the Guidelines*) do not necessarily represent the opinion held by the many health-care professionals and clinicians who are specialized in the evaluation, diagnosis, and treatment of women's health in androgen insufficiency states. The recommendations provided in the published *Guidelines* are neither accurate nor complete. We disagree with the therapeutic nihilism promoted by these *Guidelines*. The members of the Guidelines Panel (henceforth referred to as *the Panel*), in their own disclaimer, stated that *the Guidelines do not establish a standard of care*.

Based on data available in the contemporary literature, on the role of androgens in women's health, we provide in this commentary a point-by-point discussion of the arguments made by *the Panel* in arriving at their recommendations. It is our view that the *Guidelines* are not based on the preponderance of scientific evidence.

Health-care professionals, physicians, and scientists often disagree when determining how best to address and manage new and emerging clinical issues. This is where we stand now as we endeavor to understand the role of androgens in a woman's health and welfare. Indeed, some basic facts are not in contention. All agree that dehydroepiandrosterone sulfate (DHEA-S) production from the adrenal gland begins during the preteen years, peaks in the mid 20s, then declines progressively over time. In contrast, ovarian androgen (i.e., testosterone) secretion commences at puberty, is sustained during a woman's peak reproductive years and declines as a woman ages, with a more rapid and steep decrease after surgical menopause. However, there are ample data to suggest that adrenal androgens play a role in the development of axillary and pubic hair, and that testosterone is critical for women's libido and sexual function.

We take this opportunity to invite members of *the Panel* on Androgen Therapy in Women to discuss, clarify, comment, or rebut any of the points made in this Commentary. It is our goal to elevate this debate in order to provide women who are afflicted with androgen insufficiency and sexual disorders with the highest quality health care and to relieve their distress and suffering, as well as to improve their quality of life.

Key Words: Women's Sexual Dysfunction; Testosterone; Sexual Desire and Arousal; Endocrine Society; Guidelines; Androgen Treatment for Women

Introduction

In the recently published Endocrine Society's Clinical Practice Guidelines on Androgen Therapy in Women [1], *the Panel* recommended against making a diagnosis of androgen insuffi- ciency and treatment of women at present. These recommendations were formulated based on the following arguments:

1. Purported lack of well-defined clinical syndrome of androgen insufficiency in women;
2. Absence of normative data on total and free testosterone levels across the life span of women;
3. The lack of long-term safety data;
4. The absence of a correlation between androgen plasma levels and sexual disorders;
5. The nonavailability of accurate, precise, and reliable assays for measurements of total and free testosterone in women;
6. Limited or absent preclinical studies; and
7. The limited extent of clinical research that is needed to make a sound clinical judgment.

In the view of many health-care professionals and experts who evaluate, diagnose, and manage women in the clinic with androgen insufficiency, this "clinical" guideline document represents a mere position paper, as the only recommendation made is that physicians not treat women suffering from androgen-deficiency with androgens. The authors of this commentary unanimously and strongly disagree with the main tenets of these recommendations. To shed light on this important issue, we present a brief historical outline of the basic and clinical research, clinical diagnosis, and management of women with androgen insuffi- ciency using sex steroid hormones. We wish to focus this commentary on the following issues: (i) the definition of the disorder; (ii) availability of normative data; (iii) absence of long-term safety data in androgen therapy in women; (iv) lack of a correlation of plasma androgen levels and sexual disorders in women; (v) the absence of a reliable, sensitive, accurate, and precise testosterone assay for women; (vi) limited or absent preclinical studies; and (vii) the extent of clinical research needed to make an informed clinical judgment.

A historical perspective on androgen therapy in women

Androgens are not foreign to women's physiology and are produced by the ovaries, the adrenal glands, [2,3] and other peripheral tissues [4,5]. Thus, use of androgens for the treatment of women's androgen insufficiency is by no means artificial. In women, androgens have been known to exert physiological function in many tissues and organs [2–6]. Shorr et al. [7] first noted the actions of androgens on women's sexual interest in 1938. The authors noted that treatment of women with androgens increased sexual desire. In this historical study, it was concluded that, "Libido and sexual response were definitely greater than that experienced with estradiol alone." Shorr et al. postulated that androgens not only act on the central nervous system but also at the peripheral genital level [7]. Shortly thereafter, Loeser reported that all women treated with testosterone experienced increased sexual drive, suggesting that androgens play a physiological role in enhancing libido and arousal in women [8]. These observations were further confirmed by several subsequent studies [6,9, 10,11,12]. Based on these early observations, the effects of androgens on increasing libido in women were considered universal as early as 1948. In contrast, stimulation of sex drive in women by estrogen alone has not been commonly encountered in clinical experience [13]. Libido and sexual response were greater when testosterone was coadministered with estrogen. This combined estrogen-androgen treatment resulted in heightened sexual desire, easier attainment of orgasm, and heightened satisfaction during intercourse. Salmon and Geist [12] postulated that androgens have a three-fold action in women: (i) to increase the susceptibility to psychosexual stimulation; (ii) to increase the sensitivity of external genitalia; and (iii) to increase the intensity of sexual gratification.
In the 1960s, several reports suggested that ovariectomy, when followed by adrenalectomy for treatment of women with breast cancer, resulted in marked decrease in libido [14]. It is surprising that 60 years later, the scientific community in general, and *the Panel* in particular, are still debating whether androgens have a role in women's sexual function.
The Endocrine Society's Clinical Guidelines Panel on Androgen Therapy in Women [1] pointed to a number of issues to support their recommendations *not to treat women with androgendeficiency with androgens*. In this forthcoming section, we discuss the merits of each point raised and provide alternative views and considerations that differ significantly from *the Panel's* conclusion and share a reasoned perspective for our differing views. We hope that this discussion will further stimulate the debate on this vital and timely issue of women's health.

Has androgen insufficiency disorder in women been defined?

The Panel recommended against making a diagnosis of androgen insufficiency in women because of the lack of a well-defined clinical syndrome. It should be noted that the concept of androgen insufficiency syndrome in women, although not altogether new, has been recently discussed and defined by a panel of health-care professionals with expertise in the fields of psychology, endocrinology, urology, obstetrics and gynecology, and sexual medicine. The Princeton Consensus Statement on Female Androgen Insufficiency provided a clear framework for definition, classification, and assessment of androgen insufficiency in women [15]. Based on the consensus statement, the term "female androgen insufficiency" was defined as consisting of a pattern of clinical symptoms in the presence of decreased bioavailable testosterone (T) and normal estrogen status [15]. The statement indicated that many clinical symptoms of androgen insufficiency are similar in men and women. These symptoms include (but are not limited to) diminished wellbeing, lethargy, fatigue, loss of sexual drive and interest, and blunted motivation. We emphasize that the diagnosis of androgen insufficiency in women should include both symptoms and biochemical markers (e.g., decreased androgen levels). Braunstein [16] stated that "based on our current knowledge, it is clear that some women develop symptomatic androgen insufficiency and that androgen replacement therapy has a beneficial effect on libido, sexual satisfaction, quality of life and bone mineralization. Androgen replacement therapy should be given the same consideration that we give estrogen replacement therapy." Many clinical trials investigating androgen treatment in women who have androgen insufficiency, due to surgical or natural menopause, have provided solid evidence that reinforces the conclusion made in the 1940s that androgen insufficiency in women exists [3,17–40]. Furthermore, several recent phase III clinical trials using the androgen patch were conducted based on the well-recognized and accepted definition of androgen insufficiency in women [29,30,39,41]. A recent discussion of this issue by Braunstein [42] and a concise review by Kingsberg [43] on this very critical topic provides much needed information on the data from the recent clinical trials.We, therefore, seriously question the panel's disregard for the vast available evidence that defines this clinical syndrome in women.

Do normative data on androgens in women exist?

The Panel recommended against making a diagnosis of androgen insufficiency in women based on their contention that there are no normative data on total testosterone or free testosterone levels across the lifespan in women that can be used to define the disorder.
We are surprised that the panel ignored a seminal article by Davison et al. [40], published in a peer-reviewed Endocrine Society publication, which provided adequate normative androgen data in a study of over 1,400 women, from ages 18 to

75, and separated by decade. In our view, these data are superior to the limited normative data reported thus far in men, and yet androgen treatment of men with testosterone deficiency has been carried out for decades. In addition, normal ranges of androgens were also reported in a subset of premenopausal healthy women who were screened for symptoms of sexual disorders [44], and these data correlated well with those reported by Davison et al. (See Figure 1 and [40,45]).

In addition, several studies have been published on androgens in women during the menopause transition [46,47]. A prospective longitudinal study of serum testosterone, DHEA-S, and sex hormone-binding globulin levels through the menopause transition [48], as well as a study of decreasing androgen levels in women of all ages using the more accurate mass spectrometry technique [49], demonstrated a marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. In view of such findings, we are perplexed with *the Panel's* suggestion that there is a lack of normative data on androgens in women.

Are safety data on androgen treatment in women insufficient?

The Panel suggested that there were not enough long-term safety data in women. Yet, only a single 3-year study on generalized chronic safety data in men is found in the North American literature [50]. In spite of these limited data, androgen therapy in men has been approved by the U.S. Food and Drug Administration (FDA) and was endorsed by the Endocrine Society in their recently sponsored guidelines [51]. We wonder why the standards for women should be different from those for men. *The Panel* cited the poorly designed and much criticized Women Health Initiative (WHI) study of postmenopausal women on hormone replacement therapy with equine estrogens and progesterone as an example of the need for additional long-term safety data. We do not feel that the WHI study should be the reason for the denial of therapy for women with androgen insufficiency, because that study had no androgen arm in it. The clinical findings from 1938 to the present have indicated minor adverse events associated with androgen therapy. In phase III studies, for the androgen patch, only minor adverse events were observed; these include skin changes, oiliness, hair growth, or acne [29,30,39,41]. Similarly, no major adverse events were reported in other studies [52]. Clearly, the unfounded fears from the negative publicity of the WHI studies on hormone replacement therapy in women has placed an obstacle in the clinical management of women with androgen insufficiency, and it may be decades before it will be recognized as a profound mistake. We agree that additional long-term safety data are needed, but this should not be the basis for halting or withholding the treatment of women with androgen insufficiency, who are distressed about their medical condition.

In a recent publication, Basaria and Dobs [53] have suggested that because we have safety data up to 24 weeks, we should consider treatment of women with androgen insufficiency with testosterone for periods of 24 weeks. Clearly, safety is one of the most important issues. No major adverse events, however, have been reported to warrant withholding or halting androgen therapy in women. Furthermore, *the Panel's* position is contradictory to the World Health Organization's mandate that women have the right to sexual health care, which would include the use of hormones in hormone deficiency states.

In a recent editorial by Burger entitled "Should testosterone be added to estrogen and progesterone therapy for breast protection" [54] the author discussed the potential protective effect of testosterone in women with regard to breast cancer. Considerable evidence is emerging suggesting that testosterone counteracts the proliferative effects of estrogen and progestins in the mammary gland. Several studies [55–58] have suggested that there is no evidence that testosterone is implicated in breast cancer and may provide a protective effect, contrary to fear implied in the Society Guidelines.

Is there a correlation between plasma androgen levels and sexual function?

The Panel recommended against making a diagnosis of androgen insufficiency in women due to the lack of correlation between androgen levels and symptoms of sexual dysfunction.Turna et al. [59] noted a good correlation between total testosterone, free testosterone, and DHEA-S with a number of sexual parameters using the Female Sexual Function Index, a validated questionnaire in studying female sexual dysfunction. The Study ofWomen's Health Across the Nation (SWAN) study [60] of women between 42 and 52 years old did show a weak, albeit significant ($P<0.05$) correlation between androgens, sexual desire, and sexual arousal. Braunstein et al., found significant direct correlations between sexual desire and total testosterone, as well as with free testosterone, bioavailable testosterone, and 5 α-dihydrotestosterone (5αDHT) [41]. Guay et al. [61] investigated a small group of healthy premenopausal women with and without symptoms of sexual disorders. They found that women with symptoms of sexual disorders had a significant decrease in the concentrations of Δ^5 androgenic steroids, predominant in the adrenal gland. Interestingly, Davis et al. [62] were unable to demonstrate a correlation between total testosterone plasma levels and symptoms of sexual function. However, good correlations were found between various parameters of sexual function and the adrenal androgen DHEA-S. This is similar to the observations of the longitudinal study in men, in the Massachusetts Male Aging Study, in which a good correlation of sexual function with DHEA-S was observed [63]. Perhaps this reflects the fact that men and women produce significantly more DHEA than testosterone, which makes the accurate detection of DHEA-S relatively simpler and more accurate. In addition, the level of total plasma testosterone in women is approximately one-

tenth that found in men, making accurate measurements of testosterone less accurate in women and may contribute to the difficulty in establishing the correlation between hormone plasma levels and symptoms of sexual disorders.
Interestingly, *the Panel* acknowledged that there were more than 24 separate clinical studies and/or trials on androgen treatment of sexual disorders in women. Indeed, most of these trials provided very valuable data supporting the concept of improved sexual function in women with androgen insufficiency subsequent to androgen treatment (Table 1). Sherwin [52] reviewed several randomized, placebo-controlled studies from 1984 to 2000, and found a good correlation between androgen therapy and the amelioration of a number of sexual symptoms. A recent review by Arlt [3] summarized the data from several reported clinical trials on the relationship between androgens and sexual disorders in women and showed a positive association. Similarly, Kingsberg [43] reviewed the recent clinical trials on testosterone and sexual function and reported significant improvement in sexual function with minimal adverse events. *The Panel* agreed that the recent, FDA-approved, clinical trials on testosterone and sexual function correlated with desire, arousal, orgasm, pleasure, responsiveness, and the number of satisfying sexual events. Nevertheless, *the Panel* suggested against initiating therapy in women and attributed this to the lack of long-term safety data, as well as a lack of consistent positive results. This is contradictory, as the FDA, after careful analyses, approved the definition of the disorder and permitted multiple clinical trials to be conducted. The FDA's disapproval of the testosterone patch was not based on the lack of a definition of the disorder nor the absence of beneficial outcome of the studies, but rather on the availability of long-term safety studies exceeding the 24-week period of these trials. This is in contrast to the approval of androgen therapy in men in which there is only scant safety data, as discussed previously [50]. Unfortunately, the panel disregarded the elegant work of Sherwin and colleagues [17,18,19], Davis and her colleagues [32–40], Sarrell [20–23], Shifren & colleagues [26–28], Buster et al. [30], Simon et al. [29], and Braunstein and colleagues [41,42] on the beneficial effect of androgen therapy in women with androgen insuf- ficiency and the minimally associated adverse events.
A careful review of the relationship between estradiol levels and hot flashes showed only a very loose correlation, yet estrogen treatments are frequently used for these symptoms, and blood estradiol levels are not required to measure efficacy [108]. In fact, an attempt to titrate estradiol administration by using follicle-stimulating hormone (FSH) suppression in the treatment of hot flashes will result in entirely too much estradiol replacement. One could use this parallel to argue that use of androgen in women is by no means different from that applied in the use of estrogens.

Accuracy and precision of testosterone assays in women

In a recent article, Rosner stated that "The measurement of testosterone (T) in plasma or serum, as carried out in most laboratories, suffers from a number of serious limitations. In women and children, the lack of accuracy and sensitivity has resulted in severely limited utility. For men, most T assays have adequate sensitivity and reasonable clinical utility, but are relatively inaccurate" [64]. The limitations of the assay for the measurement of total testosterone used to calculate the free testosterone are applicable to both sexes [64]. Indeed, the accuracy, precision, and reliability of the current testosterone assays in women are debatable and the need for more accurate, precise, and reliable assays remains urgent. However, the FDA has permitted phase II and III clinical studies on a testosterone patch for postmenopausal women using the equilibrium dialysis free testosterone and the bioavailable testosterone assays and deemed them adequate for both the diagnosis and the monitoring of therapy in women with androgen insufficiency.
The authors of the recent position paper on testosterone measurements [64] state that mass spectroscopy is required to obtain accurate total testosterone measurements, especially since the equilibrium dialysis free testosterone and the bioavailable testosterone measurements are dependent on its accuracy. It should be noted that several national commercial referral laboratories (Quest—Nichols Institute, Esoterix, LabCorp) offer the mass spectroscopy technique after column chromatography separation of the steroids. This new testosterone assay method offers precise and accurate measurements of testosterone and is deemed worth the increased cost charged for the assay.
The arguments about which testosterone assay better identifies women's androgen insufficient state are welcome; however, the recommendation to put on hold further evaluation and withhold treatment of the symptomatic androgen-deficient women seems, at best, cavalier and, at worst, irresponsible. In our view, the recommendations made by *the Panel* would discourage qualified, competent, and caring health-care professionals from treating their female patients with androgens for fear of legal repercussions.

Do we halt all clinical research until the "biological, physiological, and psychological underpinnings of the role of androgens in women are elucidated"?

We disagree with this statement by *the Panel* that clinical research cannot occur until the underlying mechanisms of the biological, physiological, and psychological aspects of androgen action in women are further defined. If this were the case, the FDA would not have allowed Phase II and Phase III studies on the testosterone patch treatment of surgically menopausal women to have gone forward. The trials were conducted because there was adequate and substantiated basic information available to warrant their execution.
The alternative treatment for women with androgen insufficiency, as proposed recently by Basson [65], would be a "combination of cognitive behavioral and sex therapy." It is surprising that the author's recommendation is made in the

absence of any evidence-based medicine or any placebo-controlled trials in cognitive behavior and sex therapy in women. The author suggested that there were no clinical trials in pharmacotherapy for women and, in the absence of such evidence, no pharmacotherapy should be pursued. This claim [65] was made in spite of the 24 clinical studies on androgen therapy in women, previously referenced in this commentary. Unfortunately, *the Panel's* view runs counter to the recommendations of a number of expert sex therapists who believe that a combination treatment that integrates sex therapy and pharmacotherapy (including hormone replacement) may be the best approach for many individuals suffering from sexual dysfunction [66–68].

Is withholding androgen therapy in women, based on limited preclinical research, a valid concern?

The Panel stated, "We recommend additional investigation using rodents and primates to further define the specific targets of androgen action."We fully agree with the panel that additional preclinical animal research is necessary to further elucidate the physiological mechanisms of androgen action. However, the panel failed to discuss or cite several published reports in well-accepted animal models [69–75], as indicated by the limited bibliography accompanying the published guidelines. Preclinical studies in ovariectomized animals have shown that androgen treatment maintains the vaginal muscularis, facilitates vaginal smooth muscle relaxation, enhances nitric oxide synthase expression and activity, and increases vaginal blood flow and mucification [69–78].

Based on the aforementioned discussion, we, as a group of concerned health-care professionals, who are interested in the fields of endocrinology, sexual medicine, and women's health, and who encounter in our clinics many women with androgen insuffi- ciency and sexual disorders who are distressed and concerned with their health, collectively feel that *the Panel* did not provide sufficient in-depth analysis of the currently available data or appreciation of the issues facing women suffering from androgen insufficiency and the physicians who treat them. The following points support this conclusion:

1. There are clear and apparent discrepancies between the negative views expressed in the *Guidelines*, and the fact that some members of *the Panel* have participated and reported successful treatments of women with androgen insufficiency using testosterone [31–40,79–93].
2. A large number of pertinent references concerning androgen therapy in women were not cited in this *Guidelines*' publication. Examples of the literature that have not been cited are included in the references herein. Although we believe this is not a deliberate omission, it suggests that some of the conclusions were derived without adequate analyses of pertinent existing data in the literature.
3. It is disconcerting that *the Panel* suggested that *no treatment* should be recommended until the research is complete; however, the panel seemed to ignore a substantial body of research literature on this topic, which we think establishes the fact that to treat women in most cases is justified. The North American Menopause Society reviewed the literature, and noted similar deficiencies; however, they arrived at a different conclusion in 2005, and once again in 2007 [107]. They concluded that, while we are still gathering data, we may treat if other causes of hypoactive sexual desire disorders have been ruled out. Such inconsistencies raise fundamental questions on how *the Panel* arrived at its recommendations.
4. The Endocrine Society Guidelines on the Treatment of Male Androgen Deficiency [51] has made very good recommendations to guide physicians despite their stated opinion that much more information is needed in many areas of androgen deficiency in men. The *Guidelines* for women do not recommend any treatment using the data available. This is inconsistent in light of the fact that androgens have been used clinically in women nearly as long as they have been used in men.

Conclusion

The current *Guidelines* issued by the Endocrine Society Panel on Androgen Therapy in Women do not represent the opinions held by health-care professionals who are specialized in the evaluation, diagnosis, and treatment of women's sexual health issues in androgen insufficient states. The idea that physicians should not treat women distressed with androgen insufficiency until all of the data are in does not conform to our view of good standards of medical care.

There are numerous health-care professionals and clinicians who do not consider themselves specialists in women's sexual dysfunction, but who feel that they could offer help with certain aspects of the condition. If they consider offering androgen therapy to women, they must be sufficiently trained and educated about the definition of androgen insufficiency, the most accurate way to measure plasma hormones, and the correct use of formulated androgen products. Recognizing androgen insufficiency in women and its treatment is a skill that requires knowledge and training, and may be offered in many clinical settings, not just by sexual medicine specialists.

None of the clinicians and scientists who participated in discussing and writing this commentary believes that women's sexual dysfunction is solely an endocrinopathy devoid of any other medical, social, psychological, and environmental inputs. However, most believe that the hormonal milieu, and in particular testosterone levels, is an important part of women's sexual physiology.

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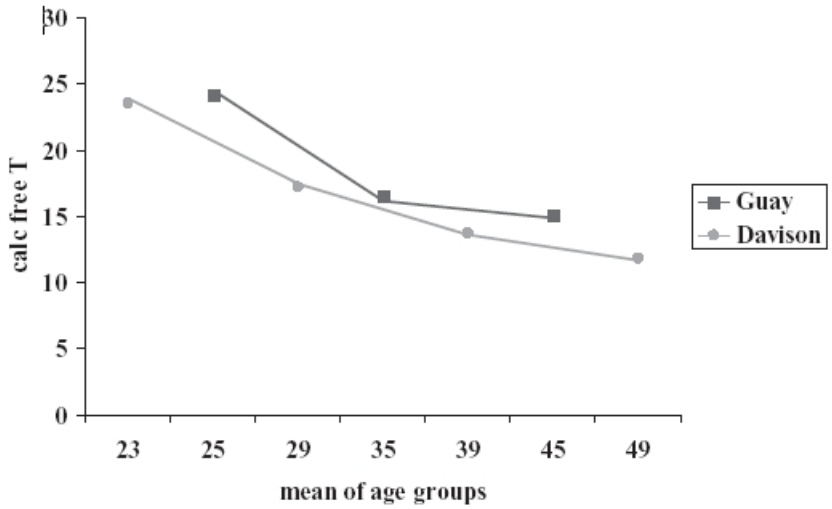
Figure 1



Similarity in normative free testosterone data in young women derived from two separate and independent studies [40,44]. The units for the calculated free testosterone are expressed in pmole/L.

Table 1

Randomized controlled trials of testosterone treatment in women

Reference	N	Duration	Outcome
Sherwin, 1985 [105,106]	53	12 weeks	↑ Desire, arousal, fantasies
Myers, 1990 [94]	40	10 weeks	↑ Masturbatory pleasure. No change in sexual behavior and arousal. Normal sexual function at baseline
Davis, 1995 [95]	34	12 months	↑ Bone density, sexual activity, pleasure, satisfaction and orgasm
Watts, 1995 [96]	66	24 months	↑ Bone density, ↓ HDL Chol, ↓ TG
Raisz, 1996 [97]	28	9 weeks	↑ Bone formation, ↓ TG, ↓ HDL Chol
Miller, 1998 [98]	53	12 weeks	↓ BMI, ↑ Sense of well-being
Shifren, 2000 [27]	75	12 weeks	↑ Sexual activity, pleasure, orgasm, fantasies, well being
Dobs, 2002 [99]	36	16 weeks	↑ Sexual activity and pleasure, lean body mass, selective strength, ↓ Fat mass
Lobo, 2003 [100]	218	16 weeks	↑ Sexual desire and responsiveness
Warnock, 2005 [101]	107	8 weeks	↑ Sexual desire/interest
Braunstein, 2005 [41]	447	24 weeks	↑ Frequency satisfying sexual activity, desire
Buster, 2005 [30]	533	24 weeks	↑ Frequency satisfying sexual activity, desire
Simon, 2005 [29]	562	24 weeks	↑ Frequency satisfying sexual activity, desire
Shifren, 2006 [102]	549	24 weeks	↑ Frequency satisfying sexual activity, desire, ↓ Personal distress
Davis, 2006 [103]	77	24 weeks	↑ Sexual desire, arousal, orgasm, responsiveness, self-image, ↓ Sexual concerns, distress
Shah, 2006 [104]	61	16 weeks	↑ Immediate and delayed visual and verbal memory, simple concentration (unaffected by aromatase inhibitor)

HDL = high-density lipoprotein; TG = triglycerides; BMI = body mass index.