

Is it Time to Consider Androgen Therapy for Androgen Deficient Women?

Clinical and Research Implications

This is the fourth appearance of the tri-point perspective articles in Endocrine News. The tri-point perspectives were initiated by The Endocrine Society's Research Affairs Committee in the fall of 2003 as an editorial feature that would appeal to all of the Society's members. The topics, authors and outside reviewers are selected by the committee to deal with subject areas from three different angles—that of the basic researcher, the clinical researcher and the physician in practice. The authors write their articles independently and later work together to coordinate them. The drafts are reviewed by the Research Affairs Committee chairs, by independent experts in the

specific topic area and then by the Endocrine News editors and staff for grammar and style.

The Endocrine News staff would like to thank the efforts of Dr. Steven Grinspoon, Co-Chair, Research Affairs Committee, for his dedication and efforts in developing this series for our readers.

If you have any comments or questions about the tri-point perspectives feature, please email [Endocrine News@endo-society.org](mailto:EndocrineNews@endo-society.org) If you would like to submit a Letter to the Editor responding to a tri-point perspective please send your letter (not longer than 400 words) to ENLetters@endo-society.org

Disclaimer: Due to the clinical nature of this topic, the Research Affairs Committee could not find a volunteer to write from a basic research perspective. Instead, a clinical researcher wrote about the clinical implications of this therapy.

CLINICAL RESEARCHER VIEW

Androgen Insufficiency and Hypoactive Sexual Desire Disorder in Women: Efficiency and Safety of Testosterone Treatment

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When former Senator Robert Dole brought the topic of erectile dysfunction out of the closet, the Viagra revolution was launched, prompting many women to ask: "What about us?" Now, advances in our understanding of female sexual physiology and interest on the part of the pharmaceutical industry to develop effective treatments for women with sexual dysfunction have allowed us to begin to address this question.

nal insufficiency, and premature ovarian failure, as well as following bilateral oophorectomy, chronic use of glucocorticoids, and with use of oral estrogen. The latter results in elevations of sex hormone binding globulin (SHBG) due to the first pass effect on liver protein production. As most of the circulating testosterone is bound to SHBG, elevations of this protein result in a decrease in the free and bioavailable fractions of testosterone.

estrogen controlled trials of testosterone treatment in naturally or surgically menopausal women, and a trial in premenopausal women with HSDD. Although there is a strong placebo effect in these studies, all have shown statistically significant improvements from testosterone over placebo in various parameters of sexual function in women with preexisting HSDD.



Glenn D. Braunstein

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One type of sexual dysfunction among women called, "hypoactive sexual desire disorder (HSDD)," represents a deficiency of sexual fantasies and desire for, or receptivity to sexual activity that causes the woman personal distress. This is a relatively common condition that can be the result of relationship difficulties, depression, chronic illness, medications, or hormonal imbalance. Often, a combination of these factors culminates in low sexual desire.

HSDD may be associated with androgen insufficiency. Since the sources of androgens in women are the adrenals and ovaries, androgen insufficiency has been found in women with hypopituitarism, adre-

For over 50 years, clinicians have administered varying types of testosterone preparations to women in order to treat the loss of libido and sexual responsiveness found in some women following adrenalectomy, oophorectomy, or natural menopause. In addition to

At present, there is no FDA approved androgen therapy for HSDD in women, although the results of Phase II and III clinical trials on a testosterone patch are currently under review by the agency. Nevertheless, as noted above, physicians have administered a variety of testosterone preparations in an off-label manner to women for low libido. A combination of esterified estrogens and methyltestosterone (Estratest® and Estratest-H.S.®, Solvay Pharmaceuticals, Inc., Marietta, GA),

Cutting patches and using a dab of testosterone gel formulated for men results in variable serum testosterone levels in women.

multiple uncontrolled studies, there have been about a dozen randomized, double-blind, placebo or whose approved indication is for treatment of vasomotor symptoms associated with menopause in

patients who do not improve with estrogens alone, has been shown to help HSDD in postmenopausal women. A surprisingly large number of prescriptions for androgen products specifically designed for the treatment of hypogonadism in men

levels are within or slightly above the reproductive-age reference range. Side effects included an increase in hirsutism and acne, but these were noted in some studies using oral methyltestosterone and have generally not been a problem

ment Study and Women's Health Initiative studies.

Some critics have suggested that the topic of female androgen insufficiency is a construct of the pharmaceutical industry intent on creating a condition in order to sell a product. Their arguments belie the data that androgens are important for female sexuality, that androgen insufficiency can result in HSDD, and that restoration of free testosterone levels to those found during the reproductive years can improve libido and reduce the associated distress. In addition, the collective experience of physicians who treat women with sexual dysfunction and those of us who are involved in clinical trials in this area, support the conclusion that symptomatic androgen insufficiency in women is real and that effective therapies with predictable pharmacokinetic profiles are badly needed to help our patients. **EN**

Despite the safety data, most of the information is derived from studies of women receiving both estrogens and testosterone.

are written for women, a practice that should be discouraged because testosterone levels in men are 10 to 20 times higher than those in women. Cutting patches and using a dab of testosterone gel formulated for men results in variable serum testosterone levels in women. Similarly, a great deal of variability in serum testosterone levels are found in women using testosterone gels, creams, drops, and buccal lozenges or the androgen precursor, dehydroepiandrosterone (DHEA), made by compounding pharmacies.

Most of the concerns about the safety of androgen therapy for

with intramuscular, subcutaneous, or transdermal testosterone treatment. Further, treatment-induced polycythemia, hepatic injury, sleep apnea, and breast or endometrial cancers have not been found, although none of the studies have been adequately powered to fully examine the latter two conditions. A reduction in high density lipoprotein may be seen with the oral androgen administration, but is not found with parental delivery.

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Some critics have suggested that the topic of female androgen insufficiency is a construct of the pharmaceutical industry intent on creating a condition in order to sell a product.

HSDD in women have arisen from supraphysiological doses taken by men and women for athletic performance-enhancement or bodybuilding. In fact, the data from several of the trials in women who have received testosterone preparations for low libido are reassuring and show that serum free testosterone

not known whether a similar efficacy and safety profile will be found in women taking androgens alone. It is essential that this be examined, since many women are discontinuing or not starting estrogen therapy at the time of menopause in response to results from the Heart and Estrogen/Progestin Replace-

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Conflict-of-Interest Statement: Dr. Braunstein has been a Principal Investigator and consultant for studies conducted by Procter & Gamble Pharmaceuticals, Inc. on a transdermal matrix delivery system of testosterone for women.

CLINICAL PRACTITIONER VIEW

Androgen Replacement in Women

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Women rely on two main sources for their androgens, the ovary and the adrenal gland, with approximately equal contribution from each source. Androgen production in women declines with aging. At menopause, circulating androgen levels decrease by more than 50 percent. The adrenal gland produces dehydroepiandrosterone (DHEA), an androgen precursor. Levels of this hormone start to decline after the late teenage years at a rate of about 10 percent per decade, with no precipitous drop at the menopause. It is becoming increasingly apparent that androgens are important in women for a variety of physiological and psychological processes.

Androgens and Bones

Androgens and estrogens are important in maintaining bone density (BMD) in women. In contrast to estrogens, which are antiresorptive in their action, androgens are proanabolic and act to stimulate bone formation. In premenopausal women observational data show a linear relationship between circulating androgen levels and BMD. Hyperandrogenic women with polycystic ovarian syndrome have higher BMD. The relationship between androgens and bone density is less clear in postmenopausal women. There are data to show that testosterone treatment given to postmenopausal women significantly increases BMD, but it is not known if this is due to a direct effect of the androgen, or as an indirect result of

changes in body composition, such as increases in lean body mass, or from conversion to estrogen. The question of using DHEA replacement in postmenopausal women in the maintenance of BMD has yet to be defined, and is currently being addressed in clinical studies. Although there are potential benefits of androgens therapy for postmenopausal bone loss, long term outcome data are needed before such treatment can be endorsed.

Androgens, Sexual Function and Wellbeing

Awareness of the impact of low androgen levels on emotional, social, psychological and sexual wellbeing in pre- and postmen-

opausal women is also increasing. Several studies now show that the prevalence of female sexual dysfunction in the USA and Europe is estimated between 40 percent and 45 percent. It is clear that the causes of low quality of life and sexual dysfunction are multifactorial. Androgen deficiency is just one facet of this complicated issue, however several studies have now shown that androgen supplementation improves quality of life in women receiving estrogen. Improvements in general wellbeing, energy and mood, as well as

reductions in irritability, nervousness, memory, and insomnia have been shown. Use of androgen therapy to improve quality of life in postmenopausal women can not yet be endorsed until the results of long term studies are available. In addition, androgen therapy may be best targeted toward

populations most likely to benefit, including oophorectomized women, or those who lack adrenally derived androgens. There are now several studies showing that the addition of an



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androgen to these women significantly improve sexual function as measured by arousal, frequency, masturbation, coitus, and completion. In these studies, androgens were given as an implant, intramuscular depot, daily pill, ointment or gel, or as a patch.

The data using DHEA replacement has not been as convincing as other androgens, but DHEA has been shown to improve sexual function scores in women with very low androgen levels due to adrenal dysfunction. Whether the use of androgen therapy will

improve sexual dysfunction among otherwise healthy premenopausal women remains to be determined. Sexual function has been shown to correlate with lower testosterone levels among premenopausal women, but the risk benefit ratio of androgen therapy in this population needs to be carefully determined.

Androgens in the Prevention and Treatment of Cancer

Epidemiological work has shown that low DHEA levels have been associated with higher rates of breast and ovarian cancer. There has also been recent work showing that androgen treatment may protect against the development of breast cancer. In cases of established cancer, androgens have been shown to have an inhibitory effect on affected tissues, with treatment leading to increases in response rates and disease free survival. This works remains in its early stages, and at present androgens or

DHEA are not licensed for this indication. Furthermore DHEA replacement remains controversial. In the United States, its availability across the counter as a 'health food supplement' means that it is not regulated, and that quality control issues remain a valid concern.

Summary

There is now increasing awareness amongst physicians treating women who have low levels of ovarian or adrenally derived androgens, that replacement could be important. Estrogens and androgens have individual roles to play in several key areas. However, their routine use in women remains at an early stage, with limited long term outcome data. Whilst there are several studies showing that androgen replacement improves outcomes of physical and psychological wellbeing, there are also early data to suggest that androgen replacement in women may worsen components of the metabolic syn-

drome. In addition, the development of hirsutism and acne, with the need for continued monitoring of liver function, lipids and hematocrit remain important considerations. Importantly, androgen use in a pregnant women could potentially virilize a female fetus and this risk needs to be considered in premenopausal women. Following from the tantalising animal and epidemiological data, much work remains to be done to clearly establish the role of androgen replacement in women. **EN**

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CLINICAL RESEARCHER ON CLINICAL IMPLICATIONS

Use of Androgens in Androgen Deficient Women— Physiologic and Therapeutic Implications

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Recent data regarding the effects of androgen therapy on libido and sexual function in women and the clinical development of a testosterone patch for women raise a number of questions regarding androgen administration in women. We need to better define an androgen deficiency syndrome and differentiate between hormone replacement and pharmacologic use of hormonal therapy. Research is needed to determine in which subsets of women androgen administration is effective. In addition to androgen effects on libido and sexual function, other endpoints, including bone, body composition, cardiovascular risk, breast tissue and brain effects require study. Finally, the long-term safety of androgen therapy in women needs to be established.

Because the ovaries and adrenals are the primary sources of androgens in women, disease or iatrogenic intervention which compromises the function of these glands may result in hypoandrogenemia. Bilateral oophorectomy has been demonstrated to result in a 60 percent reduction in serum testosterone in premenopausal women and a 50 percent decrease in postmenopausal women, suggesting that the ovaries produce approximately half of circulating testosterone in women, with the other half derived from adrenal precursors. In contrast, more than 90 percent of dehydroepiandrosterone (DHEAS) is produced by the adrenal glands. Therefore, bilateral oophorectomy and/or adrenal insufficiency result in a marked diminution in circulating testosterone, with a reduction in DHEAS

also observed in women with adrenal insufficiency. Women with hypopituitarism, particularly those with both hypoadrenalism and hypogonadism, have severe androgen deficiency, including decreased testosterone, free testosterone, androstenedione and DHEAS. Medications that suppress ovarian function, such as oral contraceptives, and those that suppress adrenal function, including glucocorticoids, also reduce androgen levels in women. Oral estrogens, even at low doses, reduce free testosterone by increasing SHBG levels.

Physiologic age-related declines in androgens may result in lower levels than healthy younger women. Whether this represents a state of relative androgen deficiency is a key question. Testosterone levels decrease linearly between ages 20 and 40 by approximately 50 percent but may then increase after menopause, resulting in levels comparable to premenopausal women. In contrast to testosterone, DHEAS levels decline linearly with age, such that levels at age 70 are about 20-25 percent of those of a 20-year-old. The recent Women's Health Initiative (WHI) results highlight the importance of randomized, placebo-controlled studies to determine the efficacy and safety of use of hormones in physiologic, rather than pathologic, hormone deficiency states.

Is biochemical androgen deficiency in women associated with a clinical syndrome? There are few data firmly establishing clinical effects of androgen deficiency in women. Hypoandrogenic women with bilateral oophorectomy have decreased libido and sexual function. Our cross-sectional data in androgen-

deficient women with hypopituitarism suggest an association between circulating androgen levels and both lean body mass and hip bone density. Data in larger populations of healthy women without androgen deficiency also show associations of androgen levels with bone density.

Diagnosing androgen deficiency in a particular patient is difficult due to lack of both validated assays in the female range—10 to 20 times lower than male range—and established normal age-based ranges. As more normative data is amassed, and testosterone assays are better validated, specifically at the lower range, establishing androgen deficiency in a specific patient should become easier.

Although data regarding the effects of androgen therapy on libido and sexual function strongly support an effect in a subset of androgen-deficient women, effects on other endpoints are not well established. Androgen effects on brain and body composition are beginning to be studied. Brain effects of androgens likely exist, but are not adequately characterized. In a study of functional brain changes, we have shown increases in posterior cingulate cortical metabolism in women with anorexia nervosa with low-dose testosterone administration. However, the functional implications of this are not established. Studies examining improvements in mood and/or quality of life with androgen replacement have been conflicting. The variability in response

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Karen Klahr Miller

to address health disparity issues in the minority community. During the last Session of Congress, the Society supported several minority health disparity bills in the US House of Representatives and US Senate.

Other changes within Congressional Caucuses include a new Co-Chair of the Congressional Diabetes Caucus, Congressman Mike Castle (R-DE). Castle will join The Endocrine Society's friend, Congresswoman Diana DeGette (D-CO), in leading the Diabetes Caucus in 2005. Congressman Castle is a Subcommittee Chairman of the House Education and the Workforce Committee. According to Capitol Hill staff, Castle would like to use his new Co-Chairmanship of the Diabetes Caucus to examine and address diabetes issues in the workforce.

Although the new 109th Session of Congress has not yet convened, The Endocrine Society government relations team has already been very active in reaching-out to new Members of Congress, Cabinet officials, and potential new champions to advance the Society's government relations priorities. In addition, the Society has also been working with many of its veteran Congressional champions to identify and address both opportunities and challenges in the new year. **EN**

For more information on Government Relations activities contact Chris Rorick, Manager Government Relations, crorick@endo-society.org

The Endocrine Society

IN THE NEWS

The Endocrine Society is working to build awareness of endocrinology through public relations efforts. In recent months, The Endocrine Society and several of its experts have been highlighted in the news. Here are a few examples:

- The November 17 issue of *USA Today* highlighted a study from the November issue of *The Journal of Clinical Endocrinology & Metabolism*. The study highlights the possible link between obesity and lack of sleep.
- In November, The Endocrine Society participated in a series of media briefings on the issue of open access. Lenne Miller, Senior Director of Publications, met with reporters from *The Wall Street Journal*, *The USA Today*, *The Hill*, Washington FAX and *The National Journal*. Following the meetings, the Society was quoted in news stories from several of these news outlets.
- The December 14 issue of *USA Today* included a quote from Endocrine Society President, Anthony Means in a story on open access.
- In December, the Food and Drug Administration Advisory Committee for Reproductive Health Drugs met to consider approval of Intrinsic, a transdermal testosterone system for women. After reviewing the current data, the committee called for additional research and safety information before approving Intrinsic, which is intended for the treatment of hypoactive sexual desire disorder in surgically menopausal women receiving concomitant estrogen therapy. The Endocrine Society issued a press release in conjunction with this meeting. Endocrine Society spokespersons were interviewed by several news outlets including *Time Magazine*, *WebMD*, *The San Jose Mercury News*, *Fort Worth Star Telegram* and *The New Jersey Star Ledger*.
- The January 17 issue of *Newsweek* included a letter to the Editor from Society President Anthony Means on steroid abuse. **EN**

If you are interested in serving as a media spokesperson for The Endocrine Society, please contact Tadu Yimam, Coordinator, Public Relations at media@endo-society.org

Use of Androgens

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may reflect differences in underlying degrees of depression and well-being, doses used, failure to identify subsets in which the hormonal therapy is effective or other factors. Two randomized, placebo-controlled studies show promising preliminary results on bone density,

but there are few data regarding effects on lean and fat mass.

Finally, a few studies have investigated the effects of androgen administration in normal young women. Efficacy of this "pharmacologic" use of androgens raises questions regarding the implications and safety of supraphysiologic hormone administration, which require further study before evidence-based recommendations can be made.

Establishing the characteristics of an androgen deficiency syndrome in women, investigating long-term safety of androgen use in women, determining the effects of androgens on a number of clinical endpoints, establishing normal androgen ranges and valid androgen assays are all important. Finally, identification of subsets of women for which the therapies are effective and safe is critical. **EN**