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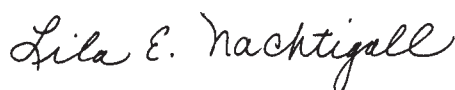
Among the satellite symposia presented at the 12th Annual Meeting of The North American Menopause Society (NAMS) were two that addressed important therapeutic issues in menopause management: the role of androgen therapy and the trend toward low-dose estrogen replacement therapy (ERT) and low-dose combined estrogen-progestogen therapy (hormone replacement therapy; HRT). This supplement to *Menopause Management* presents highlights from these two symposia.

The topics and faculties of all satellite symposia are selected by the NAMS Scientific Committee, based primarily on the needs assessments of meeting participants. The unrestricted educational grants that support the symposia are provided by pharmaceutical companies committed to the dissemination of unbiased information. We are grateful for their support.

According to three experts who considered the role of androgen therapy, androgen deficiency is a valid diagnosis in women. Indeed, according to Dr. Fernand Labrie, the age-related loss of dehydroepiandrosterone and androgen is implicated in bone loss associated with menopause. In addition to physical consequences, androgen deficiency can also interfere with psychological and social well-being, observed Dr. Susan R. Davis. In Dr. Jan Shifren's practical guide to androgen use, she clearly defined suitable candidates for therapy and stressed the need to continue to inform the patient completely about associated risks and uncertainties.

The Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study evaluated low-dose ERT and HRT. The multicenter, 2-year trial considered whether relatively low doses of conjugated equine estrogens (CEE), with presumably fewer side effects, would have therapeutic benefits equivalent to those seen with standard, higher doses. The study used medroxyprogesterone acetate (MPA) as the progestogen. In this symposium's exploration of the study's results, Dr. David F. Archer reviewed the safety issues and noted that, as expected, patients on low-dose therapy had fewer side effects as well as less uterine bleeding. Dr. Bruce R. Carr observed that the lower-dose regimens resulted in lipid profiles that were similar to those achieved with standard doses, and they caused beneficial changes in fibrinogen and PAI-I. Dr. Wulf H. Utian noted that all dosage regimens reduced the incidence of hot flashes; however, low-dose combination therapy (CEE plus MPA) was more effective than the same CEE dose alone, suggesting additional benefits from the progestogen. The favorable effects of low-dose ERT/HRT on vasomotor symptoms and metabolic function, combined with non-diminished efficacy, have promise for improved compliance.

NAMS will continue to offer high-quality sessions such as the satellite symposia highlighted in this supplement. I invite you to attend the Society's 13th Annual Meeting to be held October 3-5, 2002, in Chicago. Program details are available on the NAMS Web site (www.menopause.org).



Lila E. Nachtigall, MD

2000-2001 President

The North American Menopause Society

The Role of Androgen Therapy in Postmenopausal Women

October 5, 2001 • New Orleans, Louisiana

12th Annual Meeting of The North American Menopause Society

Supported by an unrestricted educational grant provided by Solvay Pharmaceuticals, Inc.

Physiology of Androgens in Women

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Recent evidence indicates that androgens play an important but underestimated and underrealized role in female physiology. A crucial aspect of androgen physiology in women is that most androgens in women are not of direct ovarian or adrenal origin. In fact, following menopause, nearly all androgens and estrogens are produced locally in peripheral tissues that contain the enzymes required for the transformation of dehydroepiandrosterone (DHEA) into dihydrotestosterone (DHT) or estradiol.

Androgens are inactivated by specific glucuronyl transferases in the same cells where androgen synthesis occurs. The active androgens testosterone and DHT are first transformed into androsterone (ADT) and androstane 3- α , 17- β -diol (3- α -diol), which are then transformed into the glucuronide derivatives ADT-G and 3- α -diol-G.

Since the active androgens diffuse poorly to the extracellular compartment, in order to ascertain true androgen activity in tissues, it is necessary to measure their metabolites in the blood instead of or in addition to measuring testosterone and DHT. Plasma concentrations of ADT-G and 3- α -diol-G are the only accurate parameters.

Androgen Levels in Women

As estimated from the circulating levels of the DHT metabolites ADT-G, 3- α -diol-G and androstane-3- β , 17- β -diol-G (3- β -diol-G), women produce approximately two-thirds of the androgens found in men (Table 1).¹

Because nearly 100% of estrogens and androgens are synthesized in peripheral target tissues, the plasma concentrations of the

active sex steroids have limited value in estimating intracellular androgen and estrogen concentrations and activity.² This makes it difficult to ascertain androgen levels in women. Moreover, because of the lack of specificity, precision and accuracy, most information derived from radioimmunoassays of serum steroids must be re-examined with new technology using liquid or gas chromatography and mass spectrometry.

The rate of formation of each sex steroid depends on the level of expression of each steroidogenic enzyme in each cell of each tissue.^{3,4} Such a specialized and highly specific intracrine system permits each target tissue to: (1) make its own sex steroids according to its needs, and (2) regulate their intracellular concentrations by controlling the level of activity of both the steroidogenic and steroid-inactivating enzymes.

Table 1.
Comparison of Serum Androgen Metabolites (nM)
in Men and Women, 20–80 Years¹

	Men	Women (% compared with men)
ADT-G	37.5	32.5 (87%)
3- α -diol-G	8.5	4.3(51%)
3- β -diol-G	30.2	17.3 (57%)
Total	76.2	54.1 (71%)

Table 2.
Intracrinology: Tissue-Specific Effects of DHEA

Androgenic effects

- Bone formation*
- Sebaceous gland stimulation*
- Mammary gland inhibition*
- Muscle mass increase*

Estrogenic effects

- Vaginal mucosa maturation*
- Insulin resistance decreased*†

No Effect

- Endometrium*

* demonstrated in postmenopausal women

† possibly also androgenic

In premenopausal women, the origin of the serum levels of androstenedione is split equally between the adrenals and the ovaries. In postmenopausal women, 80% of the serum androstenedione concentration is from the adrenals' serum. Testosterone levels in both pre- and postmenopausal women are divided equally between the adrenals and the ovaries.⁵

Androgen Therapy

By menopause, the serum concentration of the androgen metabolites is greatly diminished.¹ DHEA levels decline markedly from age 30 to 60, and by age 75 they are at only 20% of their maximum

level. Thus, it is not surprising that androgen therapy is beneficial for this age group. The loss of bone that occurs before menopause is most likely a consequence of the decrease of DHEA and androgen formation in the bone (Table 2).

Androgen plays several important therapeutic roles for women: *Bone mineral density.* Androgens increase bone mineral density (BMD) in postmenopausal women. Need et al⁶ found that injections of the anabolic steroid nandrolone decanoate caused a significant increase in bone mineral content. In a trial measuring the effects of estradiol and testosterone on BMD, women on the combined therapy had more rapid increases in BMD of total body, lumbar vertebrae and hip area than women on estradiol alone.⁷ Postmenopausal women who received DHEA percutaneously had increased BMD (Figure).⁸

Skin. DHEA increases sebum secretion and epidermal thickness and improves the papery appearance of postmenopausal skin.^{8,9} The epidermis, dermis, sebaceous glands, hair follicles and sweat glands all make androgens from DHEA.¹⁰

Hot flashes. In a placebo-controlled study of parenteral administration of estrogen and androgen for their effect on hot flashes, surgically menopausal women who were given a combined estrogen-androgen preparation reported a significantly reduced frequency of hot flashes compared with estrogen alone.¹¹

Libido and sexual satisfaction. Androgens given with hormone replacement therapy (HRT) improve libido and sexual satisfaction to a greater degree than HRT alone. Women who received an estrogen-androgen preparation reported higher rates of sexual desire and sexual arousal than those who were given estrogen alone.¹² These responses correlated with higher levels of plasma testosterone.

Leiblum et al¹³ investigated the effects of sexual activity on vaginal atrophy and the role of hormones. Sexually active women had less vaginal atrophy compared with sexually inactive women. In addition, women with less vaginal atrophy had significantly higher mean levels of androgens (androstenedione and testosterone).

Conclusions

It is now recognized that androgens are an important, yet underappreciated, constituent in the physiology of women. Better appreciation of their role, and the place of androgens in therapy for women—including the areas of BMD, skin, vasomotor symptoms, libido and sexual satisfaction—is a necessary component in providing quality health care to women of menopausal age.

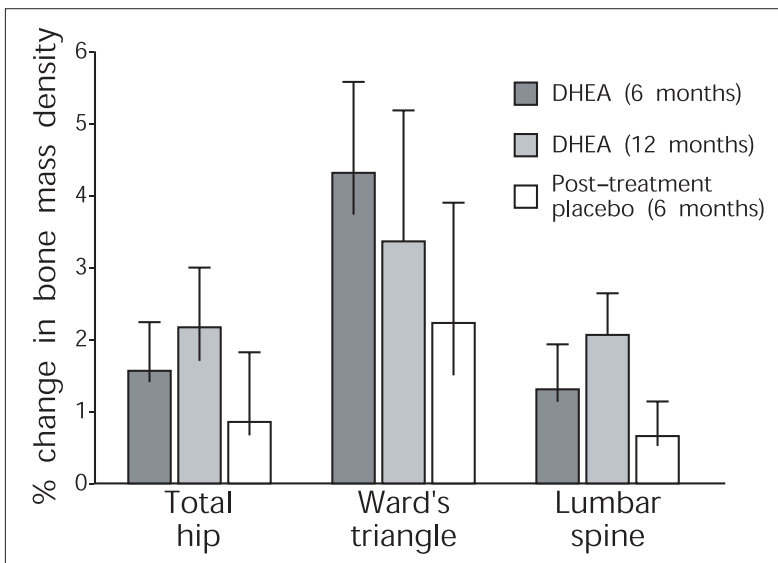


Figure. Percent change in bone mineral density in total hip, Ward's triangle and lumbar spine with DHEA. Increases in all three areas were seen at 6 and 12 months with administration of DHEA.⁸

Dr. Labrie reports no significant financial relationships.

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Is There an Androgen-Deficiency Syndrome?

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The need for testosterone replacement is being increasingly diagnosed among surgically and naturally menopausal women. There are two fundamental questions, however: (1) What are we treating? and (2) Is there an androgen-deficiency syndrome?

Testosterone is an important compound for women. In addition to its direct androgenic actions, it is a prohormone for estradiol in the brain and other tissues. In the human female brain, there is much more testosterone in the important behavioral areas than there is estradiol. In contrast to the abrupt decline in estradiol at menopause, testosterone levels drop gradually with age from the midreproductive years and do not change acutely across the menopause transition (Figure).¹ Consequently, testosterone levels can be insufficient in the late premenopausal years. (Women who undergo surgical menopause experience a sudden drop in both testosterone and estradiol levels.)

Testosterone circulates in the bloodstream highly bound to sex-hormone-binding globulin (SHBG). Total androgen production is best reflected by total testosterone, but the free testosterone value determines whether deficiency is present. The gold stan-

dard for measurement of free testosterone is equilibrium dialysis. Because non-SHBG-bound testosterone is indicative of the free testosterone level, the SHBG levels can guide the management of the patient with low testosterone levels.

Causes of Androgen Deficiency in Women

A clinical or biochemical definition of androgen deficiency in women does not exist, and no large cross-sectional study has been conducted that correlates proposed symptoms with circulating levels. Consequently, clinicians must manage androgen deficiency without a defined syndrome to treat. Androgen deficiency in women has both endogenous and exogenous causes:

Aging. Between the ages of 20 and 40, total circulating testosterone in women decreases by 50%. This reduction predates menopause. It occurs because of a reduction in dehydroepiandrosterone (DHEA) and a loss of cyclical ovarian production of testosterone.

Ovarian insufficiency unassociated with natural menopause. Ovarian dysfunction before menopause can result in a 50% reduction in androgen and testosterone production.

Oophorectomy. Removal of the ovaries reduces testosterone production by half.

Adrenal and pituitary insufficiency. Loss of adrenal function also cuts androgen production in half. Loss of pituitary function causes a loss of both adrenal and ovarian production.

Glucocorticosteroid therapy. Glucocorticosteroid therapy is one of the most common causes of androgen deficiency. This type of therapy suppresses the adrenals and DHEA production, and may contribute to bone loss.

The central effects of testosterone deficiency include decreased estradiol production, low libido, decreased vaginal blood flow and lowered mood and motivation. General effects include loss of bone and lean mass.

Symptoms and Consequences of Androgen Deficiency

According to the Princeton Consensus Statement from June 2001,² the clinical symptoms of androgen insufficiency in women include diminished sense of well-being; dysphoric mood or blunted motivation; persistent, unexplained fatigue and sexual function changes, including decreased libido, sexual receptivity and pleasure. Other possible signs and symptoms include bone loss, decreased muscle strength and changes in cognition and memory.

Testosterone insufficiency in women has implications for sexual function. Testosterone and estradiol both help to maintain vascu-

lar function and vaginal lubrication. Testosterone insufficiency leads to decreased blood flow to the vagina and therefore reduced lubrication. Women might need testosterone to achieve adequate arousal and response in the peripheral tissues. Because of the effect of low testosterone on mood and motivation, women whose levels are low might have less energy and a poorer sense of well-being along with reduced libido. Sexual dysfunction is more prevalent with age and with oophorectomy.³ Low testosterone is also most closely correlated with decreased coital frequency and loss of desire.^{4,5}

Measuring Testosterone Levels

Measuring testosterone levels in women is a challenge. The currently available assays are insensitive for detecting testosterone levels at the lower-normal female range, and they discriminate poorly for values below this range. Therefore, values in the lower quarter of the normal range with clinically consistent symptoms might indicate testosterone insufficiency.

Testosterone measurements should include total testosterone, SHBG and, if indicated, thyroid-stimulating hormone and iron stores. Testosterone should be measured before midday and, for premenopausal women, during the middle third of the cycle. Women who have testosterone values in the lower 25% of the assay that is available to the clinician, *and* consistent symptoms, should be considered for androgen therapy. Symptoms of low testosterone levels alone are insufficient for a diagnosis of androgen deficiency.⁶

Treating Testosterone Deficiency

One of the most important reasons to treat testosterone deficiency is that the addition of testosterone to estrogen increases bone density.⁷ Testosterone is converted to estradiol and helps stop reabsorption.⁸ Oral estrogen replacement therapy reduces the bioavailable testosterone because of a rise in SHBG associated with oral therapy. Testosterone-deficient patients taking oral estrogen therapy might require androgen therapy, as well; however, switching to a nonoral hormone replacement therapy might obviate the need for androgen replacement.

Testosterone therapy in various forms can improve sexual motivation,⁹⁻¹² including desire, fantasy, arousal, increased frequency and orgasm^{7,11,13} and increased pleasure and satisfaction.⁷

Conclusions

Testosterone deficiency is a valid entity in women with manifestations that interfere with psychological, physical and social well-being. More

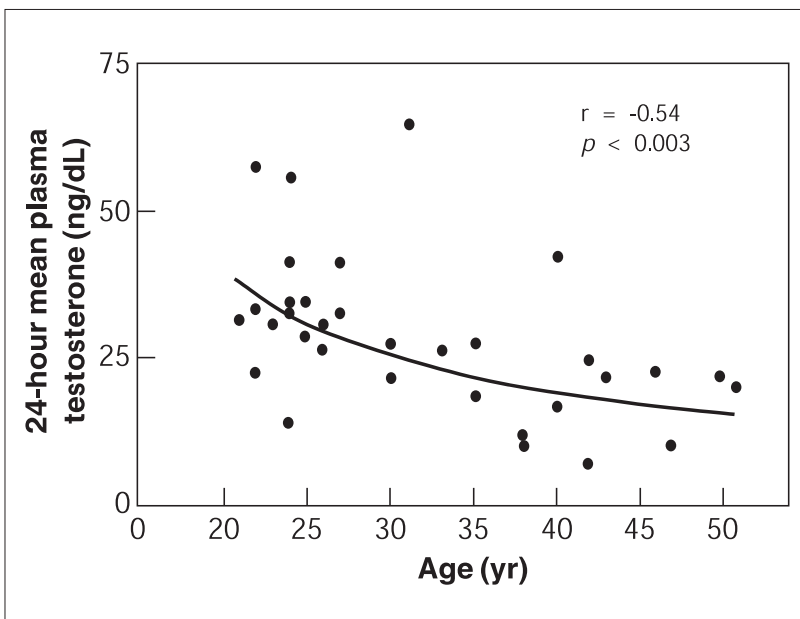


Figure. Testosterone levels in normal premenopausal women start to decline by age 20 and are nearly half depleted by age 50. Reproduced with permission from Zumoff B, Strain GW, Miller LK, Rosner W. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. *J Clin Endocrinol Metab* 1995;80:1429-30. ©The Endocrine Society.

research is urgently needed in this field to establish normal ranges. Therapeutic options designed for women need to become widely available.

Dr. Davis reports no significant financial relationships.

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A Clinician's Guide to Androgen Use in Women

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Androgens promote the development and maintenance of male secondary sex characteristics and structures, but increasing evidence suggests that these hormones are important for women, as well. Androgens in women are likely important for libido and sexual function, with potentially beneficial effects on bone mineral density, body composition, energy level and psychological well-being.

Causes of Decreased Androgens

The ovary and adrenal gland are the principal sources of androgens for women, suggesting several important causes of low androgen concentrations in women:

Ovarian insufficiency. Oophorectomy, premature ovarian failure, Turner's syndrome, chemotherapy and autoimmune disease result in decreased or absent ovarian androgen production.

Adrenal insufficiency. Addison's disease and adrenalectomy result in decreased or absent adrenal androgen production.

Hypothalamic or pituitary dysfunction. Ovarian and adrenal hormone levels are regulated by the hypothalamus and the pituitary

gland. Impaired function in these central structures can contribute to decreased androgen concentrations.

Medications. Oral contraceptives and oral estrogen replacement therapy suppress luteinizing hormone and increase sex-hormone-binding globulin (SHBG), leading to reduced concentrations of free, or bioactive, testosterone. Corticosteroids decrease adrenocorticotropic hormone (ACTH) levels, thereby also decreasing adrenal androgen synthesis.

Aging. Both ovarian and adrenal androgen production decrease with advancing age; of note, androgens do not decrease abruptly at the time of the menopausal transition.

Sexual Dysfunction

In certain cases, sexual dysfunction in women can be a symptom of androgen insufficiency. Many possible symptoms of androgen insufficiency are nonspecific and characteristic of other medical, psychological and psychosocial problems; for example, decreased libido, sexual receptivity and pleasure; dysphoric mood; dimin-

ished sense of well-being and low energy all can be symptomatic of androgen insufficiency, as well as other problems. Therefore, alternate causes of the presenting symptoms must be identified and treated. Before considering androgen therapy, it might be necessary to treat underlying medical and gynecologic problems and to adjust the patient's medications, including selective serotonin reuptake inhibitors and antihypertensives. Depression or anxiety should be addressed, and lifestyle changes recommended, to overcome such problems as stress, fatigue and lack of privacy. In certain situations, referrals should be made for relationship and psychological counseling, and for sex therapy.

Estrogen replacement therapy (ERT) should be initiated before considering androgen therapy; ERT may improve genital comfort, sensation and arousal, and it can reduce the likelihood of several adverse effects associated with androgen use. Oral, but not transdermal, ERT increases SHBG concentrations and therefore decreases free testosterone levels. For that reason, a woman who presents with decreased libido following treatment with oral ERT theoretically could benefit from a trial of transdermal ERT.

Androgen Therapy

The ideal patient for androgen therapy is an estrogen-replete woman with a physiologic reason for reduced androgen levels, for whom other causes and treatments have been considered. The patient must be fully informed about androgen therapy; i.e., no androgen therapies have been proven effective and safe for the treatment of female sexual dysfunction in large, randomized, placebo-controlled trials, there are no Food and Drug Administration (FDA)-approved androgen therapies for female sexual dysfunction, and any such use is considered off-label.

Androgen Therapy Options

Currently available androgen products include topical testosterone ointments and gels, oral methyltestosterone (MT), micronized testosterone, dehydroepiandrosterone (DHEA), intramuscular (IM) testosterone¹ and testosterone implants.² Many of these therapies are compounded locally and not regulated by the FDA. Lot-to-lot consistency, bioavailability and dose, therefore, are unpredictable and not well standardized.

The goal of androgen therapy for women is to provide physiologic replacement, increasing testosterone levels to the normal range for reproductive-aged women. Unfortunately, free, or bioactive, testosterone levels are difficult to measure accurately. Response to therapy, therefore, is primarily subjective, requiring close monitoring for improved sexual response in the setting of

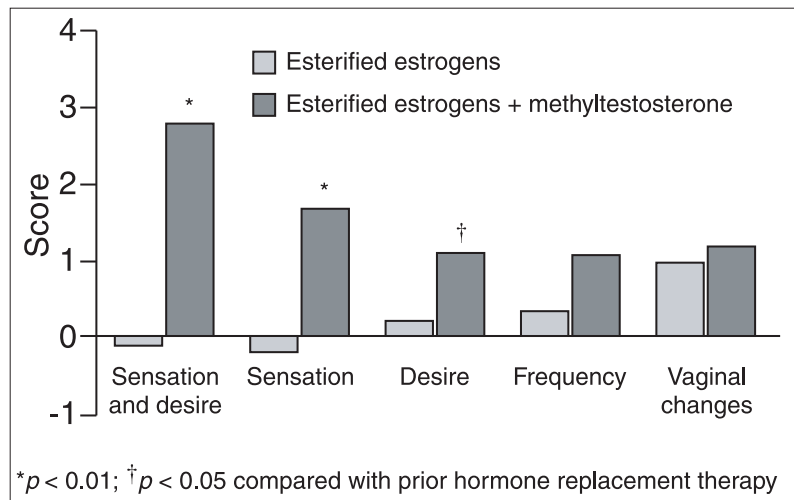


Figure 1. Sexual parameters, including sensation and desire, showed greater improvement with esterified estrogen/methyltestosterone compared with prior estrogen therapy or baseline measures. Reproduced with permission from Sarrel et al.³

minimal adverse effects. With certain agents, such as topical testosterone or DHEA, free testosterone levels may be checked to ensure that serum concentrations of androgens remain in the physiologic range. MT is not measured in testosterone assays.

Topical testosterone may be prescribed as a 2% ointment, applied nightly to the genital area as a "fingertipful." Testosterone administered by IM injection or implants can be inconvenient or uncomfortable for patients and often results in supraphysiologic levels. Topical products available for men, including skin patches (Androderm, Testoderm) and gels (Androgel), are inappropriately dosed for women and should not be used.

Among oral androgen preparations, the options include micronized testosterone, MT and DHEA. Micronized testosterone is very poorly absorbed and therefore not recommended. MT combined with esterified estrogens is available in the hormone replacement product Estratest. Indicated for vasomotor symptoms unresponsive to ERT and not for sexual dysfunction, this is the only testosterone product available for women with FDA-regulated production and extensive published safety data. Although MT is not measured in testosterone assays, the full-strength form is likely supraphysiologic. The "half-strength" form, containing MT 1.25 mg and EE 0.625 mg, is preferable. Lower doses of MT are available through compounding pharmacies. In one small study,³ sexual parameters, including sensation and desire, showed greater improvement with esterified estrogen/methyltestosterone compared with prior estrogen therapy or baseline measures (Figure 1).³

DHEA is available as a "dietary supplement" and may be purchased without a prescription. The recommended replacement dose for women with low androgen levels is 50 mg daily, but the amount of hormone in over-the-counter preparations varies greatly because of lack of regulation.⁴ In a small study of women with

adrenal insufficiency,⁵ women taking DHEA had greater sexual activity scores for physical and mental satisfaction, interest level and thoughts/fantasies than when taking a placebo (Figure 2). Similar results with DHEA have not been observed in studies of women with normal adrenal function.

Monitoring of Androgen Therapy and Risks

Patients on androgen therapy should be seen at regular intervals for assessment of their subjective response to treatment and for monitoring of adverse effects. The risks of androgen therapy include hirsutism, acne, adverse lipid effects (especially lowering of HDL-cholesterol) and impaired liver function. A baseline fasting lipid profile and liver function testing are recommended for every woman planning androgen therapy, with a repeat evaluation to be considered at 6 months. Other potential adverse effects of androgen therapy include virilization (clitorimegaly, lowering of the voice and temporal balding), fluid retention with edema, hypertension, exacerbation of heart disease, psychological and behavioral changes and virilization of a female fetus. Because many androgens are aromatized to estrogens, it is possible that androgen therapy might be associated with an increased risk of breast cancer, venous thromboembolic events and gallbladder disease. Adverse effects clearly are more likely with supraphysiologic dosing of androgens.

Conclusions

Androgen replacement therapy can be appropriate for estrogen-replete menopausal women who are experiencing sexual dysfunction associated with low circulating androgen concentrations and a physiologic reason for androgen insufficiency. Women who elect androgen replacement therapy must be fully informed of the lack of approved products for this indication and the limited data on safety and efficacy. Early evidence, though, suggests that physiologic dosing of androgens in menopausal women might improve libido and sexual function, with potential for beneficial effects on bone mineral density, body composition and overall psychological well-being.

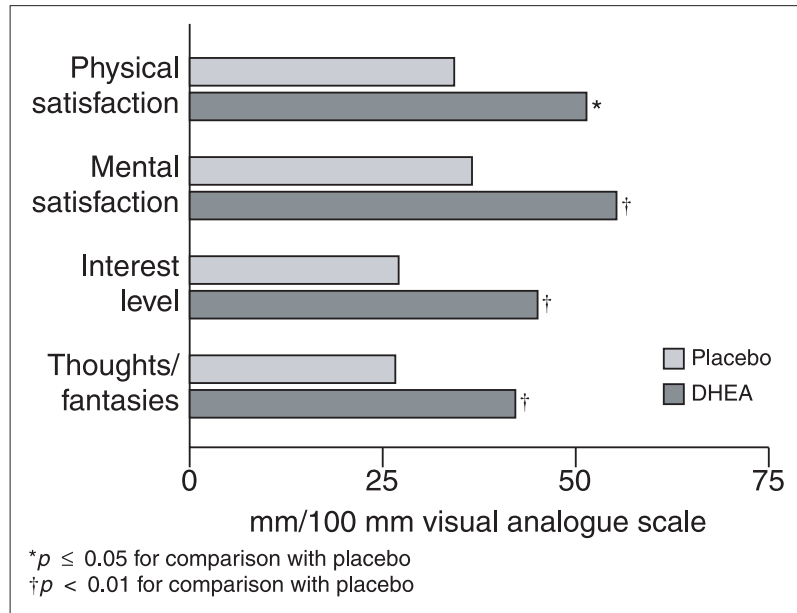


Figure 2. Women with adrenal insufficiency who took DHEA had higher sexual activity scores for physical and mental satisfaction, interest level and thoughts/fantasies than when taking a placebo.⁵

Dr. Shifren receives research/grant support from Procter & Gamble Pharmaceuticals, Inc., and Solvay Pharmaceuticals, Inc. She also is a consultant to Solvay Pharmaceuticals, Inc., and is on the speakers' bureau for Eli Lilly and Company.

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Justifying the Trend to Low-Dose ERT/HRT

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Introduction: The HOPE Study

The Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study, a 2-year, multicenter trial, was designed to assess whether lower doses of estrogen and progestin worked as well as higher doses in hormone replacement therapy (HRT). The investigation included 2,673 healthy, postmenopausal women from 57 study sites. The women in the study all had an intact uterus and were about 5 years postmenopausal. All of them received a daily calcium carbonate supplement (600 mg elemental calcium per day).

The study subjects were randomized to one of eight groups receiving either the commonly used combination of conjugated equine estrogens (CEE), 0.625 mg, and medroxyprogesterone (MPA), 2.5 mg; a combination of lower CEE and various MPA doses; various doses of CEE alone; or placebo. The treatment groups were:

- CEE 0.625 mg/MPA 2.5 mg
- CEE 0.45 mg/MPA 2.5 mg
- CEE 0.45 mg/MPA 1.5 mg
- CEE 0.3 mg/MPA 1.5 mg
- CEE 0.625 mg
- CEE 0.45 mg
- CEE 0.3 mg
- Placebo

At the end of the first year of the study, subjects were assessed for vasomotor symptoms, vaginal atrophy, bleeding profile, metabolic profile and endometrial hyperplasia. Outcomes measured after the second year were bone mineral density, metabolic profile and endometrial hyperplasia.

The symposium "Justifying the Trend to Low-Dose ERT/HRT" presented selected findings from the HOPE study, including discussions of side effects, metabolic issues with implications for cardiovascular disease and the impact of body mass index on HRT. Highlights from the symposium presentations follow.

Safety and Side Effects of Low-Dose ERT/HRT

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Despite the known and potential health benefits of estrogen replacement therapy (ERT) and hormone replacement therapy with combined estrogen plus progestogen (HRT), many women are either unwilling to start therapy or they discontinue treatment. Women who start ERT/HRT do so primarily for treatment of vasomotor instability (hot flashes) and urogenital atrophy, and to prevent osteoporosis. Those who discontinue therapy or decline to start are concerned mostly with HRT-related bleeding or other side effects, or with the risk of endometrial or breast cancer.

An improved benefit/risk profile would encourage more women to initiate and continue ERT/HRT. Studies in the past decade have demonstrated that lower doses of ERT/HRT may impart benefits similar to those provided by standard (higher) doses,^{1,2} while reducing the occurrence of side effects.³ These studies have not documented the safety and tolerability of lower-dose regimens, however, and the dose of progestogen needed to provide endometrial protection in combination with a lower dose of estrogen has not been determined.

The reduced incidence of side effects with lower-dose ERT/HRT regimens would help reach the therapeutic goal of continued efficacy with minimal side effects, potential for greater patient acceptability and improved compliance to achieve long-term health benefits.

One objective of the HOPE study was to evaluate the occurrence of adverse effects, with assessments of endometrial hyperplasia, bleeding profiles and other side effects such as breast pain.

Endometrial Hyperplasia

Endometrial biopsies were performed at baseline, cycle 6 and cycle 13 in the HOPE study. Endometrial hyperplasia was diagnosed in 32 women by cycle 13; of these, 29 were taking estrogen alone, and the other three were taking lower-dose combinations of conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA).

At 1 year, hyperplasia rates were highest in the CEE alone 0.625 (~8%) and 0.45 mg groups. The only diagnoses of hyperplasia in the combination therapy groups were one each in the lower-dose arms (CEE 0.45 mg/MPA 1.5 mg and CEE 0.3 mg/MPA 1.5 mg). The incidence of endometrial hyperplasia

was significantly lower in the CEE/MPA groups ($\leq 0.37\%$) than in the groups receiving the corresponding dose of CEE alone. Indeed, the addition of MPA made hyperplasia almost nonexistent—implying that even at low doses there is an adequate amount and duration of exposure to progestogen to counter the estrogen effect on the endometrium.

Bleeding Profiles

Bleeding experience was assessed in terms of presence of bleeding and the need for sanitary protection. *Amenorrhea* was defined as no bleeding or spotting that required sanitary protection. *No bleeding* was defined as bleeding that did not require sanitary protection (spotting). The efficacy-evaluable population of women from the original HOPE study was 1,555.

The rates of cumulative amenorrhea and no bleeding were higher for women treated with lower-dose CEE/MPA than for those treated with the most commonly prescribed regimen of CEE 0.625/MPA 2.5 mg (Figures 1 and 2). As evidence of the improved bleeding profile of the lower-dose HRT regimen, more than 80% of the women taking lower HRT doses experienced no bleeding during the first 3 months of therapy. In contrast, during the initial months of therapy with the standard CEE 0.625/MPA 2.5 mg regimen, the incidence of no bleeding was 66 to 72%. By cycle 13, $\leq 10\%$ of women receiving the lower-dose CEE/MPA regi-

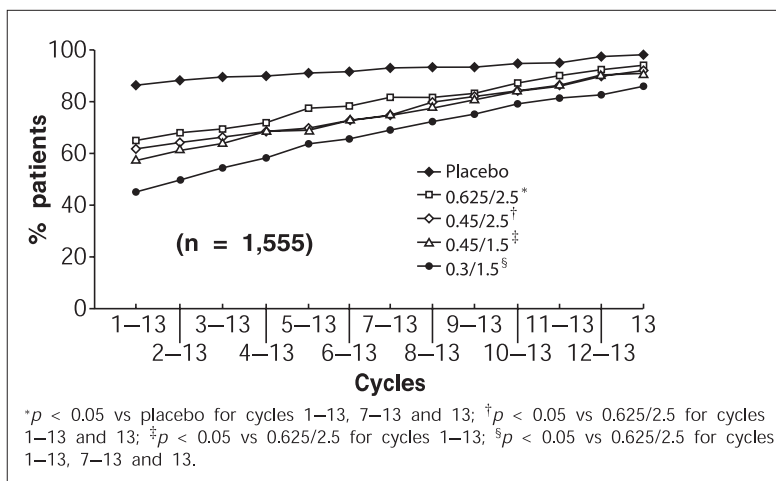


Figure 1. The rates of cumulative no bleeding (bleeding that did not require sanitary protection) were higher for women treated with lower-dose CEE/MPA than for those treated with CEE 0.625/MPA 2.5 mg.

men were experiencing bleeding that required sanitary protection. When the dose of estrogen was reduced while the MPA was maintained (to protect against hyperplasia), the bleeding profile was improved by approximately 10 to 20%. The lower dose eliminated the spotting.

Approximately 30% of the women taking placebo had bleeding or spotting in the first cycle. This implies that postmenopausal women who are not taking HRT might have a high incidence of bleeding and spotting that does not concern them enough to report it to their physicians.

Adverse Events

Some 521 patients (19%) withdrew from the HOPE study, most because of adverse events. The highest rate of discontinuation because of adverse events occurred in the CEE 0.625 mg group. The most common adverse events were breast pain (26% in the CEE 0.625/MPA 2.5 mg group), leg cramps, breast enlargement, dysmenorrhea, vaginal hemorrhage (e.g., vaginal bleeding), vaginal moniliasis and vaginitis.

Clinical Implications

The clinical implications from the Women's HOPE study are important for menopausal women. Because the risk of endometrial cancer increases with the use of unopposed estrogen, its use at any dose in women who have intact uteri should be discouraged.

Lower-dose continuous combined regimens, such as CEE 0.45/MPA 1.5 mg or CEE 0.3/MPA 1.5 mg, may produce more favorable bleeding profiles than standard higher-dose regimens. The combination of higher amenorrhea rates and fewer side effects with lower-dose HRT may aid in initiating and sustaining hormone therapy for women, which can in turn enhance long-term health benefits.

Conclusions

The Women's HOPE study offers substantial evidence that lower-dose HRT regimens can offer endometrial protection equal to that of standard higher-dose (CEE 0.625/MPA 2.5 mg) therapy.

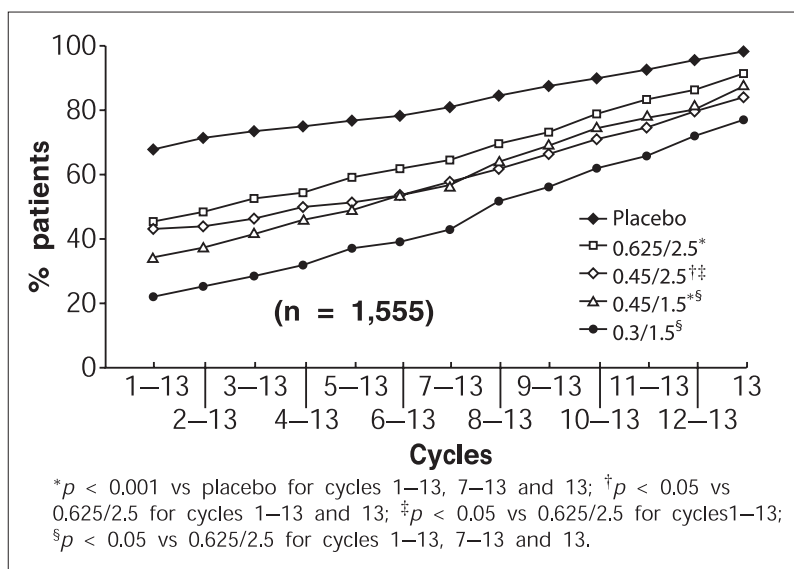


Figure 2. In the Women's HOPE study, the rates of cumulative amenorrhea were higher for women treated with lower-dose CEE/MPA than for those treated with the most commonly prescribed regimen of CEE 0.625/MPA 2.5 mg.

After 1 year of treatment with all CEE/MPA regimens, a relatively small percentage of women reported vaginal bleeding. Patients in the lower-dose CEE/MPA groups exhibited higher rates of amenorrhea and no bleeding compared with those in the CEE 0.625/MPA 2.5 mg group. In general, treatment-emergent adverse events, including breast discomfort, were reported less frequently in the lower-dose groups.

Dr. Archer receives research/grant support from Wyeth-Ayerst Pharmaceuticals.

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Metabolic Effects of Low-Dose ERT/HRT

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Cardiovascular disease (CVD) is the leading cause of death in women, responsible for more than half a million deaths each year. CVD deaths remain low until menopause and increase exponentially in the postmenopausal years.

Estrogen and CVD

The risk of CVD is exacerbated by several factors, including decreased estrogen levels during menopause. Estrogen replacement therapy (ERT) has been associated with potentially favorable biologic and physiologic changes that strongly support its role in lowering the risk of heart disease,¹ although its role in established heart disease remains unclear.²

Estrogen has been shown to have favorable effects on the vascular endothelium and lipid/lipoprotein profiles. It reduces levels of low-density lipoprotein (LDL) cholesterol, increases levels of high-density lipoprotein (HDL) cholesterol, decreases lipoprotein(a) (Lp[a]) levels, improves endothelial vascular function and reverses the increases in fibrinogen and plasminogen-activator inhibitor-1 (PAI-1) that occur in menopause—all factors that may reduce the risk of CVD. On the other hand, estrogen may increase activation of coagulation, and oral estrogen may increase triglyceride levels.³

The association between ERT and hormone replacement therapy (HRT) and hemostatic factors remains unclear. Estrogen increases fibrinolytic potential⁴ and decreases levels of fibrinogen and the anticoagulant proteins antithrombin III and protein S.

Another physiologic factor to consider is carbohydrate metabolism. Hyperglycemia and hyperinsulinemia are significant risk factors for CVD in women. Women who take HRT usually have lower fasting glucose and insulin levels compared with nonusers.⁵

Assessment of Metabolic Effects

Favorable effects on cardiovascular risk factors have been achieved with standard HRT therapy—i.e., conjugated equine estrogens (CEE) 0.625 mg and medroxyprogesterone acetate (MPA) 2.5 mg daily. Recent studies^{6–8} suggested that lower doses of estrogen and MPA can achieve comparable efficacy with reduced side effects. The metabolic effects of lower-dose ERT/HRT had not been investigated until a substudy of the Women's HOPE study was conducted in 749 women to assess the effects of lower-dose therapy on lipoproteins, carbohydrate metabolism and hemostatic factors.⁹ Patients were assessed prestudy, at cycle 6 and at cycle 13 for fasting

blood lipoproteins (HDL, LDL, triglycerides, Lp[a]) and coagulation and fibrinolytic measures (fibrinogen, PAI-1, antithrombin III, protein S). A 3-hour oral glucose tolerance test was also performed to evaluate carbohydrate metabolism.

Summary of Results

Total cholesterol. The changes in total cholesterol were modest. The biggest drop in total cholesterol was achieved by the women taking the standard CEE 0.625/MPA 2.5 mg regimen.

HDL. All of the estrogen and combination regimens produced significant increases in HDL from baseline to cycle 13.⁹ The largest increases were achieved with CEE 0.625 and 0.45 mg (Figure). In the combination groups, the HDL increases were comparable between the standard and lower regimens: 11% with the CEE 0.625/MPA 2.5 mg dose, and 10% with CEE 0.45/MPA 1.5 mg dose. The addition of MPA had a lessening effect on the increases of HDL compared with the comparable doses of CEE alone.

LDL. All of the hormone regimens brought decreases in LDL in similar fashion, from 7 to 9%. The addition of MPA did not have a deleterious effect.

Lp(a). Lp(a) was reduced by 8 to 12% from baseline in the groups receiving the standard and lower doses of combination therapy.

Triglycerides. Triglycerides were increased from baseline in all treatment groups, with the largest increases in the higher-dose CEE.

Coagulation and fibrinolytic measures. There were minimal changes in coagulation and fibrinolytic measures in all active treatment groups, including the lower-dose CEE 0.45/MPA 1.5 mg and the standard dose CEE 0.625/MPA 2.5 mg. Fibrinogen, PAI-1 activity, protein S activity and antithrombin III activity at cycle 13 were significantly decreased from baseline in all groups except for CEE 0.3/MPA 1.5 mg. These changes appeared to reflect a balance between increased and decreased coagulation factors.

Carbohydrate metabolism. Carbohydrate metabolism changes were minimal in all treatment groups. Approximately 6% of women who had a normal fasting glucose level at the beginning of the study developed diabetes or impaired glucose tolerance during the trial. These changes took place in all of the active treatment groups, suggesting that they were unrelated to the doses of the hormone treatments.

Clinical Implications

In the Women's HOPE study, 1 year of treatment with lower doses

of CEE alone and CEE/MPA produced acceptable lipid, fibrinolytic and metabolic profiles in healthy postmenopausal women. The success of the lower-dose regimens suggests a need for assessment of longer-term use of lower-dose therapy.

Conclusions

The results of the metabolic substudy demonstrate a beneficial cardiovascular effect from lowered doses of hormones in ERT and HRT. Lower-dose therapy produced favorable lipid and hemostatic profiles and did not adversely affect carbohydrate metabolism.

Lower doses of CEE alone or combined continuously with MPA provided improvements in LDL and HDL cholesterol. A dose of CEE 0.45/MPA 1.5 mg resulted in lipid profiles that were similar to those seen with the standard HRT dose of CEE 0.625/MPA 2.5 mg.

Lower doses of CEE alone and in combination with MPA brought beneficial changes in fibrinogen and PAI-1. After 1 year, changes in coagulation and fibrinolytic measures were similar in all active treatment groups, including the lower CEE 0.45/MPA 1.5 mg, as well as CEE 0.625/MPA 2.5 mg.

Dr. Carr receives research/grant support from Wyeth-Ayerst Pharmaceuticals.

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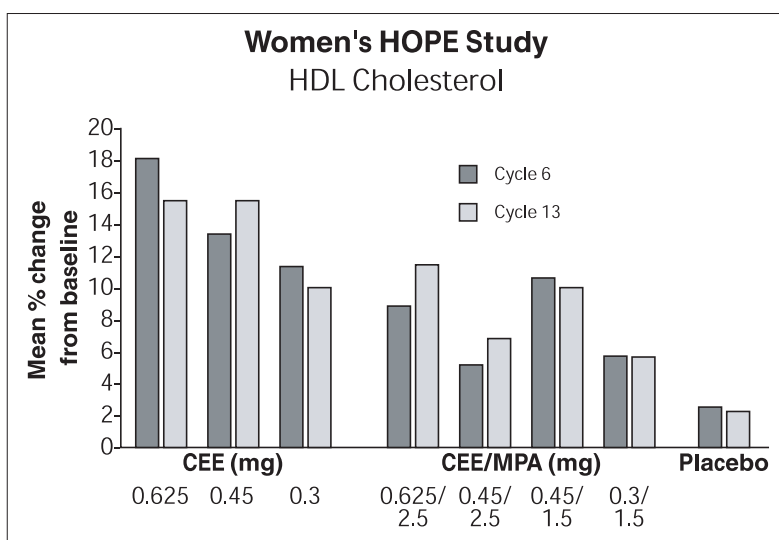


Figure. In the Women's HOPE study, all of the estrogen and combination regimens produced significant increases in HDL from baseline to cycle 13.⁹ The largest increases were achieved with CEE 0.625 and 0.45 mg. Reprinted by permission from the American Society of Reproductive Medicine.⁹

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HRT, Dose and BMI

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Women of menopausal age start and stop hormone replacement therapy (HRT) for several reasons. In one study,¹ the main reasons cited by women for taking HRT were: (1) treatment of menopause-related symptoms (47.3% of the respondents); (2) prevention of osteoporosis, bone loss, fracture; (3) prescribed by physician; (4) prevention of cardiovascular disease and (5) depression, anxiety, emotional distress. The most frequently cited reasons for quitting HRT were side effects, physician's advice and fear of cancer and bleeding. Since so many women cite relief of menopause-related symptoms as the main reason for taking HRT, it is incumbent upon clinicians to prescribe a regimen that relieves hot flashes, the most common menopause symptom.

The Women's HOPE study presented the opportunity to address some questions about the impact of body mass index (BMI) on some of the outcomes assessed in the trial, including the effect of HRT on vasomotor symptoms. For example, if a woman has a low BMI, would she have a greater or lesser response to a different dose? There are no studies in the literature to suggest an HRT dose based on body mass or weight.

Two subpopulations of the Women's HOPE study were used to examine the effects of BMI on treatment response (vasomotor symptoms, vaginal atrophy) and skeletal effects.² Two BMI categories were used for the analysis: BMI <25 kg/m² and BMI ≥25 kg/m².

Treatment Response

Vasomotor symptoms. The frequency and severity of vasomotor symptoms were analyzed in an efficacy-evaluable population (n = 241) of women who took study medication and had at least seven moderate to severe baseline hot flashes on each of the last 7 days of screening, or a total of at least 50 hot flashes during the last 7 days.³ The severity of each hot flash was defined as follows: mild = fleeting warm sensation without sweating that does not disrupt activity; moderate = warm sensation with sweating that does not disrupt activity; severe = hot sensation with sweating that disrupts activity.

Within the first 3 weeks, vasomotor symptom frequency and severity were significantly decreased in all active treatment groups

compared with baseline values and placebo groups. Notably, the mean daily number and severity of hot flashes in the lower-dose combination groups were not significantly different from the standard-dose group (CEE 0.625/MPA 2.5 mg) at any cycle (Figure).

Lower doses of the combination therapy appeared to be more effective for vasomotor symptom relief than comparable doses of CEE alone. This suggests that the benefits of MPA may extend beyond its well-established protection of the endometrium.

Vaginal atrophy. The effect of the lower-dose HRT on vaginal atrophy was assessed by the vaginal maturation index (VMI).³ The VMI measured the proportion of vaginal superficial cells relative to the number of parabasal and intermediate cells in a lateral vaginal wall smear. VMI was significantly increased from baseline and compared with placebo groups in all active treatment groups at cycles 6 and 13. The greatest improvement came with CEE 0.625 mg alone. Supporting a trend toward lower doses, the changes in VMI produced by the lower-dose CEE/MPA regimens were comparable to those seen with the standard CEE 0.625/MPA 2.5 mg dose.

BMI effect. Preliminary findings indicate that vasomotor changes and vaginal atrophy, as well as bleeding profile and hyperplasia, appear to reflect the effects of hormonal therapies and not BMI category. BMI did not influence the outcome of hot flash frequency and severity with either CEE or combination therapy. In addition, none of the hormone therapies had any significant effect on body weight at 1 and 3 years.

Skeletal Effects

A second-year substudy of 822 women assessed the effects of the various regimens on bone mineral density (BMD) and bone turnover. After 2 years of treatment, all hormone replacement doses were found to preserve BMD at all measured sites (spine, femoral neck, trochanter).

BMD increased significantly from baseline in all active treatment groups, except CEE 0.3 mg at the femoral neck. A dose-related response among treatment groups was observed for spine BMD, but not for the femoral neck or trochanter measurements. The beneficial effects of HRT on skeletal health appeared unrelated to BMI category.

Clinical Implications

The findings of the Women's HOPE study suggest the likelihood of significantly improved compliance with lower-dose HRT regimens compared with standard regimens. Lower doses of CEE alone and CEE/MPA decreased the number and severity of hot flushes and improved the VMI. Because these lower doses were as effective as the most commonly prescribed regimen, they should be considered an appropriate therapy for women seeking relief of vasomotor symptoms associated with menopause.

There might also be a therapeutic role for MPA beyond its known role in endometrial protection. Trends in statistically significant differences between active treatment groups suggest that CEE 0.45 mg and CEE 0.3 mg, combined with MPA, might provide better relief of vasomotor symptoms than the equivalent doses of unopposed CEE.

Initial HOPE substudy findings suggest that BMI should not be an issue in dosage selection.

Conclusions

The results of the Women's HOPE study indicate that lower doses of CEE combined with MPA are as effective as the standard dose of CEE 0.625/MPA 2.5 mg for relieving vasomotor symptoms and treating vaginal atrophy. Lower-dose HRT regimens were also found to be effective for the prevention of bone loss associated with menopause.

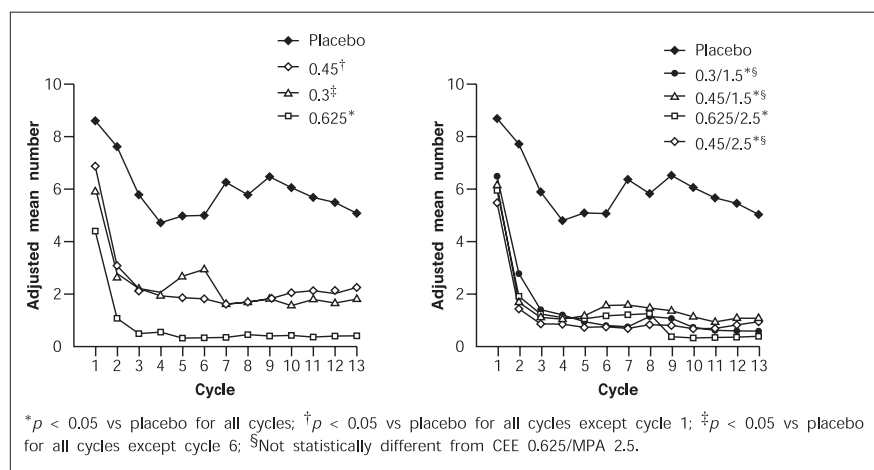


Figure. Vasomotor symptom frequency and severity were significantly decreased from baseline and compared with placebo groups within the first 3 weeks in all active treatment groups. The mean daily number and severity of hot flushes in the lower-dose combination groups were not significantly different from those in the standard-dose group at any cycle. Reprinted by permission from the American Society for Reproductive Medicine.³

BMI does not independently affect the treatment responses to vasomotor symptoms, vaginal atrophy, bleeding profiles or hyperplasia. Use of lower-dose HRT regimens appears to be effective across BMI categories.

Dr. Utian reports no significant financial relationships.

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