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Estrogen and Estrogen-Androgen Replacement in Postmenopausal Women Dissatisfied with Estrogen-Only Therapy

Sexual Behavior and Neuroendocrine Responses

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OBJECTIVE: To investigate the efficacy of esterified estrogens alone and combined with oral androgen on sexual function and menopausal symptoms in postmenopausal women.

STUDY DESIGN: Twenty postmenopausal women dissatisfied with their estrogen or estrogen-progestin therapy volunteered to enter a double-blind, randomized trial in which they received either oral esterified estrogens or esterified estrogens+androgen for eight weeks after a single-blind, placebo, lead-in period. Sexual function was assessed with a questionnaire used in the Yale midlife survey, and plasma levels of estradiol, estrone, sex hormone binding globulin (SHBG) and beta-endorphin were measured at two- to four-week intervals.

Estrogen-androgen therapy improved sexual sensation and desire in postmenopausal women who had previously taken estrogen therapy with inadequate symptom control....

RESULTS: Estrogen-androgen therapy significantly improved sexual sensation and desire after four and eight weeks of double-blind treatment in comparison to previous estrogen therapy

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and postplacebo baseline assessments. Plasma levels of estradiol and estrone increased significantly in all patients as compared to the postplacebo baseline and decreased in comparison to circulating estrogen concentrations on previous therapy. Relative proportions of free and bound steroid hormone exhibited contrasting shifts during estrogen and estrogen-androgen therapy. SHBG increased in the estrogen group and decreased in the estrogen-androgen group, leading to lower amounts of free androgens during estrogen therapy and increased free androgen levels during estrogen-androgen therapy. Since proportions of free (bioavailable) ovarian steroids would correlate inversely with plasma protein binding capacity, the beneficial effects of oral estrogen-androgen therapy on sexual sensation and desire may be due either to the administered androgen or to the increased availability of endogenous and exogenous androgens, particularly in the central nervous system.

CONCLUSION: Sexual desire, satisfaction and frequency in postmenopausal women taking hormonal therapy were improved significantly by combined estrogen-androgen therapy but not by estrogen or estrogen-progestin therapy. Sexual function improved with estrogen-androgen therapy even though circulating estrogen levels were lower than those measured during previous estrogen therapy. This leads to the conclusion that androgens play a pivotal role in sexual function but that estrogens are not a significant factor determining levels of sexual drive and enjoyment. (J Reprod Med 1998;43:847–856)

Oral estrogen-androgen therapy may exert a dual action by replacing lost androgens as well as increasing the tissue availability of endogenous androgens.

Keywords: menopause, hormone replacement therapy, estrogens, androgens, sex behavior, sex hormone-binding globulin.

Introduction

Circulating levels of estrogens and androgens decrease as women grow older. This change occurs gradually with declining ovarian function preceding natural menopause and abruptly during surgical menopause or oophorectomy, with consequent negative effects on vasomotor and climacteric symptoms and quality of life.[1,2] Similar problems are encountered after hysterectomy with ovarian conservation.[3]

Before menopause, the ovaries contribute 50% of total endogenous testosterone. Ovarian testosterone production decreases after natural menopause and is abruptly terminated by oophorectomy.[4,5] Withdrawal of ovarian estrogens leads to the immediate consequences of estrogen deficiency—i.e., vasomotor symptoms or hot flashes, insomnia, depressed mood, tension, etc.—as well as to the long-term outcomes of osteoporosis and cardiovascular disease. Circulating levels of free androgens have been linked to sexual behavior in women entering menopause who experience declining levels of ovarian estrogen and androgen secretion but have not begun to take replacement estrogens.[6,7] Although there is a clear relationship between levels of endogenous hormones and sexual function in untreated premenopausal, perimenopausal and postmenopausal women, this correlation disappears in postmenopausal women treated with hormone replacement therapy (HRT).[7] Decreased sexual response in 33–46% of women after oophorectomy-hysterectomy indicates that androgens play an important role in maintaining sex drive.[8,9] HRT is generally expected to improve sexual function besides alleviating the symptoms of menopause.

The enhanced effects of androgen replacement combined with estrogen therapy, as compared to estrogen-only or estrogen-progestin therapy, on sexual activity, drive and enjoyment in postmenopausal women have been observed in a number of clinical trials. Among the earliest studies were those done by Greenblatt et al in 1950[10] and Kupperman et al in 1959.[11] Later investigations were published by Sherwin and Gelfand[12,13] and Davis and collaborators.[14] Besides improving sexual enjoyment and libido, androgens act on menopausal symptoms to relieve hot flashes[15] and on the skeletal system to prevent bone loss and increase bone formation.[14,16,17] The protective effects of androgens on bone are evident in correlations of endogenous androgen levels with fracture incidence.[17,18]

In this double-blind trial, we investigated the effectiveness of combined estrogen-androgen therapy in alleviating symptoms and improving sexual function in postmenopausal women dissatisfied with their estrogen or estrogen-progestin therapy.

Estrogen-treated women with an inadequate symptomatic response to therapy were randomly assigned to treatment with estrogen-androgen or estrogen alone after a placebo washout period. Although these patients were being treated with conventional doses of estrogens with or without added progestins for an average of longer than 12 months, they still perceived room for improvement with their HRT and volunteered to enroll in a double-blind study, including a placebo period. All these women were experiencing deterioration in their sex lives. Because their current treatment could have an additive effect on response to study drugs, two-week placebo treatment preceded the start of double-blind treatment. Menopausal symptoms, sexual behavior and neuroendocrine parameters were evaluated at intervals in these women, and all of them chose to continue on estrogen-androgen therapy after completing this study.

Study Design

This was a double-blind, randomized, parallel-group, single-center trial in 20 healthy postmenopausal women treated with estrogen replacement therapy who volunteered to enter the double-blind investigation because they were dissatisfied with their current treatment. The total duration of the observation period was 12 weeks. Sequentially, study phases were: baseline on previous estrogen treatment for two weeks and single-blind, placebo for two weeks, followed by double-blind treatment with esterified estrogens (EE) + methyltestosterone or EE for eight weeks. Patients received either 1.25 mg EE alone or the same dose of estrogen combined with 2.5 mg methyltestosterone, once daily in the morning. The study protocol was approved by the Yale Human Subjects Investigation Committee, and all patients provided written, informed consent.

Following the two-week run-in period with previously prescribed estrogen therapy, patients received a two-week supply of placebo tablets. The contents were known to the investigator but were not known to the patient. The duration of the washout period was adequate for complete metabolic clearance of steroid hormones. After the two-week washout period, however, levels of gonadotropins did not return to hypoestrogenic levels.

After completing the single-blind, placebo phase, each patient was given a four-week supply of double-blind medication—i.e., estrogens (1.25 mg EE USP) or estrogen-androgen (1.25 mg esterified estrogens USP and 2.5 mg methyltestosterone), with double-dummy placebo tablets on each blister card. The contents were not known to either the investigators or the patients.

Postmenopausal women receiving estrogen therapy and enrolled in this study were generally healthy. During the screening evaluation, a physical examination, serum biochemistry and cervical cytology (CC) smear were done. All patients successfully completed eight weeks of treatment, 11 patients and 9 patients in the EE and estrogen-androgen groups, respectively. Thirteen patients continued therapy with 0.625 mg EE + 1.25 mg methyltestosterone after completing the double-blind study.

Combined estrogen-androgen therapy should be considered for postmenopausal women receiving HRT who continue to complain of sexual difficulties....

Patients were naturally or surgically menopausal and had an inadequate response to their current estrogen therapy (conjugated estrogens or estradiol-17β) for at least four months. Inadequate symptomatic relief included hot flashes, vaginal dryness, dyspareunia, decreased libido and decreased energy levels. Women eligible for the study were 25% above or below ideal body weight according to the 1983 Metropolitan Life Insurance Tables. Patients were excluded if they had clinically significant laboratory values outside the normal range, abnormal CC smears, clinically significant abnormal mammograms within the past 12 months or clinically significant abnormal findings during pelvic examination. History of thromboembolic disorder or active thromboembolic disease in the past 12 months or active or previous estrogen-dependent breast, uterine or ovarian cancer, as well as undiagnosed uterine or vaginal bleeding at examination or in the past year, were also reasons for not accepting patients into the study.

Menopausal symptoms and quality of life were assessed at intervals by the Menopausal Symptom Scale, which is modified from the original scale developed by Kupperman et al.[11] This scale evaluates

Table I *Sexual Activity and Libido Scale*

Unless otherwise stated, answer intensity (i) questions with: **0 = None; 1 = A little bit; 2 = Moderately; 3 = Quite a bit; 4 = Extremely**						
1. Do you produce vaginal moisture? (0 = No; 1 = Yes)		0	1			
2. Are you aware of times of vaginal dryness?	i	0	1	2	3	4
3. How would you rate your level of sexual desire this month?	i	0	1	2	3	4
4. How often have you had sexual intercourse in the past month? (0 = none; 1 = once; 2 = twice; 3 = 3 times/week; 4 = 4 or more times a week)	i	0	1	2	3	4
5. Has there been any pain associated with intercourse?	i	0	1	2	3	4
6. Are you aware of clitoral sensation?	i	0	1	2	3	4
7. Did the hormone you have been taking have an effect on clitoral sensitivity?	i	0	1	2	3	4
8. Have you experienced orgasm in the past month? (0 = No; 1 = Yes)		0	1			
9. Is there anything different about your orgasms? (0 = No; 1 = Yes)		0	1			
10. Have you experienced sexual fantasy in the past month? (0 = No; 1 = Yes)		0	1			
11. Sexual response in last 24 hours? (0 = No; 1 = Yes)		0	1			

hot flashes, sleep disturbances, memory changes, depression, anxiety and dyspareunia. Menopausal symptoms were characterized by three subscales (somatic, psychosomatic and psychological). Each subscale was the sum of intensity scores of the associated questions from the questionnaire. Menopausal symptom results were analyzed using the planned analysis for continuous variables.

Sexual behavior and enjoyment were evaluated by the 10-item Sexual Activity and Libido Scale (Table I), which was filled out weekly at home and on each postscreening visit in the presence of an observer. Answers were grouped to compile the following scores: sensation and desire—questions on level of sexual desire, clitoral sensation and clitoral sensitivity; sensation—questions on clitoral sensation and sensitivity; vaginal changes—questions on producing vaginal moisture and experiencing pain during sexual intercourse.

All other items were analyzed separately. The above-listed items and the question on frequency of sexual intercourse were analyzed using the planned analysis methods for continuous data. Questions on experiencing orgasm and sexual fantasies were analyzed using methods for categorical (ordinal) type data. Frequency and percentage of "yes" responses were tabulated for these two questions. Qualitative answers on awareness of vaginal dryness and different types of orgasms were excluded from the analysis. Scores for some items were adjusted to normalize directionality.

Vaginal smears were obtained after the placebo and after four and eight weeks of double-blind medication. The vaginal smear maturation index was classified as parabasal, intermediate or superficial, based on quantitative cytology. Each of these categories was analyzed separately using the planned analysis for continuous data.

On all study visit days, excluding the screening visit, patients were requested to fast overnight and take their medication in the morning. Four hours after taking their medication, the patients were allowed to eat a low-fat snack, and two hours following this meal, blood samples were collected for plasma/serum hormone determinations. Plasma samples were kept frozen until analysis. Estradiol and estrone levels were measured by radioimmunoassay after Celite chromatography by Nichols Research Institute, San Juan Capistrano, California. Endorphin and sex hormone-binding globulin (SHBG) assays and all clinical chemistry and cytology tests were also conducted by Nichols Research Institute.

Chronic concomitant medications were maintained at the same dose level for the duration of the study. Medications affecting hot flashes, such as clonidine, were not permitted during the study.

Patients were instructed to avoid sexual stimulation of any kind for 24 hours prior to their clinic visits. Diary cards were handed out to each patient at each visit, and detailed instructions were provided to each patient on the correct completion of the di-

Table II *Baseline and Posttreatment Plasma Levels of Estradiol, Estrone, SHBG and Beta-Endorphin*

	EE				EE + androgen (A)			
Level	Previous HRT	PostHRT washout (wk 0)	EE (wk 4)	EE (wk 8)	Previous HRT	PostHRT washout (wk 0)	E+A (wk 4)	E+A (wk 8)
Estradiol (pg/mL) Mean ± SD	106.6 ± 6.31	5.6 ± 2.7	66.5 ± 30.8	70.2 ± 31.2	63.7 ± 51.8	29.0 ± 71.6	40.8 ± 17.7	47.0 ± 23.3
Estrone (pg/mL) Mean ± SD	713.1 ± 489.1	28.8 ± 10.8	427.9 ± 256	439.8 ± 183.2	193.3 ± 150.6	34.1 ± 30.3	220.1 ± 91.3	166.0 ± 78.4
SHBG µgDHT/dl Mean ± SD	89.6 ± 40.2	58.5 ± 25.1	93.0 ± 29.9	94.1 ± 25.7	72.4 ± 38.8	48.7 ± 23.8	26.1 ± 16.9	22.6 ± 14.3
Beta-endorphin (pg/mL)	33.0 ± 13.2	32.9 ± 9.1	34.1 ± 7.6	28.6 ± 6.6	36.8 ± 11.1	38.8 ± 5.6	31.7 ± 6.3	28.9 ± 4.3

Values are given as mean ± SD.

aries at the screening visit. These forms were completed and returned at each subsequent visit, and the diary forms were reviewed by the study coordinator during each visit.

Results

Patients were predominantly Caucasian, aged 45–55 years (mean, 52). Their average height was 1.6, and their mean body mass index was within the range of 21–27.5 kg/m^2. Their duration of menopause ranged from 1 to 12 years, with 60% having experienced natural menopause. They had been on estrogen therapy for an average duration of >12 months and were dissatisfied with their therapy when they volunteered to enter the study.

Levels of estradiol, estrone and SHBG are presented in Table II. Plasma levels of estradiol for patients randomized to receive EE decreased from 106.6 ± 6.31 pg/mL on previous estrogen or estrogen-progestin therapy to 70 ± 31 pg/mL on EE after eight weeks of therapy. For the estrogen-androgen group, estradiol levels decreased from 63.7 ± 51.8 pg/mL on previous therapy to 47.0 ± 23.3 pg/mL on estrogen-androgen after eight weeks of therapy. SHBG levels declined in both groups during the placebo treatment period and subsequently increased markedly in the estrogen group and decreased markedly in the estrogen-androgen group. Plasma levels of beta-endorphin exhibited no significant changes during the study.

Marked improvements in sexual function related to androgen cotherapy were apparent in scores on several items of the Sexual Activity and Libido Scale. These increases in ratings of sexual function were observed both in comparison to previous estrogen or estrogen-progestin therapy and to postplacebo assessments. Statistically significant changes ($P < .01$–$.05$) were observed in the estrogen-androgen group for combined ratings of sexual sensation and desire at weeks 4 and 8 as compared to previous estrogen therapy or HRT. Sensation scores for patients treated with estrogen-androgen were significantly improved relative to both placebo and previous HRT at week 8. The desire score significantly improved relative to previous HRT ($P \leq .05$) in the estrogen-androgen group; changes from the postplacebo baseline were not statistically significant. Striking differences between the estrogen and estrogen-androgen groups were observed in magnitudes of improvements in combined sensation and desire scores on the sexual activity and libido scale. Since the combined score for sensation and desire includes three questions, the possible maximum score for this combined item is 12. All the estrogen-treated women except one completed the double-blind treatment period with sensation and desire scores of ≤4 indicating "a little" improvement for each parameter. In the estrogen-androgen group, six out of nine women reported sensation and desire scores >4 and 2/3 patients rated improvements in these measures as "quite a bit" or higher.

Significantly increased frequency of sexual intercourse versus placebo was observed at week 4 in the estrogen-androgen group, but changes at other assessments were not significant. Vaginal changes (moisture and pain during intercourse) did not change significantly with any treatment since these women had received estrogen therapy before entering the study. Sexual fantasies were reported by approximately half the patients in both groups, and the reported experience of fantasies did not change

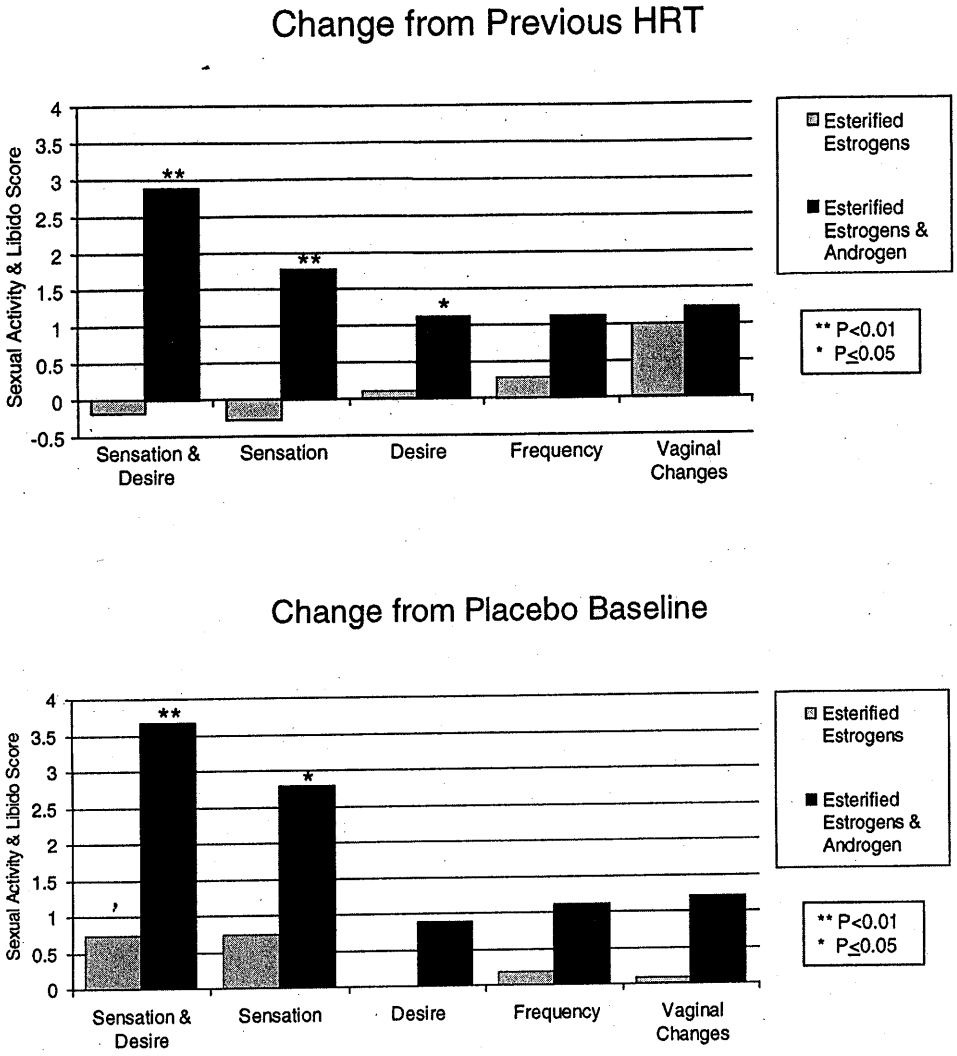

Figure 1 Mean Sexual Activity and Libido Scale scores after eight weeks of double-blind treatment.

during the study. Orgasms were initially reported by approximately half the patients in the study. This proportion increased in all patients participating in the study, perhaps in response to counseling and greater awareness. Sexual function assessment data for groups and individuals are presented in Figures 1 and 2 and Table III.

Menopausal symptoms were evaluated using a scale based on the symptom assessments first used by Kupperman et al.[11] These estrogen-dependent symptoms were generally well controlled with previous therapy and exhibited minor improvements during treatment with esterified estrogens or estrogen-androgen. Patient self-evaluations recorded in daily diaries detected no meaningful differences in the incidence of vaginal bleeding, relief from hot flashes and disturbed sleep, or consumption of alcoholic or caffeinated beverages.

Blood pressure, both systolic and diastolic, decreased in the estrogen-androgen group. Similar decreases in blood pressure were not consistently evident in the EE group. Although changes in vaginal cytology were similar in both groups, a trend toward a greater proportion of superficial cells was seen in the estrogen-androgen group (Table IV). No clinically significant changes in serum biochemistry or hematology values were observed.

Discussion

Most women decide to take HRT primarily to relieve their menopause-related somatic and psychological symptoms. In a recent survey, Sarrel and col-

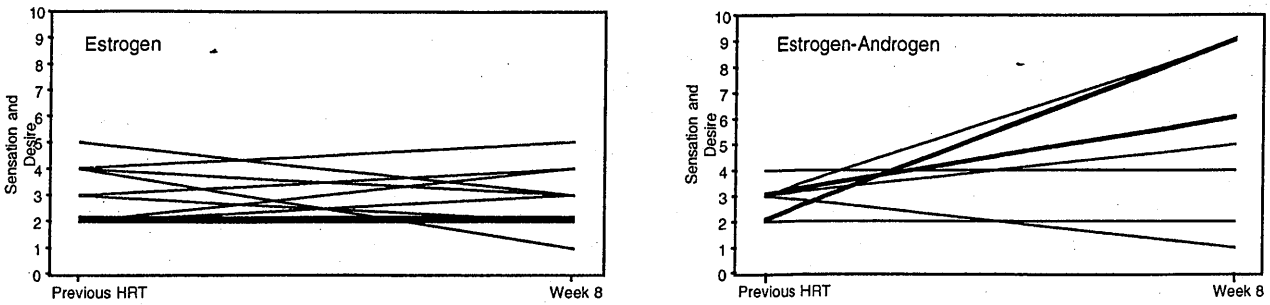

Figure 2 Individual changes in combined sensation and desire scores after eight weeks of double-blind treatment.

laborators[19] found that the most common reasons for women to discontinue HRT were the failure of treatment to meet the women's needs and the side effects of HRT. None of the women surveyed were using androgens. When women using HRT were compared to age-matched postmenopausal women not using HRT, 54% complained of loss of sexual desire vs. 55% of the untreated women, indicating that this complaint is not relieved by conventional HRT.

Postmenopausal changes in sexual function may be related to decreasing production of ovarian and adrenal androgens.[4,20,21] Androgens are generally recognized to enhance sexual drive in women and men, in both physiologic and pharmacologic settings. Endogenous androgens have been observed to play an important role in psychosexual functioning in women during the menstrual cycle[22,23] and in the perimenopausal transition, during which testosterone levels decline.[24] Correlations between endogenous androgen levels and optimal sexual functioning have been reported in two studies of perimenopausal women.[6,7] The total score on the McCoy sexual questionnaire, which evaluates sexual enjoyment, orgasm, frequency and vaginal state, significantly correlated with testosterone, dehydroepiandrosterone sulfate, androstenedione and the ratio of testosterone to SHBG, which is an indicator of free testosterone.[7] Additionally, women of reproductive age experienced increased sexual interest during midcycle, when the luteinizing hormone surge stimulates androgen synthesis by the ovaries.[25]

Davis et al[14] observed in a recent study comparing the effects of estradiol and estradiol + testosterone implants that all measures of sexuality improved to a greater extent in the estrogen-androgen group. Statistically significant treatment effects were observed for sexual activity, satisfaction, pleasure, orgasm and relevancy using the Sabbatsberg self-rating scale. Treatment effects approached significance for libido, but effects on sexual fan-

Table III *Sexual Activity and Libido Scale Scores: Changes from Previous Estrogen or Estrogen-Progestin (HRT) Therapy and from Postplacebo Baseline*

		EE		EE + androgen	
Scale item	**Wk**	**Vs. placebo**	**Vs. previous HRT**	**Vs. placebo**	**Vs. previous HRT**
Sensation and desire (combined score)	4	0.55	−0.36	2.33	1.56*
	8	0.73	−0.18	3.67**	2.89**
Sensation	4	0.55	−0.45	1.67	0.67
	8	0.73	−0.27	2.78*	1.78**
Desire	4	0	0.09	0.67	0.89*
	8	0	0.09	0.89	1.11*
Frequency of sexual intercourse	4	0.09	0.18	1.22*	1.22
	8	0.18	0.27	1.11	1.11
Vaginal changes	4	−0.18	0.73	0.22	0.67
	8	0.09	1.00	0.78	1.22

Significant changes are indicated (**$P < .01$, *$P < .05$).

Table IV *Effects of EE and Estrogen-Androgen Therapy on Vaginal Cytology*

Cells	Wk	EE		Estrogen-androgen	
		Mean	SD	Mean	SD
Parabasal (%)					
Baseline	0	8.64	27.03	21.11	41.97
Change from baseline	4	−8.64	27.03	−21.11	41.97
	8	−6.82	24.52	−21.11	41.97
Intermediate (%)					
Baseline	0	71.36	40.93	58.89	40.06
Change from baseline	4	−4.27	39.20	13.56	59.02
	8	−1.00	37.80	5.56	57.09
Superficial (%)					
Baseline	0	20.00	36.33	20.00	28.17
	4	12.91	30.26	7.56	44.45
Change from baseline	8	7.82	31.55	15.56	38.20

tasies were nonsignificant. In the present study, similar enhancement of sexual function was detected in an interview situation. Sherwin et al[13] reported significant increases in sexual fantasies in surgically menopausal women treated with relatively high doses of androgens and estrogens in long-acting injectable preparations.

Except for local vaginal changes, which relieve pain and increase vaginal lubrication during sexual intercourse, previous studies have failed to detect a significant improvement in sexual function by estrogen therapy. In this investigation, sexual behavior enhancement in the estrogen-androgen treatment as compared to previous HRT occurred even though average estradiol levels were lower during the double-blind treatment phase than on previous estrogen therapy, and vaginal effects were not significantly different between treatments. This finding further demonstrates that estrogens do not play a significant role in determining sexual drive and enjoyment in women.

While the majority of clinical investigations of postmenopausal estrogen-androgen therapy have been done with injectable or implanted androgens,[12-14] methyltestosterone has been used in the treatment of postmenopausal women since the 1930s.[26-29] Reduction of the methyltestosterone dose in the oral estrogen-androgen preparation investigated in this study is drastically decreased to 1–20% of the oral doses used in the 1940s and 1950s. This hormonal combination has improved the safety profile of estrogen-androgen therapy and retained beneficial effects on sexual function. In a recent review of the safety literature on estrogen-androgen, Gelfand and Wiita[29] found that there are no published reports of serious hepatic or cardiovascular events with postmenopausal estrogen-androgen therapy, probably because the doses of androgens are 1/25–100 of the male doses that have been associated with adverse hepatic events. Additionally, it is possible that coadministered estrogens may reduce the side effects of androgens on the liver and cardiovascular system in women.

Both contraceptive and noncontraceptive estrogen therapy significantly stimulate synthesis of SHBG, with consequent reductions in the freely diffusible and biologically active circulating fractions of androgens and estrogens. The endogenous androgens testosterone and dihydrotestosterone (DHT) are preferentially bound by SHBG. Oral estrogen-androgen therapy reduces circulating levels of SHBG, potentially increasing the amounts of testosterone and estradiol that can cross the blood-brain barrier and improve mood and sexual function.[16,30] Additionally, methyltestosterone reduces the androgen-binding capacity of SHBG by binding to this plasma protein with an affinity similar to that of testosterone and DHT.[30] Both these peripheral actions of methyltestosterone reduce SHBG binding capacity, thereby facilitating the entry of both endogenous and exogenous androgens and estrogens into the central nervous system and inducing changes in sexual behavior and mood. Significantly decreased SHBG in patients treated with estrogen-androgen therapy in this study was accompanied by significant improvements in sexual drive and satisfaction, which were maintained for eight weeks. Oral estrogen therapy significantly increases SHBG levels, and this leads to significant reductions in circulating bioavailable androgens by

reducing the plasma reservoir capacity for testosterone and DHT.[31] The consequent relative androgen deficiency may be linked to complaints of reduced sexual drive and satisfaction in postmenopausal women, both untreated and treated with HRT.[19] The marked improvements in sexual drive and satisfaction in women who discontinued estrogen or estrogen-progestin therapy and initiated therapy with EE combined with androgen in this trial may be a consequence of both increased availability of endogenous ovarian and adrenal androgens as well as administered androgen.

The physiology of androgen-dependent sexual enhancement and experimental investigations in animals as well as earlier clinical findings clearly support the current observations of androgen-mediated stimulation of sexual desire and satisfaction and related components of sexual activity. Patient satisfaction with improved sexual enjoyment and emotional well-being was evident in those women who switched from estrogens alone to blind estrogen-androgen treatment as well as after the study, when most women chose to continue treatment with estrogen-androgen. Improvements were particularly striking in comparison to previous HRT values, suggesting that estrogen therapy had dampened sexual drive and enjoyment in these patients, who were dissatisfied with their HRT. Estrogen therapy produced slight improvements in perception of sexual sensation and desire, but estrogen-androgen therapy produced much larger improvements in these measures. This observation reflects the contrast between localized vaginal actions of estrogen therapy and the broader actions of estrogen-androgen therapy, which encompass significant desirable changes in sexual drive and enjoyment.

Conclusion

Estrogen-androgen therapy improved sexual sensation and desire in postmenopausal women who had previously taken estrogen therapy with inadequate symptom control, primarily complaints of lowered sexual drive and satisfaction. Endogenous and exogenous androgens have been proven to stimulate sexual drive and enjoyment in women, and oral estrogen-androgen therapy may exert a dual action by replacing lost androgens as well as increasing the tissue availability of endogenous androgens. Reduction of circulating SHBG levels by methyltestosterone treatment tends to elevate free or non–protein-bound testosterone, which can freely diffuse across the blood-brain barrier and may increase androgen levels in the central nervous system. Combined estrogen-androgen therapy should be considered for postmenopausal women receiving HRT who continue to complain of sexual difficulties or for postmenopausal women with sexual complaints who are not undergoing estrogen therapy.

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