

# Randomized clinical trials of combined estrogen-androgen preparations: effects on sexual functioning

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**Objective:** To review the randomized controlled trials of the efficacy of combined estrogen-androgen (E-A) preparations on sexual functioning in postmenopausal women.

**Patient(s):** Naturally and surgically menopausal women.

**Main Outcome Measure(s):** Changes in aspects of sexual functioning.

**Result(s):** In general, a high degree of agreement exists among the findings of these well-controlled trials that combined E-A preparations enhance psychological well-being as well as sexual desire and interest and, sometimes, increases the frequency of sexual intercourse and orgasm compared with estrogen-alone treatment in both naturally and surgically postmenopausal women

**Conclusion(s):** In selected cases, combined E-A therapy can enhance the quality of life for both naturally and surgically postmenopausal women. (*Fertil Steril*® 2002;77(Suppl 4):S49–54. ©2002 by American Society for Reproductive Medicine.)

**Key Words:** Estrogen, androgen, replacement therapy, menopause, sexuality, psychological well-being

A considerable amount of evidence is now available about the effects of estrogen on various organ systems in postmenopausal women, which provide protection against diseases such as osteoporosis and improvement in symptoms such as hot flashes and atrophic vaginitis. Although androgen production decreases in women during their 40s, before spontaneous menopause has usually occurred (1), far less is known of the biological effects of this sex steroid and of its potential to enhance the quality of life in aging women. This article reviews the evidence from randomized clinical trials of the efficacy of combined E-A preparations on sexual functioning in postmenopausal women.

## TESTOSTERONE AND THE CENTRAL NERVOUS SYSTEM

Autoradiographic studies have demonstrated that neurons containing specific receptors for testosterone are predominantly found in the preoptic area of the hypothalamus, with smaller concentrations in the limbic system (amygdala and hippocampus) and the cerebral cortex (2). Of course, testosterone can exert effects on

behavior by binding to the androgen receptors in these brain areas. Importantly, some proportion of testosterone is converted to estradiol in the brain (3) so that it is sometimes difficult to distinguish, especially in studies that do not have an estrogen-alone group as a comparison, whether the observed behavioral change is due to the testosterone in combined E-A preparations or to its conversion to estradiol. Added to the complexity is the fact that estrogen increases the sex hormone-binding globulin (SHBG) while androgen reduces it (4), so that an equal dose of estrogen-alone to that in a combined E-A drug will result in different concentrations of bioavailable serum estradiol.

## Animal Studies

Effects of testosterone on various components of mating behavior have been studied intensively in female, nonhuman primates. On the whole, these studies show that the administration of testosterone to ovariectomized rhesus monkeys increased proceptive behavior (i.e., increased attempts to solicit mounts from the male). Implantation of minute amounts of testosterone into the anterior hypothalamus of estrogen-treated ovariectomized and adrenalect-

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TABLE 1

Randomized controlled trials of estrogen-androgen drugs and sexual functioning.

Study	No. of subjects	Naturally or surgically menopausal	Drug	Changes in sexual functioning in the E-A groups
Burger et al. (13)	17	5 NM 12 SM	estradiol 40 mg + testosterone 100 mg pellet	↑ libido ↑ enjoyment of sex ↑ orgasms ↑ initiation of sex
Burger et al. (14)	20	14 NM 6 SM	estradiol 40 mg or orstradiol 40 mg + testosterone 50 mg pellets	↑ libido ↑ enjoyment of sex
Davis et al. (15)	32	30 NM	estradiol 50 mg or estradiol 50 mg + testosterone 50 mg pellets	↑ sexual activity ↑ satisfaction ↑ pleasure ↑ orgasms
Sherwin et al. (19)	53	10 premenopausal 43 SM	estradiol 8.5 mg + testosterone 150 mg or estradiol 8.5 mg or testosterone 150 mg or placebo 1M	↑ sexual desire ↑ sexual arousal ↑ sexual fantasies
Sherwin et al. (20)	44	44 SM	estrogen 10 mg or estrogen 8.5 mg + testosterone 150 mg 1M	↑ sexual desire ↑ sexual arousal ↑ sexual fantasies
Sarrel et al. (22)	20	12 NM 8 SM	1.25 EE or 1.25 EE + 2.5 mg MT	↑ sexual sensation ↑ sexual desire
Shifren et al. (23)	75	75 SM	CEE + 150 µg testosterone or + 300 µg testosterone or + placebo patch in random order transdermal	↑ BISF with 300 µg T patch

Note: NM = naturally menopausal; SM = surgically menopausal; EE = esterified estrogens; MT = methyltestosterone; E-A = estrogen-androgen; ↑ = increased; BISF = Brief Index of Sexual Functioning for Women.

Sherwin. Randomized trials of estrogen-androgen drugs. *Fertil Steril* 2002.

tomized unreceptive female rhesus monkeys also resulted in restoration of their proceptivity without affecting other aspects of sexual behavior such as attractivity (5).

These studies on testosterone and sexual behavior in female, nonhuman primates serve to underscore two points. One is that there is a specificity of action of testosterone on components of sexual behavior such that it enhances proceptivity (the animal's motivation to engage in sexual behavior) but has no effect on the female's attractivity or its receptivity to males. Second, the fact that a very small dose of testosterone implanted in the hypothalamus was effective in restoring sexual desire in rhesus monkeys (5) suggests that testosterone exerts its affect on sexual desire, in the female rhesus, directly on the brain instead of influencing peripheral tissues.

### TESTOSTERONE AND SEXUALITY IN THE POSTMENOPAUSE CROSS-SECTIONAL STUDIES

Several cross-sectional studies have investigated whether associations occur between circulating levels of the sex steroids and aspects of sexual behavior in postmenopausal women. Leiblum et al. (6) reported that neither estradiol nor testosterone discriminated between sexually active and inactive, untreated postmenopausal women, but sexually active

women had less vaginal atrophy than the inactive women. In a longitudinal study of perimenopausal women, plasma testosterone levels were positively associated with coital frequency (7). Moreover, a positive correlation occurred between testosterone levels and sexual desire, as well as sexual arousal, in premenopausal women over the age of 40 (8). Other epidemiological studies that have investigated changes in sexual functioning in peri- and postmenopausal women failed to measure circulating levels of hormones (9, 10). One recent population-based study in middle-aged women failed to find an association between testosterone levels and any aspect of sexual functioning (11). These findings were subsequently confirmed in another report of 40–60-year-old untreated women in which endogenous androgen levels failed to predict scores on any of the measures of sexuality (12).

### Randomized Controlled Trials

The randomized, controlled treatment trials of the efficacy of combined E-A preparations compared with estrogen-alone treatment on sexual functioning in postmenopausal women provide more definitive information (Table 1). In Britain and Australia, subcutaneous implantation of pellets containing estradiol and testosterone has been used as a treatment for menopausal symptoms for several decades. This route of sex-steroid administration results in a slow,

constant release of the sex hormones over a period of at least 6 months. In a single-blind study, a mixed group of 17 surgically and naturally menopausal women, who complained of loss of libido despite treatment with estrogen received subcutaneous implants of 40 mg estradiol and 100 mg testosterone (13). By the third month following implantation, patients reported a significant increase in libido, in enjoyment of sex, and in the frequency of orgasm and initiation of sexual activities. Whereas the normal range of total testosterone levels for cycling women was 1–3 nmol/L in the assay used, the mean baseline level of these women was  $2.3 \pm 1.2$  nmol/L and rose to  $4.2 \pm 1.8$  nmol/L, 3 months postimplantation. Therefore, the improvements in sexual functioning experienced by these postmenopausal women occurred coincident with an increase in their serum total testosterone to supraphysiological levels. One woman developed very mild hirsutism, and another had a change in her voice range.

These findings gained support from a double-blind study of women complaining of loss of libido despite treatment with oral estrogens and progestins that adequately relieved other symptoms such as hot flashes and vaginal dryness (14). They randomly received a subcutaneous implant containing either estrogen (40 mg) or estrogen (40 mg) plus testosterone (50 mg). After 6 weeks, the loss of libido in the estrogen-alone implant group remained, whereas the combined estrogen-testosterone group showed significant symptomatic relief. The mean peak testosterone concentrations after implantation of the combined pellet slightly exceeded the upper limit of the normal female range (3 nmol/L), reaching 3.5 nmol/L in the combined pellet group.

In a prospective, 2-year, single-blind randomized trial, 34 postmenopausal women received subcutaneous implantation of pellets containing either estradiol (50 mg) or estradiol (50 mg) plus testosterone (50 mg) administered every 3 months (15). Although all sexual behaviors (measured by the Sabbatsberg Sexual Self-Rating Scale) improved in both treatment groups, women in the combined E-A group reported a significantly greater improvement in sexual activity, satisfaction, pleasure, and orgasm compared with the estrogen-alone group. Women who complained of low libido at the time of recruitment had been excluded from the study. Mean serum testosterone levels rose from  $1.2 \pm 0.55$  nmol/L at baseline to  $2.7 \pm 1.39$  nmols at 6 months postimplantation in women treated with the combined pellets, so that they remained within the normal female physiological range of testosterone values (1.0–2.8 nmol/L) throughout the treatment.

Although these implant studies were single-blind, in two of them, (12, 13) patients were preselected on the basis of loss of libido that had been unresponsive to treatment with estrogen alone. Two studies (14, 15) contained an estrogen-alone group as a basis for comparison. Even bearing in mind their methodological flaws, the findings of these studies

serve to point out that the addition of testosterone to an estrogen replacement regimen reversed the loss of libido in postmenopausal women that had not been alleviated with an equivalent dose of estrogen alone.

Perhaps the most powerful research paradigm for investigating the role of testosterone in women involves administering hormone replacement therapy to women who have just undergone total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). When both ovaries are removed from premenopausal women, circulating testosterone levels decrease significantly within the first 24–48 hours postoperatively (16). The fact that these women are deprived of ovarian androgen production following this surgical procedure has provided a rationale for administering both estrogen and androgen as a replacement therapy.

During the past two decades, several prospective, controlled studies of general and sexual effects of combined estrogen-androgen parenteral preparations in surgically menopausal women were carried out in our laboratory. One mL of the combined preparation we used contains testosterone enanthate (150 mg), estradiol dienanthate (7.5 mg), and estradiol benzoate (1.0 mg). The recommendation for the treatment of postmenopausal women, at the time, was for the injection of 1 mL of this preparation intramuscularly (i.m.) every 28 days. Because the marketing of this drug predated the development of radioimmunoassays, it was not known at the time these studies were undertaken what serum levels of testosterone this dose would induce.

The women who participated in these controlled studies all had surgery for benign conditions (uterine myomas or endometriosis) were in good health, not taking any medications, and were in stable, long-term marital relationships. They were tested before surgery and again at 3 months following random assignment to either a combined E-A group, to an estrogen-alone group (E), to an androgen-alone group (A), or to a placebo group (PL) (17). Women in the E-alone and A-alone groups received amounts of estradiol valerate or testosterone enanthate equivalent to those found in 1 mL of the combined drug administered i.m. every 28 days. During the fourth postoperative month, all women received placebo. Following placebo, they were crossed-over to a treatment they had not received during Treatment Phase 1 for an additional 3 months. A fifth group of premenopausal women who underwent TAH, but whose ovaries were retained, served as a control group for the surgical procedure.

Women who received either the E-A or A drugs following surgery had higher scores on energy level and sense of well-being than those who received E or PL. Administration of the androgen-containing preparations (A or E-A) were also associated with lower somatic and psychosomatic symptom scores than E or PL. Moreover, all women treated with hormones following surgery had more positive moods than those who had randomly received placebo (18).

Whereas total testosterone levels were a mean of  $81.1 \pm 5.3$  ng/dL at preoperative baseline when these women were cycling normally, testosterone levels rose to  $133.1 \pm 12.4$  ng/dL by the third to fifth postinjection day of the combined E-A drug.

Androgenic effects on sexual behaviors were also investigated in these women who monitored several aspects of their sexual behavior daily for the 8-month duration of that study. Women who received either of the androgen-containing preparations postoperatively reported an enhancement of sexual desire and arousal, and an increase in the number of sexual fantasies compared with those who received treatment with E or PL during both treatment phases (19). Interestingly, ratings of sexual behavior of these surgically menopausal women treated with androgen did not differ from those of the TAH control group whose ovaries were retained and who were an average of 10 years younger than the women who had undergone BSO.

Sherwin and colleagues (20) subsequently confirmed these findings on the enhancement of aspects of sexual behavior by androgen, when the E-A combined drug was administered long-term and sexual functioning was compared with a group of postmenopausal women treated with E-alone long-term, and to a third group that had remained untreated following TAH and BSO at least 2 years earlier. In these women treated chronically for 2 years with a combined i.m. drug, serum total testosterone reached peak, supraphysiological levels at day 8 postinjection ( $2.85 \pm 0.04$  ng/mL) and declined slowly across the next 3 weeks as the drug was being metabolized (21).

Recently, information became available on the effects of an oral E-A combined drug on aspects of psychological and sexual functioning in postmenopausal women. Twenty postmenopausal women, who were dissatisfied with their estrogen therapy (40% of whom were surgically menopausal), were monitored for 2 weeks while still on estrogen-alone (baseline) (22). Then, all the women received a placebo in single-blind fashion for 2 weeks, following which they were randomly assigned to treatment with either 1.25 mg esterified estrogen or 1.25 mg esterified estrogen plus 2.5 mg methyltestosterone daily for 8 weeks. Sexual functioning was measured by means of a 10-item Sexual Activity and Libido Scale.

Combined ratings of sexual sensation and desire increased significantly in the group treated with the combined E-A drug after 4 and 8 weeks of treatment in comparison with previous estrogen therapy and with postplacebo baseline assessments. In addition, an increase in the frequency of sexual intercourse occurred by week 4 of treatment in the combined group but was no longer significant by week 8. No changes in any aspect of sexual behavior occurred in the group treated with estrogen alone, despite the fact that effects of both drugs on vaginal cytology did not differ.

More recently, findings were reported on the efficacy of a

transdermal testosterone patch for the treatment of postmenopausal women. Seventy-five healthy women who had undergone TAH and BSO approximately 5 years earlier were selected because they reported impaired sexual functioning despite being on estrogen replacement therapy (ERT) (23). All the women had been receiving at least 0.625 mg CEE daily for at least 2 months before entry into the study. Sexual behavior was quantified by means of the 22-item Brief Index for Sexual Functioning for Women (BISFW) at screening and again, after 12 weeks of treatment with their usual doses of CEE as well as, in random order, placebo, 150  $\mu$ g of testosterone, and 300  $\mu$ g testosterone per day transdermally for 12 weeks each.

Despite a considerable placebo response, the 300  $\mu$ g but not the 150  $\mu$ g dose of testosterone resulted in further increases in scores for frequency of sexual activity and pleasure-orgasm as measured by the BISFW. Again, at the higher but not at the lower dose of transdermal testosterone, the percentages of women who had sexual fantasies, masturbated, or engaged in sexual intercourse at least once a week increased 2 to 3 times from baseline. Positive well-being, depressed mood, and composite scores of the Psychological General Well-Being Index also improved significantly in women when they were receiving the 300  $\mu$ g testosterone patch compared with the placebo patch.

It is noteworthy that mean bioavailable testosterone levels were  $2.0 + 1.4$  ng/dL at pretreatment (normal female range: 1.6–12.7 ng/dL), rose to  $7.1 \pm 4.1$  ng/dL with the 150  $\mu$ g patch, and rose to  $11.4 \pm 9.5$  ng/dL with the 300  $\mu$ g testosterone patch. Therefore, the enhancement of sexual behavior, reported by women who received treatment with the 300  $\mu$ g testosterone patch, was achieved when the serum levels of bioavailable testosterone it induced were at the upper limit of the normal female range.

### **Possible Side Effects of E-A Replacement Therapy**

The possibility that exogenous testosterone could induce symptoms of virilization in women has long been a concern. Although an objective measure of hirsutism was not used in our studies of the injectible E-A preparation (19–21), our clinical experience with this drug suggests that approximately 20% of women who receive 150 mg testosterone enanthate plus estradiol every 28 days i.m. will develop mild hirsutism manifested by an increased growth of hair on the chin and/or upper lip. When the dose is reduced to 75 mg testosterone/28 days (the dose currently used), less than 5% of women develop hirsutism. When they do develop hirsutism, the symptom is reversible when they are taken off the combined drug and given estrogen alone. This suggests that variability in response to the potential virilizing effects of testosterone exists among women, and that the occurrence of these symptoms is likely also dose-dependent. From 5–20% of women treated with subcutaneous pellet implants of E+T

developed hirsutism although, once again, this was not evaluated systematically (13–15).

In a safety surveillance of oral esterified estrogen and methyltestosterone (24), the risk of hirsutism was less than 5%. In another safety study of the same oral preparation, the incidence of hirsutism with the addition of methyltestosterone was not different from that of women who received estrogen alone (25). Neither did the hirsutism scores change significantly in women treated with transdermal testosterone plus estrogen (23), although the mean facial-depilation rate increased slightly but not significantly during treatment with 300  $\mu\text{g}$  of testosterone/day. Acne and deepening of the voice were reported rarely or not at all in these studies.

Some evidence exists that oral E-A preparations modify the lipoprotein lipid profile. Oral methyltestosterone plus estrogen resulted in a decrease in high-density lipoprotein (HDL) cholesterol by up to 20% compared with baseline (26). However, low-density lipoprotein (LDL) cholesterol is reduced to a similar extent as with estrogen-alone treatment, and triglycerides, which tend to increase with oral estrogen-alone treatment, decrease by approximately 15% when methyltestosterone is added (27). Moreover, testosterone may be beneficial for dilating coronary arteries (28) and does not negatively influence coronary vasodilation in cynomolgus monkeys (29). Neither did the combined i.m. preparation (30), the E-A pellet implants (31), or the transdermal testosterone patch (23) cause changes in the lipoprotein lipid profile compared with estrogen-alone treatment.

Clearly, route of administration of sex hormones modulates metabolic responses to hormone therapy, and the available data suggest that nonoral routes of administration of testosterone do not have significant negative side effects, at least in the doses and regimens tested. The addition of testosterone to an estrogen replacement regimen does not mitigate against endometrial hyperplasia (32), therefore, a progestational agent needs to be added to the hormone regimen when treatment with a combined drug is administered.

Finally, it is clear that when testosterone is administered via the subcutaneous implantation of pellets, it metabolizes very slowly and, often, levels are still supraphysiological 4 months postimplantation (13–15). Therefore, it is mandatory to assess serum levels of testosterone prior to reimplantation.

## SUMMARY

Taken together, the randomized, controlled studies on both naturally and surgically postmenopausal women that administered either subcutaneous implants of estrogen and testosterone, an i.m. E-A preparation or, more recently, an oral estrogen (CEE) combined with transdermal testosterone have consistently shown that combined treatment with estrogen and testosterone induces a greater sense of energy level and well-being, and is associated with fewer somatic and psychological symptoms compared with the administra-

tion of estrogen alone. Furthermore, E-A preparations increased motivational aspects of sexual behavior (such as desire and fantasies) (13–15, 19–22) as well as the frequency of orgasm and of sexual intercourse (21, 22).

In another study, we demonstrated that levels of sexual desire and interest covaried with plasma testosterone levels throughout a treatment month as the i.m. administered drug was being metabolized (21). The fact that, in several studies, this enhancement of sexual functioning occurred in women who complained of deficits in their sexual functions while being treated with ERT (13, 14, 22, 23) underscores the fact that, while estrogen is necessary for the integrity of reproductive tissues, it does not otherwise contribute toward the maintenance of a variety of sexual behaviors in postmenopausal women. Instead, the demonstration in these randomized, controlled trials that sexual complaints in estrogen-treated postmenopausal women responded to the addition of testosterone to their estrogen replacement regimen provides compelling evidence that testosterone is critical for the maintenance of sexual functioning in women.

It is also noteworthy that combined E-A drugs appear to be equally effective in naturally (22) and in surgically (19, 20) postmenopausal women, although there is some suggestion from the literature that younger women who have had bilateral oophorectomy and therefore experienced an abrupt decrease in their testosterone levels may be both more symptomatic and more responsive to combined therapy.

Sufficient evidence is now available from well-controlled studies to inform decisions regarding the use of combined estrogen-androgen drugs for the treatment of postmenopausal women. First, the clinical literature shows that combined preparations enhance energy level, well-being, and sexual desire and/or interest to levels over and above those that may be induced by estrogen-alone treatment. Therefore, women currently being treated with estrogen whose symptoms of fatigue and impaired sexual functioning are enduring may benefit by the addition of testosterone to their estrogen replacement regimen. It is also important, however, to acknowledge that human sexuality is very complex and has multiple determinants; it is clear that personality factors, psychological factors, relationship factors, as well as hormonal factors all play a role in determining the quality of sexual functioning in the individual woman.

The most clear-cut indication for combined estrogen-androgen therapy is for decreased libido, or sexual desire, when the onset occurred during the perimenopause or postmenopause in a woman who reports a satisfactory sexual history during her premenopausal years. In these cases, a greater likelihood exists for a perimenopausal change in libido that is due to endocrine factors and a greater probability that exogenous testosterone will reverse it. When the history is complicated by concurrent life stress, physical illness, or previous sexual dysfunctions, then it is unlikely that combined estrogen-androgen replacement therapy alone

will reverse the symptoms. Sexual counseling should also be sought.

Because different combined preparations are available in Canada, the U.S., and Europe, it is not useful to recommend specific products or doses. In general, the frequency of masculinizing side effects is rare and dose-dependent. Although the efficacy of the oral combined preparation on sexual complaints has been demonstrated, nonoral routes of administration of testosterone would appear to have fewer metabolic side effects.

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