

# Psychosexual effects of menopause: Role of androgens

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Ovarian hormones—estrogens, androgens, and progesterone—produce a myriad of effects in the nervous system. The effects of androgens in the brain are mediated through androgen-specific receptors and by the aromatization of testosterone to estradiol. Alterations in the circulating levels of androgens play an important role in psychologic and sexual changes that occur after menopause. The effects of short-term estrogen therapy in improving psychologic symptoms, maintaining vaginal lubrication, decreasing vaginal atrophy, and increasing pelvic blood flow in postmenopausal women are well documented. However, some patients require more than estrogen alone to improve psychologic dysfunction, decreased sexual desire, or other sexual problems associated with menopause. Results from clinical studies show that hormone replacement therapy with estrogen plus androgens provides greater improvement in psychologic (eg, lack of concentration, depression, and fatigue) and sexual (eg, decreased libido and inability to have an orgasm) symptoms than does estrogen alone in naturally and surgically menopausal women. (Am J Obstet Gynecol 1999;180:S319-24.)

**Key words:** Androgens, hormone replacement therapy, libido, psychologic, quality of life

The brain is an organ that suffers from the withdrawal and absence of ovarian steroids—estrogen, progesterone, and androgens.<sup>1</sup> Ovarian hormone receptors have been demonstrated in the brain, spinal cord, and peripheral nervous system. The actions of ovarian hormones in the brain and throughout the nervous system are mediated by receptor mechanisms as well as by nongenomic actions in neuronal membranes.<sup>1-4</sup> These actions provide a biologic basis for understanding the development of psychologic dysfunction associated with ovarian hormone deficiency and for the positive effects on psychologic and sexual function reported in hormone replacement studies. Sexual problems related to menopausal hormone deficiency include loss of libido, diminished sexual response, painful intercourse, decreased sexual activity, and reactive sexual dysfunction of a woman's partner.<sup>5</sup> The psychologic significance of loss of sexual function can be deeply meaningful and may contribute to postmenopausal depression and anxiety. Whether psychologic and psychiatric problems, including altered cognitive function and anxiety and depressive disorders, are true repercussions of menopausal change in ovarian hormone production remains controversial. However, epidemiologic studies have related the actions of ovarian steroids in the brain with cognitive function.<sup>6, 7</sup>

## Neurologic effects of ovarian hormones

**Estrogen and progesterone.** Estrogen promotes cell growth and replication in neurons as well as in vaginal ep-

ithelial cells and endometrial lining cells. Ongoing research has shown that estrogen can stimulate neuronal growth by increasing synaptic density.<sup>3, 8</sup> Estrogen appears to exert its neurologic effects by blocking calcium channels in cell-membrane receptors, where it also alters chloride, potassium, and sodium channels.<sup>1-3</sup> Progesterone produces the opposite effect, driving calcium into neurons. Ovarian hormones also influence the production, release, and uptake of neurotransmitters in the brain, as well as affecting brain blood flow.<sup>4</sup>

In the peripheral nervous system estrogen has been shown to alter the perception of touch through a direct effect on receptors in Pacinian corpuscles located in the glabrous skin of the lips and fingertips.<sup>9</sup> When age-matched women with adequate ovarian function were compared with postmenopausal women, there was a significant decrement in vibration sense found among the latter. Vibration sense was restored with the administration of estrogen replacement therapy.

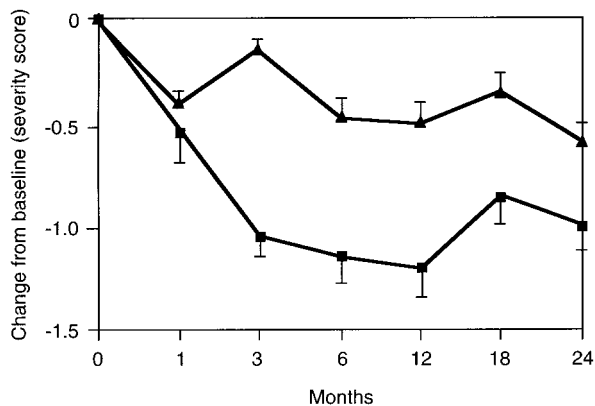
Estrogen has been shown in a number of studies to increase carotid and middle cerebral artery blood flows in postmenopausal women by decreasing arterial wall thickness and increasing arterial pulsatility, presumably through its direct effects (not receptor mediated) on the neurotransmitters epinephrine and norepinephrine.<sup>10-12</sup> The effects of esterified estrogens, with and without methyltestosterone, on blood flows in the fingertip, vagina, and urethra were recently reported by Sarrel and Wiita.<sup>13</sup> Twenty postmenopausal women who were dissatisfied with their current estrogen therapy were randomly assigned to receive either 1.25 mg esterified estrogens or 1.25 mg esterified estrogens plus 2.5 mg methyltestosterone daily for 8 weeks. Blood flow parameters in the fingertip, vagina, and urethra were measured with Doppler velocimetry. After 8 weeks both treatment

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**Fig 1.** Effects of estrogen-androgen therapy on psychologic parameters in 60 women who had undergone hysterectomy and bilateral oophorectomy. Both treatments significantly reduced the severity of an array of symptoms at 1, 3, 6, and 12 months with respect to baseline ( $P < .05$ ). Filled squares represent the group that received esterified estrogens (1.25 mg/d) plus methyltestosterone (2.5 mg/d); filled triangles represent the group that received esterified estrogens alone (1.25 mg/d). Adapted with permission from Notelovitz M, Watts N, Timmons C, Addison A, Wiita B, Downey L. Effects of estrogen plus low dose androgen vs estrogen alone on menopausal symptoms in oophorectomized/hysterectomized women [abstract]. Proceedings of the North American Menopause Society; 1991 Sept 16-19; Montreal. p. 101.

groups had an increase in the postocclusive hyperemic response of fingertip blood flow. Changes in vaginal and urethral blood flow were less consistent than were the fingertip hyperemic response. The conclusion was that the addition of methyltestosterone had no perceptible impact on the vasodilatory response to esterified estrogens for  $\leq 8$  weeks of therapy.<sup>13</sup>

Hypertension is often diagnosed at menopause when blood pressure is measured early in the morning or late in the afternoon because estrogen levels are inadequate to counter the effects of the normal diurnal increase in catecholamine release. The report of the correlation between estrogen and norepinephrine in women who are challenged with mentally stressing tasks indicates that higher plasma estradiol levels are associated with lower levels of norepinephrine when patients are stressed.<sup>14</sup>

**Androgens.** The effects of androgens on the brain are mediated through androgen receptors but also by the aromatization of testosterone to estradiol. The cortical and pituitary actions of androgens are mediated through the androgen receptor. Androgen receptors have been identified in the cortex, pituitary, hypothalamus, preoptic region, thalamus, amygdala, and brain stem. Hypothalamic and limbic system aromatization leads to estradiol receptor-mediated actions. Androgen effects in the brain influence sexual behavior, libido, temperature control, sleep control, assertiveness, cognitive function, and learning capacities, including visual-spatial skills and language flu-

ency. Some of the more widely recognized effects of androgens, such as aggressiveness, typically occur as a result of androgen excess and not with androgen levels within normal values. Surgical menopause usually leads to a marked decrease in serum androgen levels, whereas natural menopause leads to a more natural decline. Hormone replacement therapy can lead to an increase in sex hormone binding globulin. Androgen replacement therapy lowers the sex hormone binding globulin level and increases the levels of circulating free hormones.<sup>15</sup>

### Psychosexual changes associated with menopause

The myriad effects of ovarian hormones on the nervous system, and on other organ systems, clearly play a role in the psychosexual changes that occur after menopause. During the past 3 decades the relationship between mood and menopause has been extensively studied.<sup>16, 17</sup> Results from these studies indicate that there is no specific relationship between natural menopause and mood syndromes.<sup>16</sup> Nevertheless, although most women do not have a mood or anxiety disorder there is a subgroup of women who do so, and there are some women who have symptoms but not a full-blown syndrome. Common postmenopausal symptoms seen in clinical practice include depression, mood swings, irritability, and anxiety.

There are several theories relating mood disorders with menopause that include biologic and psychosocial factors. The pervasive biologic basis includes estrogen withdrawal theories, which are based on the premise that alternations in reproductive hormone activity cause changes in mood and behavior as a result of their impact on central neurotransmitter release.<sup>17</sup> In addition, psychosocial factors also have an impact on mood in postmenopausal women. Rubinow and Schmidt<sup>18</sup> also suggested that the rate of hormonal changes may be an important regulatory variable, perhaps conveying a differential sensitivity to sudden versus gradual decline of ovarian function (surgical versus natural menopause). For example, data from the Massachusetts Menopause Study suggest that there may be a significant increase in symptoms of depression after surgical menopause.<sup>19</sup> The domino theory is based on evidence that psychologic symptoms improve with exogenous administration of estrogen. This theory, offered by van Keep and Prill,<sup>20</sup> suggests that an improvement in mood and behavioral symptoms is a consequence of a reduction in somatic symptoms that accompany menopause. Finally, the life stage theory holds that affective disorders do not develop because of decline in ovarian function but because of life events occurring at middle age (eg, empty nest syndrome).<sup>21</sup>

A number of studies have determined which psychologic symptoms commonly reported by menopausal women are specific to menopause. Sarrel et al (unpublished observations) conducted a prospective randomized study to identify menopausal symptoms that were respon-

**Table I.** Improvement in psychologic symptoms with estrogen-androgen therapy in postmenopausal women with previous treatment failure of estrogen alone

Symptoms	Baseline	Estrogen-androgen therapy (% of patients)		
		1 mo	3 mo	6 mo
Lack of concentration	41	12	19*	29
Tiredness	71	35	44	66
Depression	50	43	31†	54
Reduced libido	94	70	43†	80
Reduced enjoyment of sex	100	47	29†	60
Lack of orgasm	50	13	0†	38
Limitation of sex	88	27	21†	57

*Baseline* refers to previous therapy with estrogen alone. Adapted from Burger HG, Hailes J, Menelaus M, et al. The management of persistent menopausal symptoms with oestradiol-testosterone implants: clinical, lipid and hormonal results. *Maturitas* 1984;6:351-8 with permission from Elsevier Science.

\* $P < .05$  versus baseline.

† $P < .01$  versus baseline.

sive to estrogen replacement therapy. Patients were carefully interviewed before being randomly assigned to receive either estrogen replacement therapy or placebo for 6 months. Symptoms were evaluated by conducting monthly patient interviews. At the end of the study period symptoms not developing at menopause or those that responded to placebo were determined to be unrelated to menopause. Psychologic symptoms that responded to estrogen replacement included fatigue, memory problems, anxiety, depression, and agoraphobia. Sexual difficulties included loss of desire, diminished sexual response, and dyspareunia.<sup>22</sup> In addition, Burnett<sup>23</sup> identified a number of psychologic symptoms that appear to be related to menopause, including irritability, lethargy or fatigue, depression, loss of libido, headache, sexual problems, difficulty concentrating, insomnia, and crying spells.

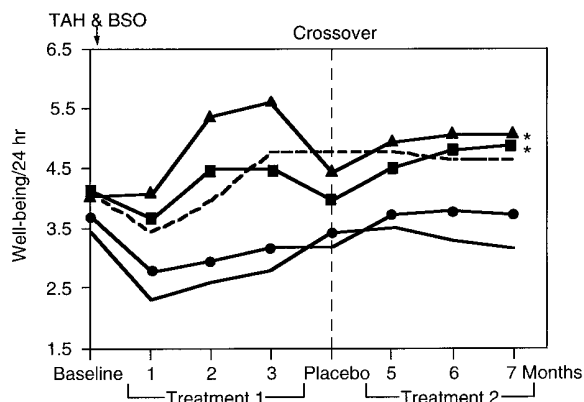
#### Androgen effects on psychologic parameters

A number of investigators have evaluated the effects of androgens in the treatment of psychologic symptoms associated with menopause. Notelovitz et al<sup>24</sup> compared the effects of an oral preparation of estrogens with and without androgens on an array of psychologic symptoms in postmenopausal women. Patients were randomly assigned to receive orally 1.25 mg/d esterified estrogens either alone or in combination with 2.5 mg/d methyltestosterone for 2 years. The mean reduction in symptom severity score from baseline was significant for both the estrogen-alone group ( $P < .05$ ) and the estrogen-androgen group ( $P < .01$ ) at 1, 3, 6, 12, 18, and 24 months after treatment was started (Fig 1). Between-group differences were not significant.

Burger et al<sup>25</sup> investigated the effects of combined subcutaneous implants of estradiol (40 mg) and testosterone (100 mg) on psychologic symptoms in 17 women who had failure of previous estrogen-alone therapy. Principal symptoms reported at baseline were decreased libido, lack of

concentration, fatigue, depression, and inability to have an orgasm.<sup>25</sup> After 3 months the patients receiving estrogen-androgen therapy reported significant improvements in libido, enjoyment of sex, tiredness, and lack of concentration (Table I). On an analog scale libido increased from a mean baseline score of 13.5 to a maximum of 86.1 after 3 months of treatment with estrogen-androgen therapy. In general symptomatic improvement reached its highest peak at 3 months. Improvements were maintained after 6 months, despite the fact that the efficacy of such implants tends to decline after 4 to 5 months. The Australian group has confirmed these findings in more recent studies.<sup>26</sup>

In a prospective crossover study<sup>27</sup> premenopausal women who were scheduled for total abdominal hysterectomy and bilateral salpingo-oophorectomy were assessed for overall well-being and energy level; that is, how patients were feeling in general. Well-being was assessed daily by patients on an interval rating scale that ranged from 0 (worse) to 7 (best). Before total abdominal hysterectomy and bilateral salpingo-oophorectomy, patients were randomly assigned to 1 of 5 groups, 3 treatment groups and 2 control groups. After 1 month of baseline monitoring patients underwent operation. After the operation patients randomly assigned to a treatment group received intramuscular injections (at 28-day intervals) of either estradiol alone (10.0 mg estradiol valerate), testosterone alone (200 mg testosterone enanthate), or estradiol (7.5 mg estradiol dianthate and 1.0 mg estradiol benzoate) and testosterone (150.0 mg testosterone enanthate benzylic acid hydrazone) in combination for 3 months. Of the control groups, the placebo group (intramuscular injection of 0.5 mL sesame oil) was used to control for endocrine changes associated with bilateral salpingo-oophorectomy, whereas the control hysterectomy group was used to control for the changes related to the surgical procedure itself. At the beginning of the fourth



**Fig 2.** Improved sense of well-being with estrogen-androgen therapy in 53 surgically menopausal women. All treatments were administered monthly as an intramuscular injection. Addition of androgen to treatment regimens significantly enhanced well-being with respect to baseline. In contrast, the effect of estrogen alone was similar to that of placebo. Well-being was assessed on a scale of 0 (worst) to 7 (best). Asterisk represents  $P < .01$  versus baseline. *TAH*, Total abdominal hysterectomy; *BSO*, bilateral salpingo-oophorectomy. *Filled triangles* represent therapy with testosterone (200 mg); *filled squares* represent therapy with estradiol (8.5 mg) plus testosterone (150 mg); *filled circles* represent therapy with estradiol (10.0 mg); the *broken line* represents control; the *solid line* represents placebo. Adapted with permission from Sherwin BB, Gelfand MM. Differential symptom response to parenteral estrogen and/or androgen administration in the surgical menopause. *Am J Obstet Gynecol* 1985;151:153-60.

month all patients received placebo. Patients were then crossed over to a different treatment group for another 3 months.<sup>27</sup>

During each treatment period patients who received either estradiol alone or placebo had significantly lower ratings of well-being (Fig 2).<sup>27</sup> In comparison, patients in the control hysterectomy group and patients who had received testosterone therapy, alone or with estradiol, had significantly higher well-being scores ( $P < .01$ ). By the end of the study patients in the control hysterectomy group and the 2 testosterone treatment groups had significant improvements with respect to baseline in well-being scores ( $P < .01$ ). The well-being scores of patients who received estradiol alone or placebo did not differ significantly from baseline.<sup>27</sup>

In addition, these authors noted that patients who received either estradiol alone or placebo reported significantly lower energy level ratings than did patients in the control hysterectomy group or patients who had received testosterone alone or estradiol and testosterone in combination ( $P < .01$ ). By the end of the study patients in the control hysterectomy group and the 2 testosterone treatment groups had significant improvements with respect to baseline in energy level scores ( $P < .01$ ). The energy

level scores of patients who received estradiol alone or placebo did not differ significantly from baseline.<sup>27</sup>

### Androgen effects on sexual parameters

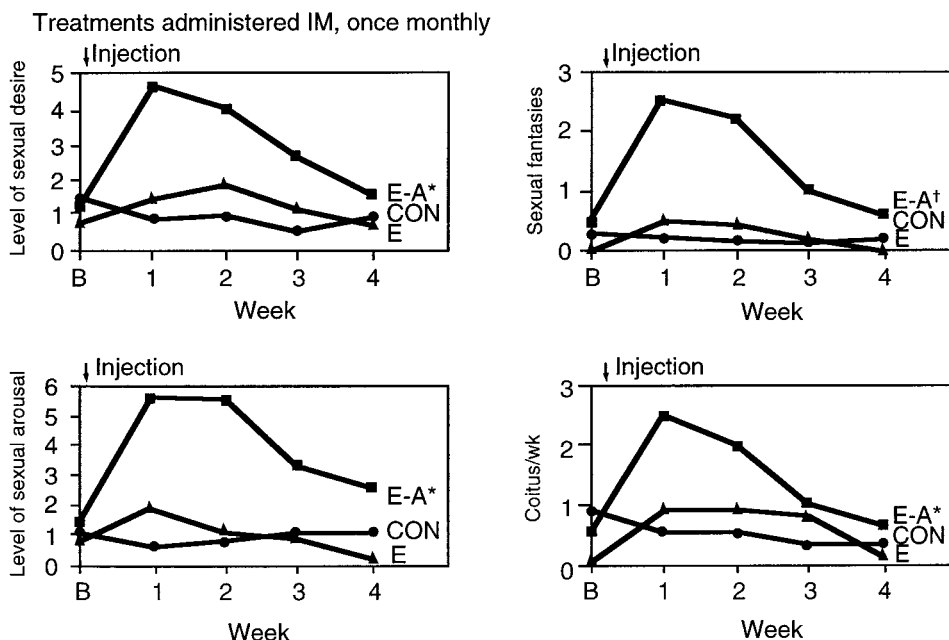
The effects in postmenopausal women of short-term estrogen therapy in maintaining vaginal lubrication, decreasing vaginal atrophy, and increasing pelvic blood flow, and the resultant effect of alleviating or preventing dyspareunia, are well documented.<sup>22</sup> However, some patients require more than estrogen alone to improve sexual desire or other sexual problems associated with menopause.

Sherwin and Gelfand<sup>28</sup> studied the role of androgens in the maintenance of sexual function in 60 postmenopausal women. Five aspects of sexual behavior were monitored daily for 1 month in 3 groups of surgically menopausal women. Women in 1 group had been receiving an estrogen-androgen combination as a monthly intramuscular injection after the operation. Women in the second group had been receiving estrogen only, and women in the third group had remained untreated. Plasma estradiol and testosterone levels were measured at baseline and on days 2, 4, 8, 15, 21, and 28 after the injection. Women treated with estrogen-androgen cotherapy reported significantly higher rates of sexual desire, rates of sexual arousal, number of fantasies, rates of coitus, and number of orgasms than did patients treated with estrogen alone or untreated (Fig 3). Changes in these sexual behaviors varied directly with plasma testosterone level but not with plasma estradiol level. These findings imply that androgens may be critical for the maintenance of optimal levels of sexual function in postmenopausal women.

Sarrel et al<sup>29</sup> assessed sexual function in a double-blind, active-control parallel-group study of 20 naturally and surgically menopausal women with inadequate responses to current estrogen therapy. After a 2-week placebo washout after cessation of previous estrogen therapy, patients were randomly assigned to receive either 1.25 mg esterified estrogens or 1.25 mg esterified estrogens plus 2.5 mg methyltestosterone daily for 8 weeks. Patients who received short-term esterified estrogen plus methyltestosterone therapy demonstrated significant improvements in sexual desire and sensation compared with improvements achieved with previous estrogen therapy. In contrast, the level of sexual desire and sensation achieved with previous estrogen therapy was not exceeded after 4 or 8 weeks of esterified estrogen therapy.<sup>29</sup>

### Conclusion

The brain has been described as an organ that suffers from the withdrawal and absence of ovarian hormones (estrogen, progesterone, and androgens). Androgens appear to play a key role in the psychophysiology of women before and after menopause. When more than estrogen



**Fig 3.** Improvement in sexual symptoms with estrogen-androgen therapy in 60 surgically menopausal women. All treatments were administered monthly as an intramuscular injection. Women who received estrogen-androgen therapy (8.5 mg estradiol plus 150 mg testosterone, *E-A*) had significantly greater sexual desire, sexual arousal, number of fantasies, and frequency of coitus than did women who received estrogen alone (10.0 mg estradiol, *E*) or control women (*CON*). Asterisk indicates  $P < .05$  versus estradiol and control; dagger indicates  $P < .05$  versus placebo. Adapted with permission from Sherwin BB, Gelfand MM. The role of androgen in the maintenance of sexual functioning in oophorectomized women. *Psychosom Med* 1987;49:397-409.

therapy alone is needed, results from clinical studies show that hormone replacement therapy with estrogen plus androgens provides greater improvement in psychologic (eg, lack of concentration, depression, and fatigue) and sexual (eg, decreased libido and inability to have an orgasm) symptoms than does estrogen alone in naturally and surgically menopausal women.

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