# JOURNAL FÜR MENOPAUSE

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*Effect of HRT on cognitive function and mood*

*Journal für Menopause 2000; 7 (Supplementum 2) (Ausgabe für Deutschland), 9-11*

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A. R. Genazzani, M. Stomati, P. Monteleone, B. Quirici, S. Puccetti, I. Lombardi, M. Luisi



# EFFECT OF HRT ON COGNITIVE FUNCTION AND MOOD


## SUMMARY

The action of sex hormones is of critical importance in determining mood disorders, food intake, reduced libido and cognitive disturbances. Experimental and clinical studies have demonstrated that estrogens exert a positive influence not only on vasomotor instability but also on psychological disturbances like depression, sexual and affective behaviour diseases and cognitive function decline. A large number of studies have shown a significant amelioration in mood in depressed postmenopausal women treated with conjugated estrogen. In fact, estrogen modulates the noradrenergic and dopaminergic systems, thus controlling movement and behaviour in both animals and humans. Moreover, estrogens act as a serotoninergic agonist by increasing serotonin synthesis and levels of its main metabolite, 5-hydroxyndolacetic acid. Different molecules of progestogens are used in association to estrogens. Progesterone and progestins can have effects opposite to those exerted by estrogens on the brain. In fact, in contrast to the psychodynamic effects of estrogens, progestins seem to have a depressant and anxiolytic effect on the CNS. These actions are most likely due to its active metabolites such as pregnanolone and allopregnanolone, which are neurosteroids, formed peripherally or at the central level from progesterone and cholesterol. Androgens play a key role in female sexuality and libido. Their decrease contributes to the decline in sexual interest experienced by many women. Treatment with dehydroepiandrosterone (DHEA) or its sulphated ester (DHEAS) is a potential means of replacing androgens in older women. A remarkable improvement in physical and psychological well-being has also been observed following DHEA replacement therapy. The administration of 50 mg/day of DHEAS determines a decrease of subjective symptoms in postmenopausal women treated with DHEAS (50 mg/day).


## INTRODUCTION

Several clinical and epidemiological studies have suggested that postmenopausal gonadal hormone withdrawal may be of critical importance in mood disorders, reduced libido and cognitive disturbances [1–3]. In postmenopausal women, hormonal replacement therapy represents a unique opportunity to investigate the actions of gonadal hormones on central nervous system (CNS). The use of regimens and routes of administration with different kinds of oestrogen, progestin and androgen molecules in postmenopausal women represent a valid tool to clarify the role of sex steroid hormones in the modulation of brain and behavioural functions.

## ESTROGENS, MOOD AND COGNITIVE FUNCTIONS

To begin, a positive relationship between circulating levels of estradiol and mood and behaviour has been demonstrated [3, 4]. A large number of studies regarding the effects of ERT on climacteric depression have shown a significant amelioration of mood in depressed postmenopausal women treated with conjugated estrogen [1, 4]. The positive effects of estrogens on mood and behaviour may be relate to its positive effects on the adrenergic and serotoninergic tone. Clinical studies have reported a frequent decrease in cognitive efficiency, including memory, in climacteric women [5–7]. Estrogen administration improves cognitive functions by exerting a positive effect especially on memory and reaction time tests [5, 7]. In addition, another important factor may be considered: in the postmenopausal period, estrogen administration enhances mood and subjective well-being, while a depressed mood can have a negative impact on psychometric performance.

## PROGESTAGENS, MOOD AND COGNITIVE FUNCTIONS

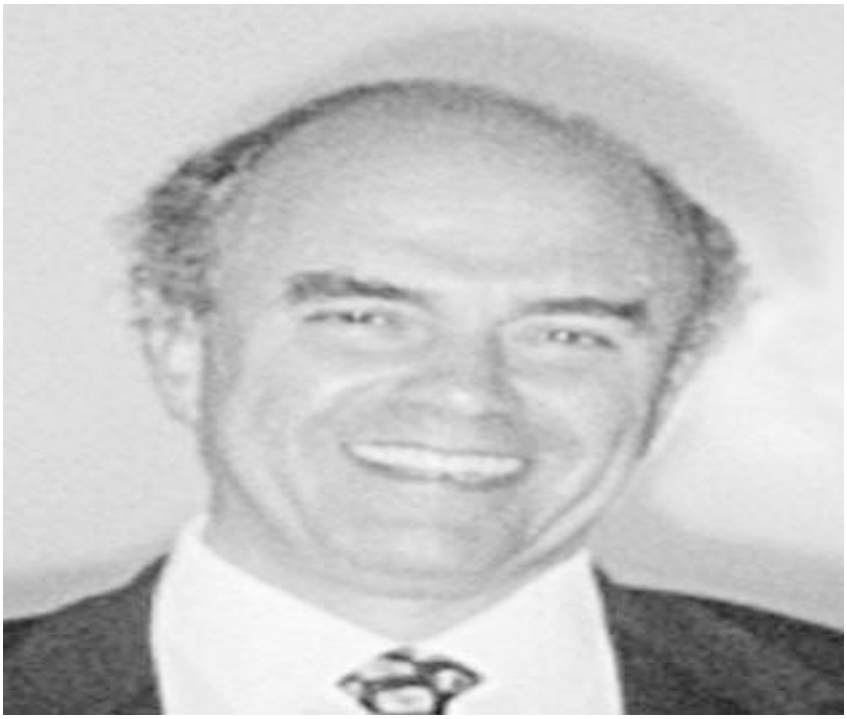
In HRT, the administration of continuous combined or cyclical progestagens is necessary in order to counteract the endometrial proliferative action of estrogens. Progesterone and progestins can have opposite effects to those exerted by estrogens on the brain, thus inducing dysphoric mood and altered behaviour in some women. In fact, in contrast to the activating effects of estrogens, progestins seem to have a depressant effect on the CNS [1, 2]. The depressant action of progesterone is most likely due to its active metabolites such as pregnanolone and allopregnanolone, which can be formed systemically or locally by progesterone and cholesterol.

These actions occur through an enhancement of MAO and GABA-A activity and by lowering brain excitability. Regarding the effect of progestins on cognitive function, the few available data suggest that progestins do not modify the positive effects of estrogens.

## Androgens, mood and cognitive functions

Hormonal replacement with androgens hormones still remains a debate because of the adverse effects that these steroids have on circulating lipids, and rare cosmetic side effects [8]. However, androgens play a key role in female sexuality and libido. Their decline contributes to the decline in sexual interest experienced by many women [8, 9]. Androgens, however, remains only a little component in the management of menopause replacement therapy. Several studies have demonstrated that androgen administration in surgical postmenopausal women affects libido, sexual performance and feeling of well-being positively [8, 9]. To obtain a good response in terms of enhanced libido with androgen supplementation, it seems that T levels need to be restored to the physiological range found in young women. Androgen therapy should be given to postmenopausal women, especially younger women with either premature or surgical menopause who suffer from decreased general well-being, decreased libido and lack of energy despite adequate estrogen and progestagen administration. In particular, treatment with dehydroepiandrosterone (DHEA) or its sulphated ester (DHEAS) is a potential means of replacing androgens in older women [10, 11]. A remarkable improvement in physical and psychological well-being has also been observed following DHEA replacement therapy. Kupperman scores show a decrease of subjective symptoms in postmenopausal women treated with DHEAS (50 mg/day) [11] (Fig. 1). These results encourage further studies to demonstrate that DHEA replacement therapy should be a safe and effective treatment for selected postmenopausal patients.

Figure 1: DHEAS supplementation in postmenopausal women ameliorates Kupperman score



## Conclusion

In conclusion, these data confirm that different regimens and routes of estrogen, progestin and androgen molecules used alone or in association exert several effects on brain functions. Gonadal hormones have a crucial role for the physiological brain functions, acting both on the development and on the maintenance of the female behaviour, cognition and reproductive function. However, at present the available data regarding the implication of sex steroid hormones in the control mechanisms of brain function are insufficient to be conclusive. Every year different kinds of molecules, numerous routes and regimens of administration are developed in HRT. Further studies are required in order to explain the specific role of endogenous and exogenous sex steroids on the CNS.

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*Andrea Genazzani qualified as a medical doctor at the University of Siena in Italy in 1966. He continued his training with a residency in obstetrics and gynecology at the same university, before completing a further residency in endocrinology and metabolism at the University of Florence. Following 5 years in the Division de Biochimie Clinique at the University of Lausanne in Switzerland, Professor Genazzani received his PhD and returned to Italy. After 10 years of research and teaching, he was awarded the position of Professor at the University of Cagliari, where he directed the Department of Obstetrics and Gynecology. Since 1994, Professor Genazzani has been the Director of the Department of Obstetrics and Gynecology at the University of Pisa.*

*Professor Genazzani is well recognized for his research, particularly in the field of reproductive neuroendocrinology, infertility and menopause. He is an active member of numerous scientific societies and is President of both the International Society of Gynecological Endocrinology and the European Society for Gynecologic and Obstetric Investigation. In addition, he is the Executive Secretary and President Elect of the International Menopause Society. The author of over 300 papers in peer reviewed journals, Professor Genazzani is Editor-in-Chief of Gynecological Endocrinology.*

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