

ABSTRACT

Hormone replacement therapy and effects on mood

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Hormone replacement therapy has been used and appreciated by millions of women in their menopause during the past five decades. As treatment for climacteric symptoms, estrogen is outstanding, and effects on hot flushes, vaginal dryness and insomnia have been widely documented.

The increased risks of venous thrombosis and breast cancer however restrict the use of estrogen. If women with a remaining uterus are treated with estrogen, a progestin is added to protect the endometrium from hyperplasia and malignancies. The long time clinical impression that the progestin addition influences mood negatively, has been shown in previous studies. Mood deterioration is, however not mortal, important to the wellbeing and daily functioning of women treated with hormones. Studies of the mental side effects also open the perspective of adding to the understanding of steroid effects in the brain.

Aims and methods:

In our studies, we aimed to find out to what extent negative side effects cause women to discontinue hormone replacement therapy, and to find out what drug compounds deteriorate mood. The questions asked were if the type of progestin, the dose of a progestin and the dose of estrogen during the progestin addition influences mood and physical symptoms during sequential hormone replacement therapy (HRT). Compliance to, and reasons to discontinue HRT was evaluated in retrospective longitudinal follow-up study. Treatment effects were studied in three randomized, double blind, cross-over trials. During continuous estrogen treatment, sequential addition of a progestin was studied in the following manners; comparing two different progestins, medroxyprogesterone acetate (MPA) and norethisterone acetate (NETA), comparing different doses of the same progestin, MPA, and comparing two doses of estrogen during the addition of the same dose of MPA. The main outcome measure was the daily ratings on mood and physical symptoms kept by the participants throughout the studies. The clinical trials were carried out at three gynaecological centres in the northern region of Sweden.

Results and conclusions:

Negative side effects is besides fear of cancer and a wish to see if climacteric symptoms have disappeared, the most common reason to discontinue HRT. Breast tension, weight gain, depressed mood, bloating and irritability are the most important side effects seen both in women who continued HRT and those who discontinued.

We have in our clinical trials shown that the addition of a progestin to estrogen treatment induce cyclical mood swings of tension, irritability and depression as well as increased breast tension, bloating and hot flushes. Women with a history of premenstrual symptoms (PMS) seem to be more sensitive to the progestin addition and respond with lower mood scores compared to women without previous PMS. MPA provokes negative mood to a lower extent than NETA. The higher dose of MPA (20 mg) surprisingly enhances mood compared to 10 mg when added to estrogen treatment. If women are treated with 3 mg estrogen continuously, mood and physical symptoms worsens during the progestin addition, compared to when 2 mg estradiol is used. The negative side effects seen during sequential hormone replacement therapy have many resemblances with the premenstrual dysphoric disorder which is a neuropsychoneuroendocrine disease with psychiatric expression. Explanations to treatment mood effects are likely to be found in drug interactions with neurotransmitter systems of the brain.

Keywords: HRT, estradiol, progestins, mood, negative side-effects, adverse effects.