**17β-estradiol reduced depressive and somatic symptoms in perimenopausal women**


**Question**
In perimenopausal women with clinically important depressive disorders, does 17β-estradiol decrease depressive symptoms?

**Design**
12-week randomized (allocation concealed*), blinded [clinicians, patients, outcome assessors, and statisticians]†, *placebo-controlled trial.

**Setting**
A gynecologic clinic and psychiatric outpatient clinic in São Paulo, Brazil.

**Patients**
50 women who were 40 to 55 years of age (mean age 50 y); had a history of menstrual-cycle irregularity or amenorrhea for < 12 months; had a serum level of follicle-stimulating hormone > 25 IU/L; and had been diagnosed with major depressive disorder, dysthymic disorder, or minor depressive disorder. Exclusion criteria were medical illness; hormone replacement therapy or psychoactive drug use in the previous 3 months; or presence of psychotic features or suicidal or severe aggressive behavior. Follow-up was 90%.

**Intervention**
Patients were allocated to a 17β-estradiol patch, 100 µg (Systen/Evorel, Janssen-Cilag Laboratories, São Paulo, Brazil) (n = 25), or a placebo patch (n = 25).

**Main Outcome Measures**
Severity of depressive symptoms measured by the Montgomery-Asberg Depression Rating Scale (MADRS) and severity of perimenopausal symptoms measured by the Blatt-Kupperman Menopausal Index (BKMI). Remission of depression was achieved if the MADRS score was < 10. A decrease of ≥ 50% from the baseline BKMI score was considered a significant improvement in somatic symptoms.

**Main Results**
Analysis was by intention to treat. At 12 weeks, MADRS scores decreased more from baseline in women who received 17β-estradiol than in those who received placebo (−16.36 vs −4.16, [95% CI for the 12.2 difference in change from baseline 8.4 to 16.0]; P < 0.001). More women who received estradiol had remission of depression (P = 0.001) and a ≥ 50% decrease in BKMI scores (P = 0.005) than did women who received placebo (Table). The groups did not differ for adverse events. At the end of a 4-week washout period, MADRS scores remained lower than those at baseline in the estradiol group (P < 0.001) but were as severe as those at baseline in the placebo group (P = 0.07).

**Conclusion**
In perimenopausal women with clinically important depressive disorders, 17β-estradiol decreased depressive and somatic symptoms. Source of funding: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)–São Paulo Research Foundation.

**Commentary**
In the landmark study from Brazil by Soares and colleagues, of the 50 perimenopausal women enrolled, 52% met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for major depressive disorder, 26% for minor depressive disorder, and 22% for dysthymic disorder. The study had a 12-week treatment phase and a 4-week washout phase. A relatively high dose of estrogen (100 µg) alone was used. Progesterone (which is the standard of care in women with a uterus and endometrium) was not used. 68% of women treated with transdermal 17β-estradiol had remission of depression, regardless of DSM-IV diagnosis, compared with 20% of women in the placebo group.

The Massachusetts Women’s Health Study, a prospective 5-year observational trial, found no link between the onset of natural menopause and an increased risk for depression (1). However, women with a lengthy perimenopause apparently had moderately increased rates of depressive symptoms. Therefore, it is not surprising that mood disturbances, which may be higher in symptomatic perimenopausal women, would respond to estrogen.

We need to determine which women with depressive symptoms benefit from estrogen alone, estrogen with a conventional antidepressant, or antidepressant therapy alone. Transdermal estradiol may be the best initial first-line therapy in women who have perimenopausal symptoms and minor mild-to-moderate mood symptoms, particularly if they do not have a uterus and do not need a progestin. Standard antidepressant therapy remains the first line of treatment for perimenopausal women with major depressive disorders alone.

We are moving beyond viewing estrogen as only a reproductive hormone to viewing it as a neural hormonal agent with effects on mood and cognition.

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**Reference**