

# 17 $\beta$ -estradiol reduced depressive and somatic symptoms in perimenopausal women

Soares CN, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women. A double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 2001 Jun;58:529-34.

## QUESTION

In perimenopausal women with clinically important depressive disorders, does 17 $\beta$ -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 17 $\beta$ -estradiol patch, 100  $\mu$ g (System/Evorel, Janssen-Cilag Laboratories, São Paulo, Brazil) ( $n = 25$ ), or a placebo patch ( $n = 25$ ).

## 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  $\mu$ g) alone was used. Progesterone (which is the standard of care in women with a uterus or endometrium) was not used. 68% of women treated with transdermal 17 $\beta$ -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.

## 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  $\geq 50\%$  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 17 $\beta$ -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  $\geq 50\%$  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, 17 $\beta$ -estradiol decreased depressive and somatic symptoms.

*Source of funding: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)—São Paulo Research Foundation.*

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\*See Glossary.

†Information provided by author.

‡CI calculated from data in article.

## 17 $\beta$ -estradiol vs placebo patch for depressive disorders in perimenopausal women§

Outcomes at 12 wk	17 $\beta$ -estradiol	Placebo	RBI (95% CI)	NNT (CI)
Remission of depression	68%	20%	71% (38 to 87)	3 (1 to 5)
$\geq 50\%$ decrease from baseline in BKMI score	68%	28%	59% (23 to 80)	3 (2 to 8)

§BKMI = Blatt-Kupperman Menopausal Index. Other abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

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

1. Avis NE, Brambilla D, McKinlay SM, Vass K. A longitudinal analysis of the association between menopause and depression. Results from the Massachusetts Women's Health Study. *Ann Epidemiol*. 1994;4:214-20.