

Natural Estrogen as an Antidepressant for Women

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Issue: *Recent well-controlled studies suggest that estrogen has antidepressant actions in perimenopausal women. Estrogen may also have antidepressant actions in postpartum women and across the life cycle for women who are resistant to treatment with various antidepressants. The question, however, of which depressed women to treat with antidepressants, which with estrogen, and which with both remains unanswered.*

In last month's BRAINSTORMS, we discussed the actions of estrogen in the central nervous system (CNS), emphasizing its key regulatory role for monoaminergic neurons via its unique receptors known as nuclear ligand-activated transcription factors.¹ Here we update the potential antidepressant properties of estrogen, which brings us to a fork in the road²: Should a woman with depression be treated with estrogen, an antidepressant, or both? Perhaps the answer lies in the advice from folk philosopher and baseball great Yogi Berra who once said, "When you come to a fork in the road, take it." What we need are guidelines to determine which women will best respond

to which treatment option so prescribers will know which fork in the road to take for individual patients.

Is Estrogen Linked to Depression?

Estrogen has long been suspected to be linked to depression in women.³⁻⁶ A critical observation is that the incidence of depression somewhat mirrors shifts in estrogen across a woman's life cycle (Figure 1). Thus, the risk for depression is higher in women when shifts in estrogen levels are large, beginning especially after estrogen levels rise during puberty, after estrogen levels fall immediately postpartum, and while estrogen levels fluctuate in a declining manner during perimenopause (Figure 2).³⁻⁶

By contrast, depression is not closely linked to testosterone levels in men, since the incidence of depression is essentially constant after puberty, but testosterone levels decline steadily after age 25 (Figure 3).⁶

Is Estrogen an Antidepressant?

Despite observations that estrogen can cause depression in some women, especially at high doses and when administered as oral contraceptives

concomitantly with estrogen antagonist progestins, it has long been recognized that estrogen replacement therapy generally reduces mood fluctuations in perimenopausal women who have vasomotor instability.^{3,4,7} On the other hand, such women do not generally suffer from a major depressive disorder (MDD). Until recently, it has been unclear from clinical trials whether physiologic doses of natural estrogens such as 17 β -estradiol showed any antidepressant properties in women with MDD.

Clinicians, on the other hand, have observed, anecdotally and in open studies of small numbers of patients, that estrogen apparently exerts antidepressant actions as a monotherapy when administered to some women who have MDD both in the postpartum period and during perimenopause.^{3,4} It is somewhat astounding that controlled clinical trials of estrogen for depressed women across their life cycle are only now being published, since not only do women of child-bearing potential have the highest rates of depression, but also women on the whole consume over 70% of antidepressants.³

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Figure 1. Correlation of Depression Rates With Estrogen Levels in Women

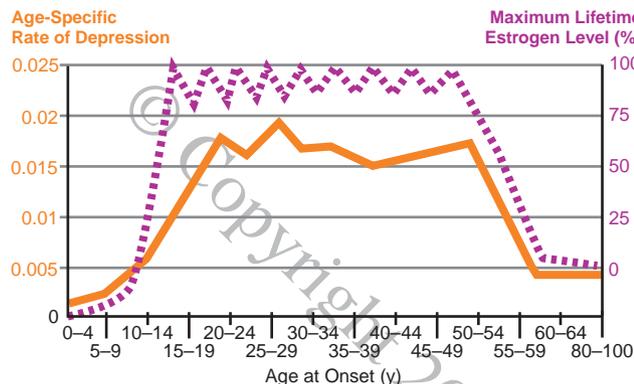
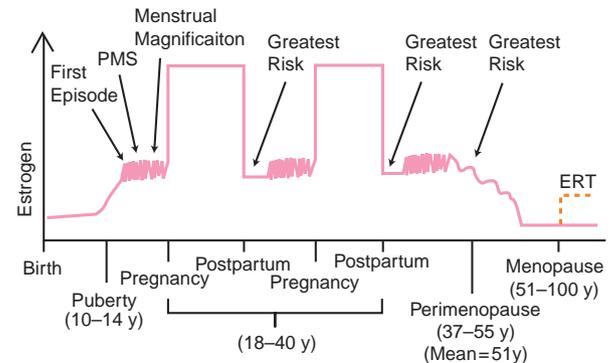
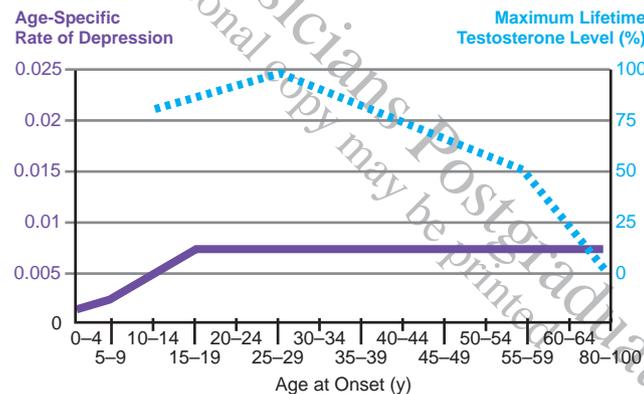


Figure 2. Risk of Depression Across Female Life Cycle^a



^aAbbreviations: ERT = estrogen replacement therapy, PMS = premenstrual syndrome.

Figure 3. Lack of Correlation of Depression Rates With Testosterone Levels in Men



Two recently published, well-designed studies now suggest that 17 β -estradiol may indeed be an antidepressant for women with depression during perimenopause, including women with MDD.^{8,9} In fact, estradiol treatment was associated with a robust treatment effect, including complete remission in the majority of patients studied.⁸

Which Estrogen Might Be an Antidepressant for Women With Depression?

Just as there are a wide variety of antidepressants, there are a wide variety of estrogens. Even though the 2 recent studies mentioned above^{8,9} were of 17 β -estradiol, the major circulating estrogen in women, many other estrogens administered to women today have agonist actions upon CNS estrogen receptors. This includes a mixture of estrogens extracted from the urine of pregnant mare that contains estrone, equilin, and 17 α -dihydroequilin, as well as a new class of estrogen ago-

nists known as SERMs (selective estrogen receptor modulators), such as raloxifene and others.²⁻⁴ Much further research needs to be done to determine the potential antidepressant actions of these estrogens, how they should be combined with antidepressants, and which women are most likely to benefit. Hopefully, the new data emerging will rapidly lead to the development of treatment guidelines so that new insights into the CNS actions of estrogen can be applied in clinical practice.

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