Special Issues in Menopause and Major Depressive Disorder

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A risk to benefit ratio of treatment must be established to determine the optimal treatment for perimenopausal depression. Untreated depression during the perimenopause exacerbates heart disease, diabetes, and osteoporosis. Details about management options here.

Kraepelin initially described involutional melancholia as a distinct clinical entity characterized by late onset, symptoms of fear, despondency, agitation, and hypochondriacal delusions, which formed the basis of the nomenclature in DSM-II. A subsequent report discounted a syndrome of depression at menopause, which served as the basis for the removal of involutional melancholia from DSM-III.¹ Subsequent findings from the Cross-National Epidemiologic Study indicated an increase in new onsets of depressive illness in the perimenopausal years (women aged 45 to 49). This later work is consistent with a developing database demonstrating an increased risk of MDD occurring in association with hormonal changes during perimenopause.

Increased incidence of MDD at menopause

Many methodological problems, especially of diagnostic and endocrine heterogeneity, characterize studies of menopausal mood disorders. More rigorous studies that use standardized, interview-based assessments of depression in endocrine-defined phases of the menopausal transition support an association between MDD and menopause. In one such study from the NIMH, Schmidt and colleagues² conducted a longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. The investigators used the Structured Clinical Interview for DSM-IV for assessment of psychiatric diagnoses, and plasma levels of follicle-stimulating hormone, obtained at 3- to 6-month intervals for an average of 5 years, to determine premenopausal, perimenopausal, or postmenopausal status. For the 24 months surrounding women’s final menses, the risk for onset of depression was 14 times higher than for a 31-year premenopausal time period. Women who had a major depressive episode (MDE) during the perimenopause were not distinguished from those who remained asymptomatic on the basis of symptom profiles; personal or family history of depression; duration of the perimenopause; vasomotor symptoms; life events; medical illness; use of medication, vitamins, or minerals; or exercise. The timing of the depressions, occurring in the context of recently elevated follicle-stimulating hormone levels, suggested that an endocrine mechanism related to the perimenopause (estradiol withdrawal and recent onset of prolonged hypogonadism) was involved in the pathophysiology of perimenopausal depression. Results of other systematic studies are consistent with these findings. In an 8-year study, Freeman and colleagues³ followed 231 women without depressive histories who were about to enter menopause. Using the Center for Epidemiological Studies of Depression scale, they found that the probability of a high depression score (more than 16) was 4-fold greater during the menopausal transition than during the premenopausal phase. Entering menopause was linked to more than double the risk of a diagnosis for depressive disorder and was associated with within-woman increases in follicle-stimulating hormone and luteinizing hormone levels and greater variability of
estradiol and follicle-stimulating hormone levels. Cohen and colleagues\(^4\) also examined the impact of the menopausal transition on depressive symptoms in 460 women without depressive histories, between 36 and 45 years of age. During 3 years of follow-up, the menopausal group, especially women with hot flashes, was twice as likely as the premenopausal group to experience significant depressive symptoms. Major mood disorders occurred in 9.5% of premenopausal and 16.6% of perimenopausal women. These studies used rigorous, standardized criteria for making psychiatric diagnoses. Together, the findings lend strong support to the hypothesis of increased vulnerability for an MDE occurring at the time of the menopausal transition.

**Clinical phenomenology and epidemiology**

According to studies from menopause clinics, the most common symptom for which women seek treatment at menopause is mood change.\(^5\) Almost half of these women are clinically depressed and more than a third experience their first episode of depression in the perimenopausal period. Two-thirds of women in London and three-quarters of women in San Diego who were attending a university or community menopause clinic met criteria for recurrent MDD when evaluated by a psychiatric interview.\(^6\) Perimenopausal women compared with premenopausal or postmenopausal women had a significant increase in depression rating scores. Mood and sleep disturbances are the most common symptoms in about 75% of women. Depressive episodes also are likely to recur at menopause in women with bipolar illness, and there is an increased number of suicides in women during this time (45 to 64 years).

Studies of past psychiatric histories, including illness related to reproductive endocrine change, of women with menopausal depression support a depressive diathesis at menopause. Women in whom psychosomatic symptoms develop in middle age are more likely to evidence psychiatric vulnerability (ie, a previous personal or family psychiatric history). More than half of these women have a past history of depressive disorder. In a 5-year study of 2565 women aged 45 to 55 years, prior depression was the variable most predictive of subsequent depression.\(^7\)

Psychiatric symptoms at menopause also are related to previous depressions associated with the reproductive cycle, such as premenstrual syndrome (PMS) and depression during pregnancy or the post-partum period. Steward and Boydell\(^8\) found that psychological distress during menopause was associated with a past history of PMS, depressive disorders treated with antidepressant medication, oral contraceptive-induced dysphorias, post-partum blues, and MDD, suggesting an increased sensitivity to reproductive hormones in these psychiatrically vulnerable women. Freeman and colleagues\(^9\) found that PMS was a predictor of menopausal symptoms and that women in the menopausal transition were up to 3 times more likely than premenopausal women to report depressive symptoms. A history of depression was the strongest predictor of these changes.\(^10\) In interviews of 347 women aged 35 to 55 years in the Seattle Midlife Women’s Health Study, Woods and Mitchell\(^11\) found that a history of either premenstrual or postpartum affective symptoms distinguished women with consistently depressed mood.

Evidence supports the contention that the perimenopause increases susceptibility to depression, particularly, but not necessarily, among women with lifelong susceptibility to MDD. This includes those whose MDEs were induced by reproductive endocrine change (eg, during the premenstruum, during pregnancy, or postpartum).

**Risks of untreated depression**

A risk to benefit ratio of treatment must be established to determine the optimal treatment for perimenopausal depression. Untreated depression during the perimenopause exacerbates heart disease, diabetes, and osteoporosis. More specifically, with regard to cardiovascular disease, a higher prevalence of depressive disorders was associated with more severe atherosclerosis.\(^12\)

Recurrent depressive, but not anxiety, disorders were associated with a 2-fold increase for the risk of carotid atherosclerosis in middle-aged women. However, a history of a single depressive episode was not associated with increased risk of plaque, suggesting that prevention of recurrent depressive episodes may prevent further progression of atherosclerosis.

Symptoms of depression are significantly related to increased risk of cardiovascular events in women in whom myocardial ischemia is suspected; to death from cardiovascular disease; and, on the basis of the findings from the Women’s Health Initiative Observational Study, to all-cause mortality, even after controlling for established cardiovascular disease risk factors.\(^13,14\) Major depression increases the risk of first heart attack (odds ratio [OR] = 3.9), stroke (OR = 2.7), and diabetes (OR = 2.23).\(^15\) Although the effects of treatment of depression on medical outcomes has not been systematically studied, remission of maternal depression symptoms after 3 months of pharmacotherapy was associated with reductions in the children’s diagnoses and symptoms of medical and psychiatric
illness.\textsuperscript{16}

**Treatment**

The effects of hormone replacement therapy (HRT) on mood in menopausal depression vary depending on the diagnosis (eg, MDD), the menopausal status (whether there are hot flashes), the dose and preparation of estrogen and progesterone, and the duration of treatment.\textsuperscript{17} In women with treatment-resistant MDD, estrogen supplementation in replacement dosages may have important additive effects. In initial studies not confined to menopausal women, 25 μg of ethinyl estradiol added to imipramine was superior to 50 mg of ethinyl estradiol plus imipramine or imipramine alone in women with primary depression.\textsuperscript{18} The higher dosage of estrogen, although associated with less insomnia, was associated with significant adverse effects (lethargy, hypotension, tremor, depersonalization). These findings suggest that there may be a therapeutic window for estrogen treatment; if endogenous levels are already high, additional estrogen supplementation may lead to toxic reactions.

In a 6-week nonrandomized trial in primarily postmenopausal women (older than 60 years) with unipolar depression, the 72 women who received fluoxetine (20 mg/d) and estrogen replacement therapy had a greater improvement in depression ratings than the 286 women who received estrogen replacement therapy alone (40% vs 17%, respectively). Fluoxetine-treated patients who did not receive estrogen replacement therapy did not show benefit greater than placebo. Thus, estrogen enhanced the efficacy of fluoxetine.\textsuperscript{19}

Liu and colleagues\textsuperscript{20} also found that HRT with 0.625 mg of conjugated estrogen and 5 mg of progesterone combined with 20 mg of fluoxetine for 2 months was more effective in reducing symptoms than HRT alone in 123 women with menopausal depression. In a study of sertraline (50 to 150 mg), women older than 60 who received estrogen replacement therapy (without progesterone) had greater global improvement, better quality of life, and less anxiety than women who received sertraline but not estrogen replacement therapy; these women also had modest improvements in cognitive functioning.\textsuperscript{21}

In contrast, we found that oral (1 to 2 mg) or transdermal (0.1 to 0.2 mg) 17β-estradiol enhanced the antidepressant effects of fluoxetine (10 to 40 mg) in an 8-week pilot study of women with perimenopausal or postmenopausal MDD.\textsuperscript{22} In a follow-up randomized clinical trial, the combination of antidepressant plus estrogen was not superior to antidepressant alone; in fact, patients who received an antidepressant plus estrogen showed smaller (nonsignificant) reductions in interview-based depression ratings than those who received an antidepressant alone.\textsuperscript{17} Estrogen treatment alone did not significantly reduce symptoms of MDD. Estrogen treatment, however, may accelerate the antidepressant response.\textsuperscript{23}

In an open-label pilot study, Freeman and colleagues\textsuperscript{24} found that escitalopram alone for 8 weeks significantly improved psychological, vasomotor, and somatic symptoms. Escitalopram was more efficacious for the treatment of depression than ethinyl estradiol and norethindrone acetate.\textsuperscript{25} Soares and colleagues\textsuperscript{26} found that after 4 weeks of estrogen therapy, perimenopausal and postmenopausal women with recalcitrant depression benefited from adjunctive treatment with 20 to 60 mg of citalopram for 8 weeks.

However, estrogen may enhance the efficacy of an antidepressant in refractory depression. The effect of gradually increasing doses of conjugated estrogens for a month was examined in 3 premenopausal and 8 postmenopausal women with refractory depression.\textsuperscript{27,28} Although there was no overall improvement in depression scores with estrogen or placebo, mania developed 9 days after estrogen treatment in one bipolar patient whose depression had been treatment-resistant for 2 years. Another patient showed striking improvement after 1 week of estrogen treatment and was no longer depressed after 2 weeks, a remission that lasted for 3 months.

In women with treatment-resistant MDD, estrogen supplementation in replacement dosages may have important additive effects to antidepressants. Depending on the dosage in relation to progesterone, estrogen also may induce or stabilize rapid mood cycling in some patients.\textsuperscript{7,29,30} Findings suggest that TCAs were more effective in and were better tolerated than SSRIs by menopausal women with chronic depression who were not receiving estrogen replacement therapy.\textsuperscript{31} To achieve the same degree of efficacy and tolerability with the SSRIs, estrogen needed to be added, presumably to down-regulate postsynaptic serotonin receptors. Although HRT enhanced the effect of SSRIs and placebo response, venlafaxine, perhaps because of its dual receptor inhibition on serotonin and norepinephrine receptors, did not differentially affect outcome as a function of the addition of HRT as did mirtazapine in an open-label trial.\textsuperscript{32} Venlafaxine alone may improve depressive and vasomotor symptoms in women with perimenopausal depression.\textsuperscript{33} Methyltestosterone further augmented the effects of venlafaxine but was
associated with a high dropout rate. In an open-label trial of the serotonin-norepinephrine reuptake inhibitor duloxetine, Joffe and colleagues found that patients who received 60 to 120 mg/d had significant improvement in depression, vasomotor symptoms, sleep, anxiety, and pain after 8 weeks of treatment.

Venlafaxine and paroxetine have been studied more extensively than any of the other antidepressants and are more consistent in effectively reducing the frequency and severity of hot flashes. Desvenlafaxine, escitalopram, fluvoxamine, and mirtazapine should be reserved as last-line therapy for hot flashes. Depressive symptoms were reduced in perimenopausal women irrespective of the presence of hot flashes or the duration (3 weeks vs 6 weeks) of daily treatment with the 0.05-mg 17β-estradiol patch.

Conclusions
Perimenopausal women in particular are at risk for new onset and recurrence of MDEs. Women with previous histories of PMS or postpartum depression are at increased risk. Patients may present with melancholia, agitation, somatic symptoms, or sleep disturbances. Untreated depression may exacerbate heart disease, diabetes, and osteoporosis; it may also contribute to the risk for suicide and a more debilitating course of the depression that is more refractory to intervention. Estrogen alone may reduce hot flushes and improve sleep, but it has not been shown consistently to be effective as monotherapy in MDD. In some women with depression refractory to SSRIs, the addition of estrogen may enhance treatment outcomes; reduce response time; and obviate the need for increasing the antidepressant dose, with its attendant adverse effects. If a woman cannot tolerate estrogen replacement, then an antidepressant other than an SSRI (eg, a TCA, such as nortriptyline or desipramine; or an SNRI, or dual receptor reuptake inhibitor, such as mirtazapine, venlafaxine, or duloxetine) should be tried. For vasomotor symptoms in women who cannot tolerate estrogen therapy, paroxetine and venlafaxine are the antidepressants found to have the most evidence for efficacy and tolerability.

Progesterone may increase depressive symptoms in women with a history of depression. Estrogen or progesterone hormone replacement should be given in conjunction with consultation with a gynecologist or primary care physician who can monitor the development of any untoward adverse effects on the uterus, breast, or cardiovascular system.

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