Treatment in Psychiatry begins with a hypothetical case illustrating a problem in current clinical practice. The authors review current data on prevalence, diagnosis, pathophysiology, and treatment. The article concludes with the authors' treatment recommendations for cases like the one presented.

Perimenopausal Depression

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"Ms. A" was a 48-year-old Caucasian woman who, like her mother, had first suffered a psychiatric disorder when she had a major depressive disorder with postpartum onset. At age 26, within a month after the birth of her first child, Ms. A developed rapid mood shifts, anxiety, agitation, somatic symptoms, and transient paranoid delusions that did not progress to psychosis; there were no episodes of mania. She was treated effectively with a combination of pharmacotherapy (monotherapy with 20 mg fluoxetine daily) and psychotherapy. The same treatment prevented relapses when it was instituted after the births of her second and third children and maintained for 6 months.

During perimenopause, when Ms. A's menstrual cycles started becoming irregular, she again developed a major depressive disorder, with symptoms similar to those she had experienced postpartum but without the transient paranoid ideation and agitation. She was started on fluoxetine, but she remained unresponsive after several weeks of treatment. Ms. A had also developed perimenopausal hot flashes, which became particularly bothersome at night. Because she had experienced problematic side effects in the past when taking larger doses of fluoxetine, including flushing, sweating, headaches, and anorgasmia, she was reluctant to increase her antidepressant dosage. What is the role of estrogen replacement therapy, with or without progesterone, in such a patient? What other factors should be taken into account in the decision on whether to institute hormone replacement therapy?

History and Definition of Perimenopausal Depression

Kraepelin initially described "involutional melancholia" as a distinct clinical entity characterized by late onset and symptoms of fear, despondency, agitation, and hypochondriacal delusions, which formed the basis of the nomenclature in DSM-II. Subsequent research discounted a syndrome of depression at menopause (1), and hence involutional melancholia was omitted from DSM with publication of the third edition in 1980. Subsequent findings from the Cross-National Epidemiologic Study indicated an increase in new onsets of depressive illness in the perimenopausal years (women 45–49 years of age). This later work is consistent with a developing body of data demonstrating an increased risk of major depressive episodes occurring in association with hormonal changes of the perimenopausal years.

The perimenopausal period refers to the interval when women's menstrual cycles become irregular, which generally occurs between the ages of 45 and 49. According to the World Health Organization and the Stages of Reproductive Aging Workshop, menopause is defined as 12 months of amenorrhea following the final menstrual cycle, which occurs at a mean age of 51 years. With menopause, levels of follicle-stimulating hormone (FSH) usually exceed 40 mIU/ml, although given the variability of individual hormonal levels, the determination of menopausal status is generally made by clinical history rather than laboratory parameters.

Link to Reproductive Endocrine Change

Studies of menopausal mood disorders often have methodological problems, notably diagnostic and endocrine heterogeneity. The more rigorous studies, which use standardized, interview-based assessments of depression in endocrine-defined phases of the menopausal transition, support an association between major depressive disorder and menopause. In one such study, Schmidt et al. (2) 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 and plasma levels of FSH, obtained at 3- to 6-month intervals for an average of 5 years, to determine pre-, peri-, and postmenopausal status. For the 24 months surrounding women's final menses, the risk of onset of depression was 14 times higher than for the 31 preceding years. Women who developed a major depressive episode during the perimenopause were not

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distinguishable 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, or use of medication, vitamins, minerals, or exercise. The timing of the depressions, occurring in the context of recently elevated FSH 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 et al. (3) followed 231 women without any depressive history 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 (>16) was four times greater during the menopausal transition than during the premenopausal phase. Entering menopause was linked to more than double the risk of being diagnosed as having a depressive disorder and was associated with within-woman increases in FSH and luteinizing hormone and greater variability of estradiol and FSH. Cohen et al. (4) examined the impact of the menopausal transition on depressive symptoms in 460 women 36–45 years of age without a depressive history. During 3 years of follow-up, the menopausal women were twice as likely as the premenopausal group to experience significant depressive symptoms, and the risk for those with hot flashes was slightly greater. Major mood disorders occurred in 9.5% of premenopausal and 16.6% of perimenopausal women.

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These studies all used rigorous, standardized criteria for making psychiatric diagnoses. Together, these findings lend strong support to the hypothesis that vulnerability to a major depressive episode is increased at the time of the menopausal transition.

Clinical Phenomenology and Epidemiology

Based on studies from menopause clinics (see review in reference 5), mood change is the most common symptom for which women seek treatment at menopause. Almost half of these women are clinically depressed, and over a third experience their first episode of depression in the perimenopausal period. Among women attending community or university menopause clinics, two-thirds of those at a London site and three-quarters of those at a San Diego site met criteria for recurrent major depression when evaluated by a psychiatric interview (6).

Perimenopausal women have significantly higher depression rating scores than pre- or postmenopausal women. The most common symptoms seen in perimenopausal women are mood and sleep disturbances, reported by about 75% of women. Depressive episodes also are likely to recur at menopause in women with bipolar illness, and the risk of suicide in women is increased during the period from age 45 to age 64.

Sleep

Systematic studies examining objective measures of sleep in carefully diagnosed patients in relation to endocrine markers of menopause are limited, and the findings are inconsistent (7). Perceptions of sleep quality may differ in depressed compared with healthy menopausal women, and although women may complain of sleep disturbances more than men, they actually have better sleep quality as documented by polysomnography. Menopausal depressed women also may report increased severity of hot flashes during sleep, but in skin conductance studies of hot flashes, they actually have fewer and shorter hot flashes that disrupt sleep than nondepressed women. Moreover, sleep disturbances at menopause are related more to underlying sleep disorders (such as restless legs syndrome or apnea) or anxiety symptoms than to hot flashes. Hot flashes are more likely to disrupt sleep in the first half of the night than the second because of the suppressive effects of REM sleep (which occurs predominantly in the second half of the night) on thermoregulation (8). Women with chronic insomnia, however, are at higher risk of developing depression. In subjective reports of sleep, lower estradiol levels have been associated with poorer sleep quality, increased hot flashes, and increased anxiety and depressive symptoms. Estrogen treatment may improve sleep independent of its effect on hot flashes. In the Women's Health Initiative, increased light exposure was associated with improved sleep and mood in older women.

Past History

Studies of past psychiatric histories, including illness related to reproductive endocrine change, in women with menopausal depression support a depressive diathesis at menopause. Women who develop psychiatric symptoms in middle age are more likely to have a psychiatric vulnerability, i.e., a previous personal or family psychiatric history. Over half of women with menopausal depression have a history of a previous depressive disorder. In a 5-year study of 2,565 women 45–55 years of age, prior depression was the variable most predictive of subsequent depression (9).

Psychiatric symptoms at menopause also are related to previous depressions associated with the reproductive cycle, such as premenstrual syndrome or depression during pregnancy or the postpartum period. Stewart and Boydell (10) found that psychological distress during menopause was associated with a past history of premenstrual syn-

drome, depressive disorders treated with antidepressant medication, oral contraceptive-induced dysphoria, postpartum blues, and major depressive disorder, suggesting an increased sensitivity to reproductive hormones in these psychiatrically vulnerable women. Freeman et al. (11, 12) found that premenstrual syndrome was a predictor of menopausal symptoms and that women in the menopausal transition were up to three times more likely to report depressive symptoms than premenopausal women; a history of depression was the strongest predictor of these changes. In interviews of 347 women 35–55 years of age in the Seattle Midlife Women's Health Study, Woods and Mitchell (13) found that a history of either premenstrual or postpartum affective symptoms distinguished women with consistently depressed mood.

In summary, evidence supports the contention that the perimenopause increases susceptibility to depression, particularly among women with lifelong susceptibility to depressive disorders, including those whose depressive episodes were induced by reproductive endocrine change (e.g., during the premenstruum, pregnancy, or postpartum).

Treatment

The studies examining the effects of hormone replacement on mood in menopausal depressed patients vary depending on the diagnosis (e.g., major depressive disorder), menopausal symptoms (including the presence of hot flashes), the dose and preparation of estrogen and progesterone replacement, and the duration of treatment (see review in reference 14).

In initial studies not confined to menopausal women, 25 μg of ethinyl estradiol added to imipramine was superior to 50 μg of ethinyl estradiol plus imipramine or imipramine alone in 30 women with primary depression. The higher dose of estrogen, although associated with less insomnia, also was associated with significant side effects (lethargy, hypotension, tremor, and 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 (15) in primarily postmenopausal women over age 60 with unipolar depression, the 72 women who received fluoxetine (20 mg/day) and estrogen replacement therapy (ERT; primarily Premarin) had a greater improvement in depression ratings than the 286 women on ERT alone (40% and 17%, respectively). Patients treated with fluoxetine who were not receiving ERT did not show benefit greater than placebo. Thus, estrogen enhanced the efficacy of fluoxetine treatment. In a study of sertraline (50–150 mg), women over age 60 receiving ERT (without progesterone) had greater global improvement, better quality of life, less anxiety, and modest improvements in cognitive functioning compared with women receiving sertraline but not ERT.

In contrast, in our laboratory, although we found in an 8-week pilot study of women with peri- or postmenopausal major depression (16) that oral or transdermal 17-beta estradiol enhanced the antidepressant effects of fluoxetine, we found in a follow-up randomized clinical trial that the combination of antidepressant plus estrogen was not superior to antidepressant alone; in fact, patients receiving antidepressant plus estrogen showed smaller (nonsignificant) reductions in interview-based depression ratings than those patients receiving antidepressant alone (14), a finding supported by other studies. Estrogen treatment alone did not significantly reduce symptoms of major depressive disorder.

In patients with refractory depression, however, estrogen may enhance the efficacy of antidepressant medication (17). In small studies in which the investigators examined the effect of gradually increasing doses of conjugated estrogens (Premarin) or placebo for a month in premenopausal and postmenopausal women with refractory depression, although there was no overall improvement in depression scores with estrogen or placebo, one bipolar patient whose depression had been treatment-resistant for 2 years developed mania that began 9 days after estrogen treatment. Another patient showed striking improvement after 1 week of estrogen treatment and was no longer depressed after 2 weeks, a remission that lasted 3 months (18). Thus, occasionally patients do appear to have therapeutic responses to estrogen. In women with treatment-resistant major depression, estrogen supplementation in replacement dosages may have important additive effects to antidepressant medication. Depending on the dosage in relation to progesterone, estrogen also may induce (19) or stabilize (20) rapid mood cycling in some patients.

Some studies suggested that in menopausal women not on estrogen replacement therapy who have chronic depression, tricyclic antidepressants offer greater efficacy and tolerability. To achieve the same degree of efficacy and tolerability with the selective serotonin reuptake inhibitors (SSRIs) in menopausal depressed women, estrogen replacement needed to be added, presumably to downregulate postsynaptic serotonin receptors (findings based on the animal literature). Additional research, however, supported this differential effect of tricyclic versus SSRI medication in premenopausal but not postmenopausal women. In a further analysis of women over age 50, although hormone replacement therapy enhanced the effect of SSRI 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 hormone replacement therapy (see review in reference 21).

Other studies suggest that estrogen treatment alone may reduce depressive symptoms in major depressive disorder. Overall, in the studies that demonstrated efficacy, 17-beta estradiol, the most active form of estrogen to cross the blood-brain barrier, was used for at least 4 weeks. The effect may be mediated by altered neurotransmitter, neuroendocrine, circadian rhythm, or brain alpha/beta activity. In the studies that used progesterone replacement in addition to estrogen, the progesterone tended to decrease

the beneficial effects of estrogen, and in some patients it exacerbated depressive symptoms, especially in those who had previous episodes of depression or who developed negative affect from progestin-containing contraceptives.

In nondepressed clinical samples, investigators in the Women's Health Initiative failed to find a significant effect of estrogen plus progestin on depressive symptom scores after 3 years. In the Heart and Estrogen/Progestin Replacement Study, only women with hot flashes who were assigned to hormone therapy benefited by having better mental health and fewer depressive symptoms. Women without hot flashes assigned to hormone therapy had greater declines in physical functions and energy and greater fatigue. In a study of 48 nondepressed women 47–57 years of age (22), estrogen treatment (Premarin) enhanced mood, but women given progesterone (Provera) showed more negative affect, unless the progesterone was counteracted by higher dosages of estrogen.

For hot flashes, randomized controlled trials of SSRIs, selective norepinephrine reuptake inhibitors, gabapentin, and clonidine have provided evidence of efficacy, although the effect was less than that with estrogen therapy (see review in reference 23).

The risks of hormonal therapies should be considered in light of other risk factors. Although the Women's Health Initiative initially reported an increased incidence of breast cancer or cardiovascular disease in 4–5 out of 10,000 women after 5 years of treatment (24), the majority of the women in this study were older (60–79 years), with higher body mass indices (25). More recent evidence suggests that use of hormonal replacement therapy within 10 years of the onset of menopause (between ages 50 and 59) is associated with a reduced risk of cardiovascular disease (26). According to the North American Menopause Society, it is appropriate to use hormonal therapies to treat menopausal symptoms in the absence of related risk factors, such as cardiovascular disease and breast cancer, and to repeatedly present the option of stopping or reducing the dose (27). The decision to use hormone replacement therapy should be made in consultation with the patient's physician, weighing the patient's particular risk factors and likely benefits.

Among alternative treatments, St. John's wort and black cohosh appear to be the most useful in alleviating mood and anxiety symptoms (not disorders) during menopause (28).

Summary and Recommendations

Perimenopausal women in particular are at risk of new onset and recurrence of major depressive episodes, and the risk is greater in women with a previous history of premenstrual syndrome or postpartum depression. Symptoms may present with features of melancholia, agitation, somatic symptoms, or sleep disturbances. The increase in major depressive episodes during the perimenopausal period has been found to be linked to hormonal changes of the menopausal transition, namely, increased FSH levels, rather than to social or environmental triggers, although changes in valued life styles associated with, for example, motherhood, family, fertility, or physical rigor and attractiveness may precipitate depressive mood changes in predisposed or vulnerable women. Women who worry about others are at increased risk of developing clinical depression. Other women may value the newfound independence these life style changes incur.

Estrogen treatment alone may reduce hot flashes and improve sleep, but it has not been shown consistently to be efficacious as monotherapy for major depressive disorder. In some women whose depressive symptoms are refractory despite treatment with an antidepressant, particularly an SSRI, the addition of estrogen may enhance the antidepressant's efficacy, reduce response time, and obviate the need for increasing the antidepressant dose and risking the attendant side effects. Progesterone may increase depressive symptoms in women who have a previous history of depression. Estrogen or progesterone hormone replacement should be given in consultation with a gynecologist or primary care physician who can monitor the development of any untoward effects on the uterus, breast, or cardiovascular system. Many women may opt to have annual endometrial biopsies, an outpatient procedure.

In the vignette, Ms. A was reluctant to increase her dosage of fluoxetine (20 mg/day) because of side effects she had experienced with higher doses in the past. Thus, instead of increasing her antidepressant dose, low-dose transdermal estrogen replacement therapy was added to her antidepressant regimen. In consultation with her gynecologist and her psychiatrist, she opted not to use progesterone replacement therapy because progestin-containing contraceptives had previously exacerbated her depressive symptoms. She elected instead to undergo annual outpatient endometrial biopsies to assess the status of any estrogen-induced uterine hyperplasia. After about a week on fluoxetine and estrogen replacement therapy, Ms. A noted a reduction of her hot flashes, particularly during sleep. Within several weeks, she noted an improvement in her mood, which progressed without any need to increase her antidepressant dosage and face her previous untoward side effects. She was able to return to her former level of active functioning at home and in the community.

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