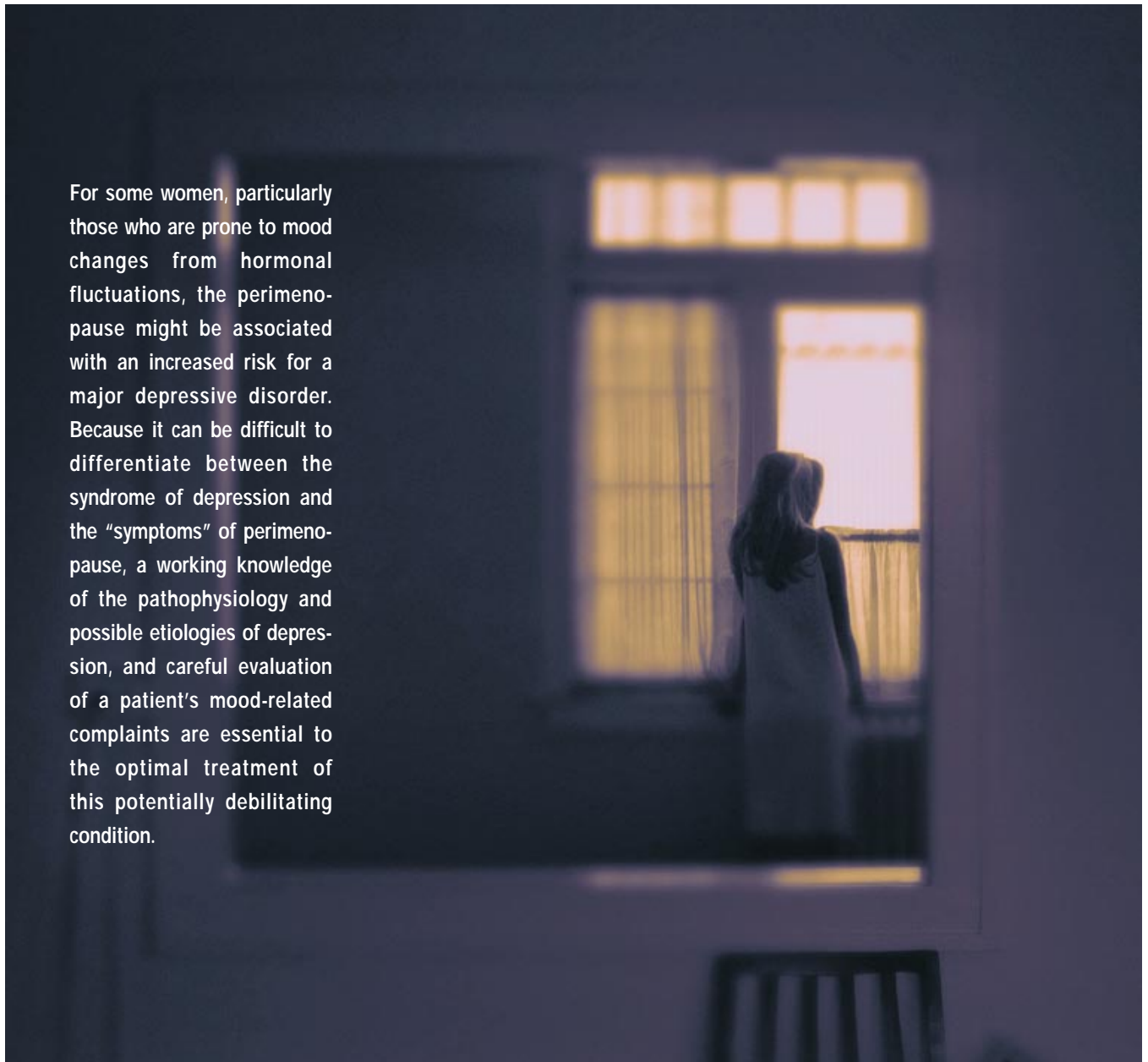

Depressive Disorders and the Menopause

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For some women, particularly those who are prone to mood changes from hormonal fluctuations, the perimenopause might be associated with an increased risk for a major depressive disorder. Because it can be difficult to differentiate between the syndrome of depression and the “symptoms” of perimenopause, a working knowledge of the pathophysiology and possible etiologies of depression, and careful evaluation of a patient’s mood-related complaints are essential to the optimal treatment of this potentially debilitating condition.



Depression is a serious and common disorder that affects 17% of the general population during their lifetimes. The National Comorbidity Survey (1994)¹ found that 10.3% of the U.S. population reported a major depressive episode during the previous year.

It is important to note that a distinction must be made between the transient “sadness” or “low spirits” experienced by everyone at some point, and the syndrome of depressive disorder, to which this article refers. Furthermore, this review will focus on one area of dramatic physiologic change in women, the menopause, and its relation to depressive disorders.

Depression and Gender

With the exception of bipolar disorder, for which the lifetime prevalence is the same for both genders, women are clearly more vulnerable to depressive disorders than are men, and experience depressions at twice the rate of men in the United States¹ and internationally.² This is evidenced by findings from the Epidemiologic Catchment Area Study,³ in which lifetime prevalence rates of major depression were 8% in women versus 3.5% in men; the rates for dysthymia were 5.4% in women and 2.6% in men. Other major epidemiologic studies confirm such gender differences. Using different measures, the National Comorbidity Survey¹ reported major depression occurring at a rate of 20% in women versus 13% in men, while dysthymia was reported in 8% of female respondents and 5% of males. In community samples the average lifetime prevalence of depression was approximately 20% for women and 10% for men.⁴ Even with bipolar disorder, women are more likely to have more depressive episodes or mixed states that include both depressive and manic symptoms. Women are also more commonly afflicted with rapid cycling of mood states than are men.⁵

In addition to this increased risk for mood disorders, women undergo dramatic hormonal changes during midlife. The relationship between the menopause

and depression demands clinical attention. Gender differences and increased rates and prevalence of depression begin around the time of puberty and persist throughout the reproductive years in women until midlife,⁶ suggesting that gonadal hormones might play a role in gender differences. The role of gonadal hormones is also suggested by the potential for depressive episodes to occur at periods of hormonal change,⁷ such as the premenstrual phase of the menstrual cycle,⁸ as well as during the postpartum period, when women with a previous history of depression, bipolar disorder or premenstrual dysphoric disorder have increased rates of depression.⁹

Depression and Its Association With Menopause

In North America the mean age at menopause (absence of menses for at least 12 consecutive months) is 50-51 years.¹⁰ The transitional period between premenopause and postmenopause is termed perimenopause,¹¹ and the term climacteric has been used to describe the entire process.¹² There is a long-standing association between depression and cessation of reproductive function. Kraepelin described “involutional melancholia” in 1906 and, for a long time, menopause was cited as an etiologic factor in depression. While involutional melancholia was categorized as a psychiatric disorder in the 1968 DSM-II (*Diagnostic and Statistical Manual of Mental Disorders, 2nd edition*),¹³ subsequent controversy and questions as to whether the condition really differed from other major mood disorders led to its deletion from subsequent DSM iterations.^{4,14,15}

Published reports about the association between menopause and depression have been inconsistent. Studies of women presenting to specialized clinics for treatment of menopausal symptoms (physical, psychological or both) have shown a higher than expected prevalence of depressive symptoms in peri- and postmenopausal women.¹⁶⁻¹⁸ In one study¹⁷ investigators reported clinically significant depression in up to 45% of their sample

population. Such observations must be tempered by the fact that most general-population-based surveys have reported no increase in depressive symptoms with menopause.^{6,19} Clinic-based samples might be biased, as they contain much larger proportions of perimenopausal women seeking care for clinically significant mood symptoms; these samples become “diluted” when examined in the community setting. Some epidemiologic studies have, however, shown an increased risk of developing depression with a prolonged perimenopausal period (at least 27 months). A prior mood disorder is the variable that is most predictive of subsequent depression in depressed postmenopausal women.¹⁹ There are also some data indicating an increased risk of new-onset depressive illness during the perimenopausal years.^{2,20}

Importance of the perimenopause. It is the perimenopause, rather than the postmenopause, that is the critical period with respect to depression; in fact, discussions of “menopause” and depression typically refer to the perimenopausal period, with its significant biologic and sociocultural changes. While women who experience surgically induced menopause are at greater risk for depressive symptoms, the onset of natural menstrual cessation is not associated with an increased rate of depression, independent of a past history of depression.¹⁹ In one study, investigators reported a relative decline in the 1-year prevalence of major depression in both women and men during midlife but, at the same time, identified an increase in the female-to-male ratio for major depression, from about 2:1 to approximately 3-4:1.⁶ A critical review of the literature that included 43 epidemiologic research articles revealed no substantial evidence that either natural menopause, with its accompanying changes in hormone concentrations, or psychosocial factors exclusive to middle age put women at increased risk for depression.²¹

It seems that advancing age might be a protective factor against the onset or recurrence of a major depression, given that

the majority of postmenopausal women do not experience depression in this phase of life. Nevertheless, the perimenopause might reduce the protective effect of aging on mood destabilization in women who develop new-onset depression between the ages of 45 and 50 years.²²

Is perimenopausal depression different? Perimenopause-related depression is defined by the onset of a depressive disorder in association with a change in menstrual cycle function and endocrine evidence of perimenopause (elevations of plasma follicle-stimulating hormone [FSH] levels).²³ Hay et al¹⁷ examined the prevalence rates of depression in endocrinologically confirmed perimenopausal women and, using a structured diagnostic interview, reported that 45% of the sample met criteria for major or minor depression. Schmidt et al²³ observed that, in their clinic experience, women in the perimenopause with depression-related complaints present most frequently with a symptom cluster similar to that of a mixed anxiety-depressive disorder. Such women report that their symptoms begin insidiously and often occur in the presence of hot flashes. The prominence of the mood and behavioral symptoms that create functional distress and impairment relative to the somatic symptoms suggests a mood disorder.

Perimenopause-related depression is diagnosed in a manner identical to that for depression occurring at other periods in the life cycle, according to the DSM-IV,⁴ but perimenopausal depression must, by definition, occur in the context of endocrinologic evidence of the perimenopause.

The concurrence of somatic complaints attributed to physiologic changes confounds accurate diagnosis of a perimenopausal mood disorder. The phenomenology of the vasomotor symptoms caused by change in the rate of gonadal hormone production, especially estrogen, can overlap with the neurovegetative symptoms of depression. Although the efficacy of estrogen treatment alone for menopausal depression has not been sup-

ported,¹⁰ very high doses of estrogen, associated with somatic side effects in pre- and postmenopausal patients, reduced, but did not completely alleviate self-reported mood symptoms in severely depressed women.²⁴ This suggests that depression during perimenopause might actually be different from other depressions, since estrogen is not an effective antidepressant in pre- and postmenopausal women.²⁴

Proposed Etiologies of Depression During the Menopause

It has been suggested that biologic, sociocultural and psychological factors might all play a role in the etiology of depression during menopause.¹⁰

Psychosocial hypothesis. The psychosocial hypothesis emphasizes that women, in general, have a lower socioeconomic status and are more prone to stressful life events, victimization and maladaptive coping styles than are men; all of these factors might contribute to a greater risk of major depression.²⁵ Schmidt et al²³ reported significantly higher rates of self-reported negative life events in women with depression (with and without the presence of hot flashes) during the 6 months prior to the onset of their depression, compared to nondepressed perimenopausal controls. In this study, the depressed perimenopausal women reported a higher degree of marital dissatisfaction than did controls. These findings raise the possibility of adverse life events and/or disrupted marital relationships as contributing factors to the onset or expression of perimenopausal depression.

Negative social expectations related to growing older and no longer being reproductively competent might also cause women to attribute adverse psychological symptoms to menopause. Developmental life stressors, such as caring for an elderly parent, having children leave or return home, assuming the dual role of running a household and working outside the home, might contribute to menopause-related symptoms, such as fatigue

and sadness.¹⁰ Chronic stressful life events can also modulate neurotransmitter activity and the hypothalamic-pituitary-thyroid and hypothalamic-pituitary-adrenal axes, contributing to a biologic basis of depression.^{22,26}

Biologic theories. Two biologic theories have been considered as explanations for the pathophysiology of perimenopausal depression resulting from the multiple changes in reproductive endocrine function.^{22,27,28}

The first of these theories, the “estrogen-withdrawal theory,” proposes that the onset of a hypoestrogenic state exacerbates mood symptoms in perimenopausal women at risk for depression.²⁸ This theory has also been supported by the observation that women who undergo bilateral oophorectomy when premenopausal have higher rates of depression than those who experience natural menopause. Nonetheless, the higher rate of depression associated with surgical menopause cannot be attributed exclusively to abrupt estrogen withdrawal, since there is also a rapid decline in testosterone and progesterone levels, with complex reproductive hormonal changes.²⁷

The second biologic theory, termed the “domino theory,” proposes that somatic symptoms of the perimenopause (hot flashes and night sweats) lead to sleep disturbances and resultant fatigue which, in turn, cause daytime mood changes. In this theory, the ability of estrogen to improve mood is secondary to the alleviation of nocturnal hot flashes, which normalizes sleep.^{28,29} Recently, Schmidt et al²² demonstrated that estrogen replacement therapy (ERT) is an effective treatment for depressive symptoms in clinically depressed perimenopausal women who do not have hot flashes, and that this is independent of its salutary effects on vasomotor symptoms.³⁰

Pathophysiology of Depression: Gonadal Hormones

The pathophysiology of depression is currently thought to involve the dysregulation of several neurotransmitter and neuro-

modulatory systems, with abnormalities in the serotonin, noradrenergic, cholinergic, dopaminergic and gamma-aminobutyric acid (GABA) systems. These neurotransmitters also play a role in the mechanism of action of psychotropic drugs used to treat depression.³¹

Estrogen. The neurobiologic effects of estrogen include increased serotonergic (5-HT) postsynaptic responsivity and increased numbers of serotonergic receptors and levels of neurotransmitter uptake. Estrogen also increases 5-HT synthesis and, thereby, levels of 5-hydroxyindoleacetic acid, its main metabolite. Because it upregulates 5-HT1 receptors and downregulates 5-HT2 receptors, estrogen's cumulative effect on serotonergic function is actually as a 5-HT agonist.³²

Estrogen deficiency might decrease serotonergic activity with alteration of mood.¹⁰ Halbreich et al³³ showed that infusions of m-chlorophenylpiperazine (m-CPP), a serotonin agonist, resulted in blunted prolactin and cortisol responses in postmenopausal women. They concluded that some serotonergic functions are decreased in postmenopausal women, compared to those in women of reproductive age, and noted that the decreases not only occur because of age, but also are associated with decreased levels of estrogen.³²

Estrogen selectively increases norepinephrine (NE) activity in the brain; its effect on the enzyme tyrosine hydroxylase and on plasma levels of NE metabolite 3-methoxy, 4-hydroxyphenylglycol (MHPG) are mixed. Increased NE activity in the brain might be caused by decreased NE reuptake and decreased NE metabolism from inhibition of monoamine oxidase (MAO), and by decreased catechol-o-methyl transferase activity caused by estrogen. Estrogen also increases beta-adrenoreceptor binding.^{7,32}

Estrogen increases acetylcholine synthesis by increasing levels of acetylcholine transferase, and it helps to maintain dendritic spine density in the hippocampus. Estrogen also alters muscarinic re-

ceptor activity in the hypothalamic and preoptic areas,^{7,31} suggesting that the hormone might be protective against age-related decline in some cognitive functions.³²

Estrogen also decreases D2 receptors and, possibly, other dopaminergic receptors. Estrogen's influence is not limited to monoamines; it acts as a GABA adjunct agonist by increasing binding of GABA agonists and their upregulation of GABA receptors. Estrogen decreases the activity of glutamic acid decarboxylase in the hypothalamus, and its effects on endorphins are mixed.³²

The sum of estrogen's multiple effects on neural functions suggests an antidepressant effect that improves mood and behavior (Table 1).^{32,34} Estrogen, however, should not be considered an adequate antidepressant for the woman with a major mood disorder, given the lack of supporting clinical evidence.

Progesterone. While the addition of continuous combined or cyclical progesterone is needed to counteract the endometrial proliferative action of estrogens in ERT-treated women with a uterus, progesterone can induce dysphoric moods (mostly depression and anxiety) in some women.^{35,36} The depressant action of progesterone, in contrast to the activating effects of estrogen, is most likely related to its active metabolites, such as pregnenolone and allopregnenolone, which have anxiolytic, anesthetic and antiepileptic effects.^{35,36} These effects are related to the potent agonist effect on the brain GABA_A receptors^{31,35} and to enhancement of MAO activity, which might decrease catecholamine and serotonin levels.^{7,36}

These effects of progesterone are promising for the development of progestins as anxiolytic and antiepilepsy medications.³⁵ Nevertheless, not all postmenopausal women experience negative psychological effects during the progesterone phase of hormone replacement

therapy (HRT) regimens; this seems to depend upon the progesterone preparation used, the dosage ratio of progesterone to estrogen, and the use of cyclic versus continuous progesterone.^{7,12}

Androgens and dehydroepiandrosterone (DHEA). After menopause, total androgen production undergoes a 50% reduction in women with intact ovaries; women who undergo bilateral oophorectomy experience a reduction of more than 50%.³⁶ Although androgens have mood-enhancing properties and suppress hot flashes in men treated with gonadal suppression, data for women are not as clear.¹² Reports of androgen administration in surgically postmenopausal women indicate positive effects on libido, sexual performance and well-being.^{7,36} Dose-related side effects associated with androgen use in women (including acne, hirsutism, voice changes, weight gain and undesirable lipid profile changes) make their use intolerable for many women,^{12,36} but many others on very low androgen doses find the treatment helpful and do not complain of intolerable side effects.

DHEA and its sulfated conjugated metabolite dehydroepiandrosterone sulfate (DHEAS) are considered neuroactive steroids. Results from different studies suggest that DHEA might act upon the central nervous system via a direct effect on neuronal cells and through its conversion into other steroids.³⁶ DHEA

Table 1.
Neurotransmitter Involvement in Depression and Effects of Estrogen on Central Neurotransmitter Levels*

	Depression	Estrogen
Serotonin	↓	↑
Norepinephrine	↓	↑
GABA	↓	↑
Opioid	↓	↑
Dopamine	↓↑	↑↓
Beta-adrenergic receptors	↑	↓
MAO	↑	↓

GABA = gamma-aminobutyric acid; MAO = monoamine oxidase

*Adapted, in part, from Reference 34.

has been shown to be the only hormone positively related to well-being in women aged 40–60 years.³⁷ In the Rancho Bernardo Study,³⁸ involving 699 postmenopausal women not taking estrogen, plasma levels of sex hormones and mood level assessment showed that levels of DHEAS were inversely and independently associated with depressed mood. Another recent, double-blind, crossover treatment study³⁹ has shown DHEA as an effective treatment for midlife-onset dysthymia, with improvements in energy level, anhedonia, lack of motivation, emotional flattening, sadness, excessive worry and inability to cope. Future prospective studies should elucidate specific indications for DHEA replacement therapy, alone or in association with estrogen, for the treatment of postmenopause-related mood disorders.³⁶

Sexual Function, Menopause and Depression

Although satisfaction with sexual relationships is, in most women, unaffected by increasing age, sexual desire does decrease in both genders, and particularly in women in their late 40s and 50s.⁴⁰ There is also a reduction in the frequency of sexual activity and in sexual response with advancing age; this might be related, in part, to dyspareunia caused by vaginal dryness and skin sensitivity changes during menopause.⁴¹ While most postmenopausal women do not develop frank sexual dysfunction, mood changes, well-being and self-esteem might all be relevant to sexual adjustment associated with menopause.⁴¹

Short-term ERT has been shown to maintain vaginal lubrication, decrease vaginal atrophy and increase pelvic blood flow, with alleviation or prevention of dyspareunia.⁴² Adding testosterone to estrogen enhances some aspects of sexual function,^{37,43} with greater improvement of libido and ability to have an orgasm in women on HRT with estrogen plus androgens.⁴⁴

Sexual dysfunction also occurs in depressed women; it can be a symptom of depression itself, a side effect of medica-

tion, including antidepressants, or a sign of a comorbidity, such as an endocrine disorder. Sexual dysfunction can also occur as a primary disorder, or as a symptom of psychosocial factors, such as relationship difficulties or a history of sexual abuse.⁴⁵ Obviously, treatment of sexual dysfunction in these circumstances should be directed toward treatment of the underlying cause and might not necessitate the use of HRT.

Diagnosing Depression During the Perimenopause

The diagnostic dilemma. In many studies of the menopause, no distinction is made between an isolated depressed mood and the syndrome of depressive disorder. Depressed mood is a symptom familiar to everyone and is denoted by common expressions, such as “sadness” or “low spirits.” On the other hand, depressive disorder is a syndrome that is less common but far more serious.⁴⁶ Depressive disorder consists of depressed mood plus several

characteristic symptoms, including depressed affect, loss of interest in pleasurable activities, low energy, poor concentration, disturbed sleep, loss of sex drive and weight changes. In extreme cases patients can experience delusions of guilt and poverty and mood-congruent hallucinations. The diagnostic criteria for major depression, established in the DSM-IV, are described in Table 2.⁴ Depressive symptoms in men and women tend to be similar, but women appear more likely to present with atypical symptoms (Table 3),⁴ such as anxiety and somatic symptoms (headaches and stomach upsets), while men tend to report more weight loss.⁴⁷

During perimenopause, vasomotor and other physical symptoms, such as hot flashes, night sweats and disturbed sleep (Table 4),⁴⁸ can mimic symptoms of major depression, especially if accompanied by mood fluctuations or depressed mood. A population-based survey of women’s experience of menopause⁴⁸ found that the majority of women in the 45- to 54-year

Table 2.
DSM-IV Diagnostic Criteria for Major Depressive Episode*

Presence of the following symptoms during the same 2-week period, representing a change from previous functioning:

- Depressed mood or loss of interest/pleasure in all or almost all activities, most of the day, nearly every day
- At least four of the following symptoms nearly every day:
 - significant weight loss or gain, or decrease or increase in appetite
 - insomnia or hypersomnia
 - observable psychomotor agitation or retardation
 - fatigue or loss of energy
 - feelings of worthlessness or excessive or inappropriate guilt
 - diminished ability to think or concentrate
 - recurrent thoughts of death (not fear of dying) or suicidal ideation, suicide attempt or plan
- Symptoms do not meet criteria for a mixed episode (manic and depressive episodes).
- Symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
- Symptoms are not due to the direct physiologic effects of a substance (drug of abuse, medication) or a general medical condition.
- Symptoms are not better accounted for by bereavement.

*Adapted from Reference 4.

Table 3.
DSM-IV Criteria for Atypical Features of Depression*

- Mood reactivity (mood brightens in response to positive events)
- Weight gain or increase in appetite
- Hypersomnia
- Leaden paralysis (heavy feelings in arms or legs)
- Interpersonal rejection sensitivity (long-standing)
- Absence of melancholic or catatonic features

*Adapted from Reference 4.

age group experience symptoms associated with the menopause, but relatively few define individual symptoms as a problem. For example, hot flashes and night sweats were experienced by 57% but defined as a problem by only 22%. A combination of classic, somatic and psychological symptoms might, however, constitute a considerable problem.

A good example of the overlap between the syndrome of major depression and vasomotor symptoms of the perimenopause is sleep disruption. The sleep of perimenopausal women is significantly more disrupted than that of age-matched controls, with sleep disruption and specific mood scales of perimenopausal subjects found to be significantly correlated.⁴⁹ These findings suggest that sleep disruption might play a role in mediating some mood and anxiety changes associated with menopause.

Differentiating between the symptom and the syndrome is more than just an academic exercise, since the implications for treatment are different. While antidepressants play a well-documented role in the treatment of full-blown disorders of mood, estrogen is much better documented to improve mood and well-being in nondepressed peri- and postmenopausal women. Estrogen's antidepressant effects are less robust than those of tradi-

Table 4.
Women's Experience of Menopausal Symptoms*

Classic	Somatic	Psychological
Hot flashes	Aching/painful joints	Irritability
Night sweats	Headaches	Concentration problem
Sleep problems	Sore breasts	Memory problem
Dry/sore vagina	Nocturia	Anxiety
	Palpitations	Depression
	Dizziness	Feeling unable to cope

*Adapted from reference 48.

tional antidepressant agents in women meeting criteria for a major depressive disorder,³¹ but the hormone might help boost the effects of these antidepressants.

The situation becomes more complicated when a self-reported history of medically treated depression is identified as a potential risk factor for early menopause, with the possibility of depression being implicated as a marker for ovarian dysfunction. This has been suggested by findings from the case-controlled study conducted by Harlow et al,⁵⁰ comparing naturally menopausal women under age 40 and those between the ages of 40 and 46 to a random control sample of premenopausal and naturally menopausal women over age 47.

Clinical evaluation. As stated previously, diagnosis of perimenopause-related depression is made in a manner identical to that for depression occurring at other periods during the life cycle.²³ Given the dilemma of differentiating symptoms of depression from perimenopausal vasomotor symptoms, modified clinical strategies, such as those described below, should be employed.

1. A careful history should be obtained at all times and should include the following:
 - determination of the patient's reproductive life-cycle status;
 - evaluation for past history of mood disorders, especially in relation to

reproductive life events (premenstrual period, pregnancy, postpartum);

- assessment of health and social circumstances;³¹
- assessment of the frequency of estrogen-sensitive somatic symptoms, such as hot flashes, which might predict the effectiveness of ERT in treating mood and behavioral symptoms;
- identification of potential risk factors for heart disease or osteoporosis, which could suggest a potential need for ERT; and
- awareness of the presence of contraindications to estrogen replacement, such as a personal or family history of breast cancer.²³

2. Perimenopause and hypoestrogenism should be established with FSH measures in women over 40 seeking treatment for depression or menopausal symptoms.²³ This should be performed in the early follicular phase; if FSH is repeatedly higher than 20 IU/L, a perimenopause state may be confirmed.
3. Standardized mood-rating scales should be employed,²² such as the Hamilton Depression Rating Scale (Ham-D)⁵¹ and the Inventory for Depressive Symptomatology (IDS).⁵² Daily symptom rating should be employed to help identify the prominence of perimenopause-related somatic symptoms (such as hot flashes) in perimenopausal depression, and their response to treatment.²³

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4. Finally, diagnostic tests should include those that will facilitate the differential diagnosis of depression during the perimenopause, such as thyroid-stimulating hormone (TSH) and free T4 levels, a complete blood count and measures of plasma prolactin to rule out associated causes of menstrual cycle irregularities. Pregnancy must also be ruled out.²³

Interventions and the Role of HRT

From what is known to date, intervention for a major depressive disorder occurring around the time of menopause should employ the use of standard treatments for depression.^{10,31} These treatments include education, psychosocial interventions, psychotherapy, pharmacotherapy with antidepressant medications, and electroconvulsive therapy. Cognitive behavioral therapy and interpersonal psychotherapy are two examples of psychotherapies for mild to moderate depression.

Antidepressants. Several antidepressant medications are available for treatment of major depression; these include selective serotonin reuptake inhibitors, tricyclic antidepressants, MAO inhibitors and the newer-generation antidepressants (bupropion, venlafaxine, nefazodone and mirtazapine), all of which have different mechanisms of action, dose ranges and side effect profiles. Several factors are involved in selecting the appropriate antidepressant medication for treatment of depression; these factors include, but are not limited to, the patient's demographics, symptoms, past history, comorbid conditions, previous response to treatment, drug-drug interactions and side effect profiles.

Estrogen as treatment for depression. The efficacy of estrogen in the treatment of perimenopausal depression was suggested as early as the 19th century by reports of symptomatic reduction following administration of ovarian extracts by organotherapists.⁵³ The first controlled trial of estrogen (Theelin injection) for depression treatment appeared in 1934, just following the isolation of estrogen, and

documented the superior efficacy of the hormone, compared to placebo.⁵³ Nevertheless, the efficacy of estrogen alone for depression occurring around the time of menopause has not been supported.¹⁰ Very high doses of estrogen (Premarin, 25 mg maximum), associated with intolerable side effects in pre- and postmenopausal patients, was found to reduce, but not completely alleviate, self-reported mood symptoms in severely depressed women.²⁴ Most studies have shown that estrogen does not have impressive antidepressant properties when used as monotherapy for major depressive disorders.³¹

A meta-analysis of 111 articles⁴³ on psychological symptoms of naturally or surgically menopausal women who were subsequently treated with HRT led the authors to conclude that there was not a clear positive correlation between HRT use and psychological improvement. The meta-analysis did suggest that there was evidence supporting improvement of psychological symptoms with the use of ERT in women who had undergone surgical menopause for benign conditions.⁴³ This finding complements those of numerous studies showing estrogen to be an effective stabilizer of mood, improving the sense of well-being in postmenopausal women who do not have a major depressive disorder.⁵⁴ Nevertheless, recent studies have shown estrogen's efficacy in the treatment of depression in perimenopausal women, independent of its effect on vasomotor symptoms³⁰ and in the absence of a history of hot flashes.⁵³

Anecdotal reports suggest that estrogen might also have a role as an adjunct to antidepressants in the treatment of postmenopausal women with major depression that is resistant to antidepressant therapy.³⁵ The routine use of estrogen as an adjunct to traditional antidepressant therapy has not yet, however, been supported in a double-blind, placebo-controlled study.⁵⁴

In conclusion, a trial of ERT is an appropriate first step for perimenopausal women with mild depression and promi-

nent vasomotor symptoms, in the absence of a prior psychiatric history.^{11,31} For an episode of full syndromal major depression in a perimenopausal woman with no prior psychiatric history, it is best to initially use standard treatments with antidepressants and psychotherapy.^{11,31} For a major depressive episode in a perimenopausal woman with a history of recurrent major depressive episodes, using standard antidepressants and psychotherapy is the rule. Also, obtaining a history of prior responses to previous antidepressant treatments and use of ERT for vasomotor symptoms and long-term consequences of menopause (such as osteoporosis and heart disease) should also be considered.³¹ For perimenopausal or postmenopausal women with treatment-resistant depression, augmentation therapy with estrogen has been suggested.⁵⁵

Summary

Depressive disorders have greater lifetime prevalence in women than in men, with an increased risk of depression during women's reproductive years. The climacteric is a time of significant biologic, psychological and social changes. Perimenopause is a vulnerable period that might be associated with an increased risk of developing a major depressive disorder in some women, particularly if they are prone to mood changes from hormonal fluctuations.

Changes in the levels of estrogen, progesterone and androgens during perimenopause cause somatic and psychological symptoms that can compromise mood, libido, sexual function and behavior. It can sometimes be difficult to differentiate between these symptoms and the manifestations of depressive disorders.

The neurobiology of gonadal hormones and their interactions with neurotransmitters (serotonergic, noradrenergic, dopaminergic, cholinergic and GABA-ergic) might have etiologic, diagnostic and treatment implications for the pathophysiology of depression.

The diagnosis of depressive disorders during perimenopause can be difficult because of the overlap between the somatic and mood symptoms of menopause and those of depression. Evaluation for depression during the climacteric should include a detailed history in the context of the reproductive life cycle, biologic confirmation of perimenopausal or postmenopausal status, and the use of standardized mood rating scales and other tests to clarify the clinical diagnosis.

While antidepressants and/or psychotherapy remain the gold standard for treatment of depressive disorders, and ERT has a role in protection against osteoporosis and heart disease in postmenopausal women, ERT and HRT might also have a role in augmentation of antidepressant medications in treatment-resistant depressive disorders in menopausal women. ■

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References

- Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8-19.
- Weissman MM, Bland RC, Canino GJ. Cross-national epidemiology of major depression and bipolar disorder. *JAMA* 1996;276:293-9.
- Robins LN, Regier DA, editors. *Psychiatric disorders in America: The Epidemiologic Catchment Area Study*. New York: Free Press, 1991.
- American Psychiatric Association. DSM-IV: *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC: American Psychiatric Association, 1994.
- Leibenluft E. Women with bipolar illness: Clinical and research issues. *Am J Psychiatry* 1996;153:163-73.
- Kessler RC, McGonagle KA, Swartz M, et al. Sex and depression in the National Comorbidity Survey. I. Lifetime prevalence, chronicity, and recurrence. *J Affect Disord (Netherlands)* 1993;29(2-3):85-96.
- Pearlstein T, Rosen K, Stone AB. Mood disorders and menopause. *Endocrinol Metab Clin N Am* 1997;26(2):279-94.
- Endicott J. The menstrual cycle and mood disorders. *J Affect Disord* 1993;29:193-200.
- Blehar MC, Oren DA. Women's increased vulnerability to mood disorders: Integrating psychobiology and epidemiology. *Depression* 1995;3:3-12.
- Haynes P, Parry B. Mood disorders and the reproductive cycle: Affective disorders during the menopause and premenstrual dysphoric disorder. *Psychopharmacol Bull* 1998;34(3):313-18.
- Utian WH. Menopause-related terminology, definitions. *Climacteric* 1999;2:284-6.
- Dell DL, Stewart DE. Menopause and mood. Is depression linked with hormone changes? *Postgrad Med* 2000;108(3):34-6,39-43.
- American Psychiatric Association. DSM-II: *Diagnostic and statistical manual of mental disorders*. 2nd ed. Washington, DC: American Psychiatric Association, 1968.
- American Psychiatric Association. DSM-III: *Diagnostic and statistical manual of mental disorders*. 3rd ed. Washington, DC: American Psychiatric Association, 1980.
- American Psychiatric Association. DSM-III-R: *Diagnostic and statistical manual of mental disorders*. 3rd rev. ed. Washington, DC: American Psychiatric Association, 1987.
- Chatel A, Fugere P, Bissonnette F, et al. Psychological distress and sexuality in a group of women attending a menopause clinic: Effect of hormonal replacement therapy. *Menopause* 1996;3:165-71.
- Hay AG, Bancroft J, Johnstone EC. Affective symptoms in women attending a menopause clinic. *Br J Psychiatry* 1994;164:513-16.
- Maoz B, Shiber A, Lazer S, et al. The prevalence of psychological distress among postmenopausal women attending a menopause clinic and the effect of hormone replacement therapy on their mental state. *Menopause* 1994;1:137-41.
- Avis NE, Brambilla D, McKinlay SM, et al. A longitudinal analysis of the association between menopause and depression. Results from the Massachusetts Women's Health Study. *Ann Epidemiol* 1994;4:214-20.
- Ballinger CB. Psychiatric aspects of the menopause. *Br J Psychiatry* 1990;156:773-87.
- Nicol-Smith L. Causality, menopause, and depression: A critical review of the literature. *BMJ* 1996;313:1229-32.
- Schmidt PJ, Roca CA, Bloch M, et al. The perimenopause and affective disorders. *Sem Reprod Endocrinol* 1997;15(1):91-100.
- Schmidt PJ, Roca CA, Rubinow DR. Clinical evaluation in studies of perimenopausal women: Position paper. *Psychopharmacol Bull* 1998;34(3):309-11.
- Klaiber EL, Broverman DM, Vogel W, et al. Estrogen therapy for severe persistent depressions in women. *Arch Gen Psychiatry* 1979;36:550-4.
- Kornstein SG. Gender differences in depression: Implications for treatment. *J Clin Psychiatry* 1997;58(Suppl 15):12-18.
- Desai HD, Jann MW. Major depression in women: A review of the literature. *J Am Pharm Assoc* 2000;40:525-37.
- Joffe H, Cohen LS. Estrogen, serotonin, and mood disturbance: Where is the therapeutic bridge? *Biol Psychiatry* 1998;44:798-811.
- Schmidt PJ, Rubinow DR. Menopause-related affective disorders: A justification for further study. *Am J Psychiatry* 1994;148:844-52.
- Campbell S, Whitehead M. Estrogen therapy and menopausal syndrome. *Clin Obstet Gynecol* 1997;4:31-47.
- Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: A preliminary report. *Am J Obstet Gynecol* 2000;183(2):414-20.
- Stahl SM. Basic psychopharmacology of antidepressants, part 2: Estrogen as an adjunct to antidepressant treatment. *J Clin Psychiatry* 1998;59(Suppl 4):15-24.
- Halbreich U. Role of estrogen in postmenopausal depression. *Neurology* 1997;48(Suppl 7):S16-20.
- Halbreich U, Rojansky N, Palter S, et al. Estrogen augments serotonergic activity in postmenopausal women. *Biol Psychiatry* 1995;37:434-41.
- Archer JS. Relationship between estrogen, serotonin and depression. *Menopause* 1999;6:71-8.
- Halbreich U. Hormonal interventions with psychopharmacological potential: An overview. *Psychopharmacol Bull* 1997;33(2):281-6.
- Genazzani AR, Spinetti A, Gallo R, et al. Menopause and the central nervous system: Intervention options. *Maturitas* 1999;31:103-10.
- Cawood EH, Bancroft J. Steroid hormones, the menopause, sexuality and well-being of women. *Psychological Med* 1996;26:925-36.
- Barrett-Connor E, Mühlen DV, Laughlin GA, et al. Endogenous levels of dehydroepiandrosterone sulfate, but not other sex hormones, are associated with depressed mood in older women: The Rancho Bernardo Study. *J Am Geriatr Soc* 1999;47:685-91.
- Bloch M, Schmidt PJ, Danaceau MA, et al. Dehydroepiandrosterone treatment of midlife dysthymia. *Biol Psychiatry* 1999;45:1533-41.
- Hawton K, Gath D, Day A. Sexual function in a community sample of middle-aged women with partners: Effects of age, marital, socioeconomic, psychiatric, gynecological and menopausal factors. *Arch Sex Behav* 1994;23(4):375-95.
- Pearce M, Hawton K. Psychological and sexual aspects of the menopause and HRT. *Baillieres Clin Obstet Gynecol* 1996;10(3):385-99.
- Sarrel PM. Sexuality and menopause. *Obstet Gynecol* 1990;75(Suppl):26S-30S.
- Pearce J, Hawton K, Blake F. Psychological and sexual symptoms associated with the menopause and the effects of hormone replacement therapy. *Br J Psychiatry* 1995;167:163-73.
- Sarrel PM. Psychosexual effects of menopause: Role of androgens. *Am J Obstet Gynecol* 1999;180:S319-24.
- Kornstein S, McEnany G. Enhancing pharmacologic effects in the treatment of depression in women. *J Clin Psychiatry* 2000;61(Suppl 11):18-27.
- Gath D. The assessment of depression in perimenopausal women. *Maturitas* 1998;29:33-9.
- Kornstein SG, Schatzberg AF, Yonkers KA, et al. Gender differences in presentation of chronic major depression. *Psychopharmacol Bull* 1996;31:711-18.
- Porter M, Penney GC, Russell D, et al. A population based survey of women's experience of the menopause. *Br J Obstet Gynecol* 1996;103:1025-8.
- Baker A, Simpson S, Dawson D. Sleep disruption and mood changes associated with menopause. *J Psychosomat Res* 1997;43(4):359-69.
- Harlow BL, Cramer DW, Annis KM. Association of medically treated depression and age at natural menopause. *Am J Epidemiol* 1995;141:1170-6.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.
- Rush AJ, Gullion CM, Basco MR, et al. The inventory of depressive symptomatology (IDS): Psychometric properties. *Psychol Med* 1996;26:477-86.
- Rubinow DR, Schmidt PJ, Roca CA. Estrogen-serotonin interactions: Implications for affective regulation. *Biol Psychiatry* 1998;44:839-50.
- Stahl SM. Augmentation of antidepressants by estrogen. *Psychopharmacol Bull* 1998;34(3):319-21.
- Schneider LS, Small GW, Hamilton S, et al. Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. *Am J Geriatr Psychiatry* 1997;5:97-106.