Hormones, antidepressants, or psychotherapy—what would you recommend?

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Symptoms of perimenopausal depression are not inherently different from those of depression diagnosed at any other time in life, but they present in a unique context:

• Hormonal fluctuations may persist for a long duration.
• Women experiencing hormonal fluctuations may be vulnerable to mood problems.
• Psychosocial/psychodynamic stressors often complicate this life transition.

Managing perimenopausal depression has become more complicated since the Women’s Health Initiative (WHI) studies found fewer benefits and greater risks with hormone replacement therapy (HRT) than had been perceived. This article discusses the clinical presentation of perimenopausal depression, its risk factors, and treatment options in post-WHI psychiatric practice.

Who is at risk?

Perimenopausal depression is diagnosed when onset of major depressive disorder (MDD) is associated with menstrual cycle irregularity and/or somatic symptoms of the menopausal transition. Diagnosis is based on the overall clinical picture, and treatment requires a thoughtful exploration of the complex relationship between hormonal function and mood regulation.

Presentation. For many women, perimenopause is characterized by mild to severe vasomotor, cognitive, and mood symptoms (Table 1, page 40). Thus, in your workup of depression in midlife women,
document somatic symptoms—such as hot flushes, vaginal dryness, and incontinence—and affective/behavioral symptoms such as mood and sleep disturbances.

Explore psychiatric and medical histories of your patient and her close relatives. Ask about depression, dysthymia, hypomania, or mood fluctuations around hormonal events such as menses, pregnancy, postpartum, or starting/stopping oral contraceptives. In the differential diagnosis, consider:

- Does the patient have another medical illness (such as thyroid disorder) with symptoms similar to depression?
- Is low mood secondary to anxiety or another psychiatric disorder?

**Screening.** Menopause is considered to have been reached after 12 months of amenorrhea not due to another cause. Median ages for this transition in the United States are 47.5 for perimenopause and 51 for menopause, with an average of 8 years between regular cycles and amenorrhea.\(^7\) Therefore, begin talking with women about perimenopausal symptoms when they turn 40.

Evidence supports screening perimenopausal women for depressive symptoms even when their primary complaints are vasomotor. The Greene Climacteric Scale\(^8\) is convenient for quantifying and monitoring perimenopausal symptoms. It includes depressive symptoms plus physical and cognitive markers. The Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR)\(^4\) questionnaire:

- takes minutes to complete
- is easy to score
- quantitates the number and severity of depressive symptoms (see Related Resources, page 50).

### Table 1

**Vasomotor, cognitive, and mood symptoms of perimenopause**

<table>
<thead>
<tr>
<th>Vasomotor</th>
<th>Cognitive and mood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
<td>Decreased concentration</td>
</tr>
<tr>
<td>Sweating</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Heart palpitations</td>
<td>Irritability</td>
</tr>
<tr>
<td>Painful intercourse</td>
<td>Mood lability</td>
</tr>
<tr>
<td>Vaginal dryness and discomfort</td>
<td>Memory difficulty</td>
</tr>
<tr>
<td>Sleep disruption</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2

**Risk factors for depression in women**

<table>
<thead>
<tr>
<th>Predictive over lifetime</th>
<th>High risk during menopausal transition</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of depression</td>
<td>History of PMS, perinatal depression, mood symptoms associated with contraceptives</td>
</tr>
<tr>
<td>Family history of affective disorders</td>
<td>Premature or surgical menopause</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Lengthy menopausal transition (&gt;27 months)</td>
</tr>
<tr>
<td>Reduced physical activities</td>
<td>Persistent and/or severe vasomotor symptoms</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Negative attitudes toward menopause and aging</td>
</tr>
<tr>
<td>Less education</td>
<td></td>
</tr>
<tr>
<td>Perceived lower economic status</td>
<td></td>
</tr>
<tr>
<td>Perceived lower social support</td>
<td></td>
</tr>
<tr>
<td>Perceived lower health status</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Stressful life events</td>
<td></td>
</tr>
<tr>
<td>History of trauma</td>
<td></td>
</tr>
<tr>
<td>Marital dissatisfaction</td>
<td></td>
</tr>
<tr>
<td>PMS: Premenstrual syndrome</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Point**

Evidence supports screening for perimenopausal depression even when primary complaints are vasomotor
Psychosocial factors can predict depression at any time in life, but some are specific to the menopausal transition (Table 2). The “empty nest syndrome,” for example, is often used to explain depressive symptoms in midlife mothers, but no evidence links mood lability with the maturation and departure of children. What may be more stressing for women is supporting adolescents/young adults in their exit to independence while caring for aging parents.

Sociocultural beliefs about sexuality and menopause may play a role in how your patient experiences and reports her symptoms. In some cultures, menopause elevates a woman’s social status and is associated with increased respect and authority. In others, such as Western societies that emphasize youth and beauty, women may view menopause and its physical changes in a negative light.

Therefore, give careful attention to the psychosocial context of menopause to your patient and the social resources available to her. Questions to ask include:
- Has your lifestyle changed recently?
- Have your husband, family members, or close friends noticed any changes in your functioning?
- Is there anyone in your life that you feel comfortable confiding in?

Explaining the complexity of this life transition may ease her anxiety by normalizing her experience, helping her understand her symptoms, and validating her distress.

**What might be the cause?**

Although the exact pathophysiology of perimenopausal depression is unknown, hormonal changes, general health, the experience of menopause, and the psychosocial context likely work together to increase vulnerability for depressive symptoms (Figure).

**Hormonal fluctuation.** The estrogen withdrawal theory explains depressive symptoms as resulting from a sustained decline in ovarian estrogen in tandem with spiking secretions of follicle-stimulating hormone by the pituitary. The finding that women with surgical menopause have a higher incidence of depressive symptoms than women with natural menopause supports this hypothesis.

Mood disorders occur across various female reproductive events, and increased risk appears to be associated with fluctuating gonadal hormones. Thus, declining estrogen may be less causative of perimenopausal depression than extreme fluctuations in estradiol activity.

Estrogen interacts with dopamine, noradrenaline, beta-endorphin, and serotonin metabolism. In particular, estrogen

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**Figure**

**Biopsychosocial milieu of depression during perimenopause**

Hormonal fluctuation; hot flushes and night sweats; disrupted sleep; painful intercourse

Personality characteristics; perceptions of menopause and aging

Biological

Psychological

Social

Structural family changes; social support; losses in peers and extended family

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Clinical Point

No evidence supports the ‘empty nest syndrome,’ linking mood lability with the maturation and departure of a woman’s children.
Perimenopausal depression facilitates serotonin delivery to neurons across the brain. These findings—and the success of selective serotonin reuptake inhibitors (SSRIs) in treating mood disorders—support the theory that fluctuating estrogen affects the serotonergic system and may cause depressive symptoms.

‘Domino theory.’ Others have hypothesized that depressive symptoms are the secondhand result of somatic symptoms of perimenopause. In a “domino effect,” hot flushes and night sweats disrupt women’s sleep, bringing fatigue and impaired daytime concentration, which lead to irritability and feelings of being overwhelmed. This theory, which incorporates perimenopausal hormone changes, is supported by elevated levels of depression in women who report frequent and intense vasomotor symptoms persisting >27 months.

The psychosocial theory suggests that depression results from increased stress or adverse events. Midlife women with depressive symptoms report many possible sources of stress:

- demanding jobs
- family responsibilities
- dual demands of career and family
- little time for self
- poverty or employment stressors
- not enough sleep
- changing social relationships.

Negative interpretations of aging or the menopausal transition also have been implicated in cross-cultural studies. The predictive nature of psychosocial issues for depression during perimenopause supports this theory.

Evidence-based treatment

HRT. Research and clinical reports suggest that estrogen may have antidepressant effects, either alone or as an adjunct to antidepressant medication. Before the WHI studies, expert consensus guidelines on treating depression in women recommended HRT as first-line treatment for patients experiencing a first lifetime onset of mild to moderate depression during perimenopause. WHI findings since 2002 that associated HRT with increased risk of stroke, deep vein thrombosis, and pulmonary embolism—without clear protection against coronary heart disease or cognitive decline—have left HRT a controversial option for treating perimenopausal depression. In the WHI trials:

- 10,739 postmenopausal women age 50 to 79 without a uterus received unopposed conjugated equine estrogens, 0.625 mg/d, or placebo for an average 6.8 years.
- 16,608 postmenopausal women age 50 to 79 with an intact uterus received combination HRT (conjugated equine estrogens, 0.625 mg/d, plus 2.5 mg of medroxyprogesterone), or placebo for an average 5.6 years.

The study using combination HRT found increased risks of breast cancer, ischemic stroke, blood clots, and coronary heart disease. A follow-up study showed that vasomotor symptoms returned in more than one-half the women after they stopped using combination HRT.

A companion WHI trial found that estrogen, 0.625 mg/d—given unopposed or with a progestin—did not prevent cognitive decline in women age 65 to 79 and may have been associated with a slightly greater risk of probable dementia.

The FDA recommends that women who want to use HRT to control menopausal symptoms use the lowest effective dose for the shortest time necessary.

Antidepressants. SSRIs may be more useful than estrogen for producing MDD remission in perimenopausal women. SSRIs and other psychotropics may reduce perimenopausal vasomotor symptoms in addition to addressing depressive symptoms (Table 3). When choosing antidepressant therapy, consider the patient’s dominant presenting perimenopausal symptoms and side effects associated with treatment.

Nonpharmacologic interventions are viable options for women who are reluctant to begin HRT or psychotropics.

Psychotherapy. Interpersonal psychotherapy (IPT) and cognitive-behavioral therapy (CBT) have been recommended to address psychosocial elements of perimenopausal mood lability. For women with climacteric
Table 3
Nonhormone medications for perimenopausal depression: Evidence-based dosages and target symptoms

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage effective for perimenopausal depression</th>
<th>Symptoms assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram‡</td>
<td>40 to 60 mg</td>
<td>Depressive and vasomotor</td>
</tr>
<tr>
<td>Escitalopram‡</td>
<td>5 to 20 mg</td>
<td>Depressive and vasomotor</td>
</tr>
<tr>
<td>Fluoxetine‡</td>
<td>20 to 40 mg</td>
<td>Depressive and vasomotor</td>
</tr>
<tr>
<td>Paroxetine‡</td>
<td>12.5 or 25 mg</td>
<td>Depressive and vasomotor</td>
</tr>
<tr>
<td>Sertraline‡</td>
<td>100 mg</td>
<td>Depressive and vasomotor</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine‡</td>
<td>60 to 120 mg</td>
<td>Depressive and vasomotor</td>
</tr>
<tr>
<td>Venlafaxine‡</td>
<td>75 to 225 mg</td>
<td>Depressive and vasomotor</td>
</tr>
<tr>
<td>Mirtazapine‡</td>
<td>30 to 60 mg</td>
<td>Severe depressive symptoms; used as an adjunct to estrogen</td>
</tr>
<tr>
<td>Hypnotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem†</td>
<td>5 to 10 mg</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Other anticonvulsants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin‡</td>
<td>300 to 900 mg</td>
<td>Vasomotor</td>
</tr>
</tbody>
</table>

SSRIs: selective serotonin reuptake inhibitors

Source: For reference citations, see this article on CurrentPsychiatry.com

If a patient has had a good response with an antidepressant in the past, consider starting with that medication.

Clinical recommendations
Explore options with your patient; discuss side effects, risks, and expected minimum duration of treatment. Antidepressants, hormonal therapies, psychotherapy, and complementary and alternative treatments each might have a role in managing perimenopausal depression. A patient’s preferences, psychiatric history, and depression severity help determine which options to consider and in what order. How she responded to past treatments also can help you individualize a plan.

HRT may be appropriate for women who express a preference for HRT, have responded well to past hormone therapy, and have no personal history or high-risk

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factors for breast cancer. Based on the WHI findings, we consider a history of breast cancer in the patient or a first- or second-degree relative a contraindication to HRT.

Estrogen can be used alone or with an antidepressant. Studies support 17β-estradiol, 0.1 to 0.3 mg/d, for 8 to 12 weeks. Concomitant progesterone may be indicated to offset the effects of unopposed estrogen in women with an intact uterus. This option calls for an informed discussion with the patient about risks and benefits.

No data support long-term use of estrogen for recurrent or chronic depression. Because HRT’s risks and benefits vary with the length of exposure, individualize the extended use of estrogen solely to augment treatment for depression. Because vasomotor symptoms may recur when HRT is discontinued, we recommend that women make an informed decision in consultation with a gynecologist or primary care physician.

Antidepressants that have serotonergic activity—such as SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs)—appear most promising for treating comorbid depressive and vasomotor symptoms. If a patient has had a good response to an antidepressant in the past, consider starting with that medication.

Common antidepressant side effects are difficult to assess in perimenopausal patients with MDD because the symptoms attributed to antidepressant side effects—such as low libido, sleep disturbance, and weight changes—also can be caused by mood disorders and hormonal changes. Therefore, inquire about these symptoms when you initiate antidepressant therapy and at follow-up assessments.

Psychotherapy. We recommend that all women who present with perimenopausal depression receive information about psychotherapy. Psychotherapy alone often is adequate for mild depression, and adding psychotherapy to antidepressant treatment usually enhances recovery from moderate and severe depression episodes. In addition, patients who engage in psychotherapy for depression may have a lower rate of relapse.

Individual psychotherapy can help patients with perimenopausal depression:

• accept this life transition
• recognize the benefits of menopause, such as no need for contraception
• develop awareness of personal potential in the years ahead

Because depression often occurs in an interpersonal context, consider including family members in psychotherapy to improve the patient’s interpersonal support.

Integrative therapies. A full evaluation and consideration of standard treatment options is indicated for all women with MDD. Integrative medicine appeals to many patients but has not been sufficiently studied for perimenopausal depression. Supplemental omega-3 fatty acids and folate are reasonable adjuncts to the treatment of MDD and deserve study in perimenopausal MDD.
Perimenopausal depression

3.  Greene JG. Constructing a standard climacteric scale. 


References

Greene Climacteric Scale. www.menopausematters.co.uk/greenscale.php.

Quick Inventory of Depressive Symptomatology. www.ids-qids.org.


Clinical Point

Integrative medicine appeals to many patients but has not been sufficiently studied in perimenopausal depression

Bottom Line

Screen women over age 40 for coexisting depressive and vasomotor symptoms. No data support the long-term use of HRT for recurrent or chronic depression. Antidepressants with serotonergic activity appear to be the most promising treatment. Make collaborative decisions based on the patient’s medical and psychiatric history, psychological characteristics, and psychosocial supports.

Related Resources

- Greene Climacteric Scale. www.menopausematters.co.uk/greenscale.php.

Drug Brand Names

- Citalopram - Celexa
- Duloxetine - Cymbalta
- Escitalopram - Lexapro
- Estradiol - various
- Eszopiclone - Lunesta
- Fluoxetine - Prozac
- Gabapentin - Neurontin
- Medroxyprogesterone - Provera
- Mirtazapine - Remeron
- Paroxetine - Paxil
- Sertaline - Zoloft
- Venlafaxine - Effexor
- Zolpidem - Ambien

Disclosures

Dr. Brandon and Dr. ShivaKumar report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Dr. Freeman receives research support from GlaxoSmithKline, Forest Pharmaceuticals, and Eli Lilly and Company. She was associate professor of psychiatry at the University of Texas Southwestern Medical Center at Dallas when this article was written and is now on the faculty at Harvard Medical School and Massachusetts General Hospital, Boston.


19. Soares CN, Arsenio H, Joffe H, et al. Escitalopram versus ethinyl estradiol and norethindrone acetate for symptomatic...