

# Menopause and Mood Disorders

Medscape: Author: Stacey B Gramann, DO, MPH; Chief Editor: Stephen Soreff, MD

## Background

Menopause is the permanent cessation of menstruation resulting in the loss of ovarian follicle development. It is considered to occur when 12 menstrual cycles are missed.<sup>[1,2]</sup>

Menopausal transition, or perimenopause, is a defined period of time beginning with the onset of irregular menstrual cycles until the last menstrual period, and is marked by fluctuations in reproductive hormones.<sup>[3]</sup> This period is characterized by menstrual irregularities; prolonged and heavy menstruation intermixed with episodes of [amenorrhea](#), [decreased fertility](#), vasomotor symptoms; and insomnia. Some of these symptoms may emerge 4 years before menses ceases, with a perimenopausal mean age of onset of 47.5 years.<sup>[4]</sup> During the menopausal transition, estrogen levels decline and levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) increase. Postmenopause is the phase following the last menstrual period.

## Depression during menopause

In the United States, 1.3 million women reach menopause annually. Although most women transition to [menopause](#) without experiencing psychiatric problems, an estimated 20% have [depression](#) at some point during menopause.<sup>[5]</sup>

Studies of mood during menopause have generally revealed an increased risk of depression during perimenopause with a decrease in risk during postmenopausal years.

The Penn Ovarian Aging Study, a cohort study, showed depressive symptoms increased during the menopausal transition, and decreased after menopause. The strongest predictors of depressed mood was a prior history of depression, along with fluctuations in reproductive hormone levels associated with depressed mood.<sup>[6]</sup>

In a cross-sectional population survey from the Netherlands, 2103 women were asked to rate their symptoms of depression before menopause and 3.5 years later, during the menopausal transition. The women experienced most symptoms of depression during the menopausal transition. In the United States, a study of a community sample of women undergoing natural menopause also demonstrated an increase in depressive symptoms during perimenopause.<sup>[7]</sup>

Investigators from the Harvard Study of Moods and Cycles recruited premenopausal women aged 36-44 years with no history of major depression and followed up these women for 9 years to detect new onsets of major depression. Women who entered perimenopause were twice as likely as women who had not yet made the menopausal transition to have clinically significant depressive symptoms.<sup>[8]</sup>

Recent research has shown that reproductive hormones produced during menopause contribute to mood alterations, such as depression. Higher testosterone levels may directly lead to higher depressive symptoms during the menopausal transition. Menopausal status, however, remains an independent predictor of depressive symptoms.<sup>[9]</sup>

## Problems with sleep during menopause

[Insomnia](#) occurs in 40-50% of women during the menopausal transition, and problems with sleep may or may not be connected to mood disorders.<sup>[10]</sup> Women with insomnia are more likely than others to report problems such as [anxiety](#), [stress](#), tension, and depressive symptoms.

Sleep disturbances during menopause have been associated with estrogen deficiency, as exogenous estrogen has been shown to improve both subjective and objective sleep, attributed to a decrease in hot flashes. A recent study proposed elevated LH levels during late menopause produce poor sleep quality through a thermoregulatory mechanism, resulting in high core body temperatures.<sup>[11]</sup> Whether the [sleep problems](#) are associated with age-related changes in sleep architecture, hormonal status, or other symptoms of menopause (eg, vasomotor symptoms) is unclear. However, in the Medical Research Council National Survey of Health, women who were transitioning into menopause were more likely to report severe sleep difficulty compared with women who were premenopausal.<sup>[12]</sup>

Rates of [sleep apnea](#) increase with age, rising from 6.5% in women aged 30-39 years to 16% in women aged 50-60 years. The pathophysiology is not known, but theories include a relationship to postmenopausal weight gain or to decreased progesterone levels because progesterone stimulates respiration.<sup>[13, 14]</sup> In addition to undergoing changes in estrogen and progesterone levels, postmenopausal women experience a decline in melatonin and [growth hormone](#) levels, both of which have effects on sleep.<sup>[15]</sup>

## Schizophrenia during menopause

In most cases, [schizophrenia](#) first manifests in young adulthood, with the rate of new cases declining in both male and female individuals after early adulthood. A second peak in the incidence of schizophrenia is noted among women aged 45-50 years; this second peak is not observed in men.<sup>[16]</sup>

Some researchers have observed a worsening of the course of schizophrenia in women during the menopausal transition. These observations may suggest that estrogen plays a modulatory role in the pathophysiology of schizophrenia.<sup>[17]</sup>

## Panic disorder during menopause

[Panic disorder](#) is common during perimenopause. New-onset panic disorder may occur during menopause, or preexisting panic disorder may worsen. Panic disorder may be most common in women with many physical symptoms of menopause.<sup>[18]</sup>

In a cross-sectional survey of 3,369 postmenopausal women aged 50-79 years, panic attacks were most prevalent among women in the menopausal transition. Panic attacks were associated with negative life events, functional impairment, and medical comorbidity.<sup>[19]</sup>

## Obsessive-compulsive disorder during menopause

New-onset [obsessive-compulsive disorder](#) (OCD), a relapse of OCD, or a change in OCD symptoms may occur during menopause. Fluctuations in OCD have been correlated with the menstrual cycle and with pregnancy, suggesting that hormone levels may contribute to the disorder.<sup>[20]</sup>

## Bipolar disorder during menopause

Exacerbation of mood symptoms during menopause has been noted in women with preexisting [bipolar disorder](#). Research has suggested that women with bipolar disorder have higher rates of depressive episodes during the menopausal transition. The frequency of depressive episodes in this population appears to be higher than during premenopausal years.<sup>[21]</sup> Earlier studies suggested an increase in rapid cycling during the menopausal transition; however, this finding has not been reproduced.<sup>[22]</sup>

## Pathophysiology

Depression during perimenopause is likely due to fluctuating and declining estrogen levels in part. Steroid hormones, such as estrogen, act in the CNS by means of various mechanisms. For instance, they stimulate the synthesis of neurotransmitters, the expression of receptors, and influence membrane permeability.<sup>[23]</sup>

Estrogen increases the effects of serotonin and norepinephrine, which are thought to be the neurotransmitters most related to the physiologic cause of depression. Among other mechanisms, estrogen decreases monoamine oxidase (MAO) activity in the CNS, hindering the break down of serotonin and norepinephrine.<sup>[21]</sup> In addition, estrogen increases serotonin synthesis, upregulates 5-hydroxytryptamine (5-HT)-1 (5-HT1) receptors, and downregulates 5-HT2 receptors. Estrogen also increases norepinephrine activity in the brain, perhaps by decreasing reuptake and degradation due to inhibition of the enzymes MAO and catechol O-methyltransferase.<sup>[24]</sup>

Although the precise mechanisms are yet unknown, regulation of serotonin and norepinephrine may change as estrogen levels fluctuate and thus contribute to depression. Because estrogen facilitates the actions of serotonin and norepinephrine, a decline in estrogen concentrations may, in turn, decrease levels of these hormones.<sup>[2, 23, 24]</sup> Changes in estrogen levels, perhaps due to mechanisms involving these neurotransmitters, may be related to depressive symptoms in the menopausal transition of some women.

## Epidemiology

### Frequency- United States

Each year, 1.3 million women reach menopause. An estimated 20% of these women experience depression.<sup>[5]</sup>

### Mortality/Morbidity

Although morbidity and mortality secondary to perimenopausal depression has not been studied, depression is known to be a significant health problem in women. According to the World Health Organization's Global Burden of Disease Study, unipolar depression is the leading cause of disease-related disability in women.<sup>[25]</sup> In the Global Burden of Disease Study, unipolar major depression was second to only ischemic heart disease in terms of associated morbidity and mortality.<sup>[26]</sup>

### Race

The racial distribution of perimenopausal depression is not known. However, in countries where older women are highly valued, women experience fewer symptoms overall during menopause.

### Sex

Depression is approximately twice as common in women as in men (21% vs 12.7%). Moreover, depressive are more recurrent, longer, worse, and more impairing for women and for men.<sup>[27, 28]</sup> In addition, the prevalence of dysthymia and minor depression is increases among women. These differences have not been noted for mania. Sex-related differences emerge at the age of 11-15 years.<sup>[25]</sup>

### Age

The mean age of onset for the menopausal transition is 47.5 years.<sup>[4]</sup>

## History

## Perimenopause

- Hot flashes
- Cold sweats
- [Irregular menstrual bleeding](#)
- Urogenital atrophy and dryness with resultant dyspareunia (see [gynecologic pain](#)), itching, and [urinary urge incontinence](#)
- Cognitive and affective disturbance

## Major depression

Essential criteria include the following:

- Depressed mood and/or
- Decreased interest or pleasure in activities

Additional criteria include the following:

- Increased or decreased appetite
- Weight change
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Feelings of worthlessness or guilt
- Decreased concentration
- Indecisiveness
- [Suicidal ideation and plans](#)
- Homicidal thoughts and plans

## Overlapping symptoms of depression and perimenopause

- Low energy
- Impaired concentration
- Sleep disturbances
- Weight changes
- Libido changes

Depression (with the following suggestive features from a [Mental Status Examination](#))

- Motor retardation or agitation
- Latency of response to questions
- Slowed thought process
- Diminished prosody of speech
- Poor eye contact
- Poor grooming or hygiene (may indicate advanced depression)

## Physical

Findings of perimenopause include urogenital atrophy, as well as flushing and diaphoresis during hot flashes.

## Causes

Causes of menopause-related mood disorders may include hormonal changes, life stressors, psychological or social conditions, and/or a preexisting tendency to develop depression.

## Hormonal changes

Depression seems to be significantly linked to times of hormonal change in women. Several observations and study data support this theory. For example, the disparity between rates of depression in women and men begins at puberty. Also, hormonal changes are thought to be major contributors to premenstrual dysphoric disorder, as well as mood changes experienced in the postpartum period and at the menopausal transition.<sup>[27, 28]</sup> Furthermore, estrogen affects both serotonin and norepinephrine, the 2 neurotransmitters thought to be most directly associated with depression.

Of note, absolute levels of gonadal hormones are not correlated with depression. Estrogen and progesterone levels do not distinguish a woman with depression from one without depression. When hormone concentrations were measured in perimenopausal or postmenopausal women with depression, no abnormal levels were found.<sup>[29]</sup> Rather, a certain subset of women seem to be predisposed to have mood disturbances triggered by hormonal fluctuations. This subset includes women with a history of mood disorders or of premenstrual and postpartum mood-related symptoms. The risk of depression appears to be higher during perimenopause, when hormone levels are changing, than during postmenopause, when estrogen and progesterone levels are low but stable.<sup>[23, 30, 6]</sup>

## Life stressors

Societal roles and expectations may contribute to the heightened rate of depression in women. Women with particular types of stressors seem to be at increased risk for perimenopausal depression. Such stressors include the following<sup>[5, 28]</sup>:

- Lack of social support
- Unemployment
- Surgical menopause
- Poor overall health status

Dysphoric mood during the early perimenopausal transition is most common in women with relatively low educational status. Therefore, low levels of education may be a marker for other stressors, such as ongoing low socioeconomic status.<sup>[31]</sup>

An Australian study of women transitioning to menopause revealed more depression in women with the following states<sup>[32]</sup>:

- Negative mood before menopause
- Negative attitude toward menopause and aging
- Smoking
- Little or no exercise
- No partner
- A number of bothersome symptoms
- Poor self-perceived health
- Negative feelings toward partner
- A number of perceived problems
- Interpersonal stress

Other stressors that tend to correspond with perimenopause and that are postulated to relate to depression include the following:

- Onset of illness in self or others
- Care of aging parents
- Changes in employment

## Psychological or social conditions

Numerous psychological and social theories have been proffered to explain why women may become depressed during perimenopause. Some of these are related to the following factors:

- Change in the childbearing role
- Loss of fertility, which may be associated with a loss of an essential meaning of life
- Empty-nest syndrome (However, surveys have indicated that women whose children have moved out of the house tend to report more happiness and enjoyment in life than do others.)
- Societal value of youth (In societies where age is valued, women tend to report having fewer symptoms at the menopause transition.)

## Preexisting tendency to develop depression

A personal or family history of major depression, [postpartum depression](#), or [premenstrual dysphoric disorder](#) seem to be a major risk factor for depression in the perimenopausal period.<sup>[5]</sup> However, perimenopausal depressive syndrome is a risk even in women without a history of depression.

## Differentials

- [Adjustment Disorders](#)
- [Anemia](#)
- [Depression](#)
- [Dysthymic Disorder](#)
- [Hypothyroidism](#)

## Laboratory Studies

- Thyroid-stimulating hormone (TSH) determination: Monitor patients for [hypothyroidism](#) because [thyroid disease](#) is an independent risk factor for depression in menopausal women.<sup>[7]</sup>
- FSH and LH measurements: Because ovarian production of inhibin and estrogen declines during perimenopause (see [Ovarian Insufficiency](#)), FSH and, later, LH levels begin to increase. An FSH level >40 IU/L is often used as a marker of menopausal changes. Patients may begin to notice changes before laboratory values reflect the changes.
- Hematocrit test: [Anemia](#) can be associated with depressive-type symptoms.

## Imaging Studies

Dexa scan to evaluate bone mineral density (BMD). Depression may be a risk factor for osteoporosis in postmenopausal women.

## Medical Care

Treatment of perimenopausal depression

For major depression, standard antidepressants are first-line treatments. Selective serotonin reuptake inhibitors (SSRIs) are the most common ones. The onset of action is 4-6 weeks.

Although results from studies of hormone treatments for depression have been inconsistent, such treatments have been helpful for managing depressive symptoms in perimenopause but not postmenopause.<sup>[4, 17]</sup>

For mild depression, hormone replacement therapy alone may be appropriate. Estrogen may be used when traditional antidepressants failed, when patients refuse psychotropic medications, or when patients experience other clinically significant vasomotor symptoms.<sup>[17, 33]</sup>

## Treatment of hot flashes

SSRIs are sometimes used to treat hot flashes. Paroxetine, paroxetine CR, venlafaxine ER, and escitalopram may provide some benefit.<sup>[3, 34, 35]</sup> Clonidine and gabapentin have been shown to reduce hot flashes.<sup>[34]</sup>

## Treatment of sleep disorders

Estrogen may be helpful in relieving vasomotor symptoms that disrupt sleep or that may have a direct effect on sleep itself.<sup>[14]</sup>

In a study of postmenopausal women with hot flashes, night sweats, insomnia, anxiety, and/or mood swings, low-dose estrogen and low-dose micronized progesterone improved sleep to a greater extent than could be explained by a reduction in vasomotor symptoms.<sup>[36]</sup>

One study using polysomnographic analysis found that isoflavone treatment is also effective in reducing insomnia symptoms.<sup>[37]</sup>

## Maintenance of cognitive function

Data from observational studies suggest that estrogen may prevent or delay the onset of [dementia](#), including [Alzheimer disease](#), especially when estrogen therapy started in young postmenopausal women.<sup>[17]</sup>

The data do not suggest that estrogen is helpful for cognitive function in all perimenopausal and postmenopausal women. The Women's Health Initiative Memory Study (WHIMS) was a study of postmenopausal women older than 65 years who were unlikely to have preexisting dementia. The women were monitored by means of serial mini-mental status examinations. No improvement in global cognitive functioning was observed with estrogen treatment.<sup>[38]</sup>

## Group therapy

Negative anticipation of menopause seems to be associated with elevated rates of depression and physical symptoms of menopause. Educational groups that help women learn what to expect during menopause decrease anxiety, depression, and irritability, both immediately after the group therapy and 1 year later.<sup>[39]</sup>

## Psychiatric hospitalization

Psychiatric hospitalization is indicated for patients who are at imminent risk of harming themselves or others and for those whose depressive symptoms render them unable to care for themselves.

## Medication Summary

### Hormone treatment for depressed perimenopausal women

Data from several studies suggested that estrogen replacement therapy had antidepressant effects or that it enhanced the effects of antidepressant treatment in perimenopausal women.<sup>[33, 41, 42, 43, 44, 45]</sup> Other studies did not show that estrogen adds to the effects of SSRIs.<sup>[44, 46]</sup>

Debate exists regarding whether the antidepressant effect is attributable to the effect of estrogen on vasomotor symptoms. Some studies reveal an antidepressant benefit only in women with vasomotor symptoms. Results of other studies suggest an independent antidepressant effect.<sup>[47, 48]</sup> Although perimenopausal women may benefit from estrogen replacement, postmenopausal women may not.<sup>[49]</sup>

### Hormone treatment to enhance mood and quality of life in nondepressed perimenopausal women

The effects of estrogen treatment have been studied in perimenopausal women without depression to see if it has a positive effect on mood or quality of life. Results from small studies have suggested a small positive impact on mood.<sup>[36, 50]</sup> However, most data suggest that, among healthy women without depression, estrogen has no favorable effect on quality of life or mood.<sup>[47, 51, 52]</sup>

### Antidepressant treatment for depressed perimenopausal women

SSRIs are the antidepressants most commonly used in the treatment of perimenopausal depression. These drugs act by inhibiting serotonin reuptake transporters in the presynaptic neuron, making more serotonin available at the synaptic cleft.

SSRIs are thought to be generally safe and effective. They do pose a risk of serotonin syndrome, as well as several common adverse effects such as GI effects (nausea, diarrhea, anorexia), excessive sweating, decreased libido and/or anorgasmia, headache, jitteriness, dizziness, sedation or activation, insomnia, and akathisia. Several of these medications inhibit the cytochrome P450 (CYP) enzymes; therefore, it is prudent to check for drug interactions.

### Antidepressant treatment for nondepressed perimenopausal women

In women with mild mood-disorder symptoms that do not meet the criteria for depression, hormone replacement therapy may be considered. Hormone replacement therapy may also be an adjunctive treatment for women with perimenopausal depression and prominent vasomotor symptoms.

## Estrogen replacement

### Class Summary

In women with mild mood-disorder symptoms not meeting the criteria for depression, hormone replacement therapy may be considered. Hormone replacement therapy may also be an adjunctive treatment for women with perimenopausal depression and prominent vasomotor symptoms.

### [View full drug information](#)

### Conjugated equine estrogen (CEE) and medroxyprogesterone (Premphase, Prempro)

Hormone replacement therapy that induces synthesis of DNA, RNA, and various proteins in target tissues. Inhibits secretion of pituitary gonadotropins.

## Patient Education

Patients may benefit from learning that mood symptoms are not uncommon during menopause. Providing education about depressive symptoms can help women understand their experiences and recognize depression as a treatable illness. Family members may also benefit from learning about the symptoms of major depression and the association of its onset with the menopausal transition. This information may help them understand changes they observe in their family member.

Patients should be educated about emergency mental health services that are available in their area. They should be aware of how to access help if they have suicidal thoughts.

Listed below are some useful patient education resources:

- [Menopause Center](#) from eMedicineHealth, which addresses numerous topics related the change of life, such as causes, symptoms, when to seek medical care, self-care at home, and prevention of problems associated with menopause
- [Menopause Health Center](#) from WebMD
- [Midlife Transitions: A Guide to Approaching Menopause](#) available from the American College of Obstetricians and Gynecologists (ACOG)
- [Menopause](#) from Medline Plus, a service of the US National Library of Medicine and the NIH
- [Menopause Age Page](#) (also available in [Spanish](#)) from the NIH, National Institute on Aging
- NIH State-of-the Science Conference Statement on [Management of Menopause-Related Symptoms](#)
- [Women's Health Initiative](#) conducted by the Department of Health and Human Services, NIH, National Heart, Lung, and Blood Institute, including these pages:
  - Information for the Public: [Questions and Answers About Estrogen-Plus-Progestin Hormone Therapy](#)
  - Information for the Public: [Facts About Menopausal Hormone Therapy](#)
  - [Health Recommendations for Postmenopausal Women](#) based on results from the Women's Health Initiative and other studies
- [Menopause & Hormones informational materials \(also available in Spanish\) from the US Food and Drug Administration](#)
- [Understanding Menopause](#) from the National Women's Health Information Center, US Department of Health and Human Services
- [The North American Menopause Society](#) (NAMS)
- [Menopause Support Group message boards](#) hosted by WebMD