

# Psychiatric considerations in menopause

## Women's risk of psychiatric symptoms and disorders is increased during menopause

**M**rs. J, age 49, presents to your psychiatric clinic. For the last few years, she has been experiencing night sweats and hot flashes, which she has attributed to being perimenopausal. Over the last year, she has noticed that her mood has declined; however, she has suffered several life events that she feels have contributed. Her mother was diagnosed with Alzheimer's disease and had to move into a nursing home, which Mrs. J found very stressful. At the same time, her daughter left home for college, and her son is exploring his college options. Recently, Mrs. J has not been able to work due to her mood, and she is afraid she may lose her job as a consequence. She has struggled to talk to her husband about how she is feeling, and feels increasingly isolated. Over the last month, she has had increased problems sleeping and less energy; some days she struggles to get out of bed. She is finding it difficult to concentrate and is more forgetful. She has lost interest in her hobbies and is no longer meeting with her friends. She has no history of depression or anxiety, although she recalls feeling very low in mood for months after the birth of each of her children.

Are Mrs. J's symptoms related to menopause or depression? What further investigations are necessary? Would you modify your treatment plan because of her menopausal status?

Women are at elevated risk of developing psychiatric symptoms and disorders throughout their reproductive lives, including during menopause. Menopause is a time of life transition, when women may experience multiple physical



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## Psychiatric illness during menopause

### Clinical Point

In menopause, decreasing estrogen levels may correlate with increased mood symptoms, physical symptoms, and psychotic symptoms



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Table 1

### Periods of increased vulnerability for mental health disorders

Menstruation (eg, premenstrual dysphoric disorder)
Pregnancy
Postpartum <sup>a</sup>
Menopausal transition
<sup>a</sup> Highest vulnerability
Source: References 1,2

Table 2

### Physical symptoms of menopause

Irregular menstrual periods
Vasomotor symptoms (hot flashes, night sweats)
Sleep disturbances
Sexual dysfunction (dyspareunia, vaginal dryness, decreased libido)
Elevated risk: osteoporosis, cardiovascular
Source: Reference 3

symptoms, including vasomotor symptoms (night sweats and hot flashes), sexual symptoms, and sleep difficulties. Depressive symptoms occur more frequently during menopause, and symptoms of schizophrenia may worsen.

Estrogen plays a role in mental illness throughout a woman's life. In menopause, decreasing estrogen levels may correlate with increased mood symptoms, physical symptoms, and psychotic symptoms. As such, psychiatrists should consider whether collaboration regarding adjunctive hormone replacement therapy would be beneficial, and whether the benefits outweigh the potential risks. Otherwise, treatment of depression in menopause is similar to treatment outside of the menopausal transition, though serotonergic antidepressants may help target vasomotor symptoms while therapy may focus on role transition and loss. In this article, we review why women are at increased risk for mental illness during menopause, the role of estrogen, and treatment of mood and psychotic disorders during this phase of a woman's life.

## Increased vulnerability across the lifespan

The female lifecycle includes several periods of increased vulnerability to mental illness related to reproductive hormones and life changes. Compared with men, women have approximately twice the risk of developing depression in their lifetime.<sup>1</sup> With the onset of menarche, the increased risk of mental health problems begins (*Table 1*<sup>1,2</sup>). Women are at elevated risk of mood disorders in both pregnancy and postpartum; approximately one-seventh to one-quarter of women experience postpartum depression, depending on the population studied. Finally, women are at risk of mood difficulties in the perimenopause. Those with a history of depression are at particularly elevated risk in the perimenopause.<sup>2</sup>

## Why menopause?

Menopause is a significant life event. The menopause transition begins around age 47 and lasts 4 to 7 years. By age 55, most women are postmenopausal. Symptoms of menopause are described in *Table 2*.<sup>3</sup> Menopause is colloquially known as the “change of life”—not only because of the physical changes, but because of the meaning a woman may attribute to these changes. She may associate menopause with loss of femininity or attractiveness. Also, menopause may coincide with social and developmental changes, such as having an “empty nest”—her children having left home. How menopause is construed by a woman (and the culture/society in which she lives) impacts her experience of menopause.<sup>4</sup>

## Perimenopausal mood disorders

The SWAN Study (Study of Women's Health Across the Nation) found that women's risk of experiencing depressive symptoms was greater both during and after the menopause transition.<sup>5</sup> A history of depression was the strongest predictor. Interestingly, the effect of menopausal status on the risk of depression was found to be independent of the woman's personal history of depression, upsetting life events, vasomotor symptoms, and reproductive hormone changes. Two recent studies demonstrated that among women

without a history of depression, depressive symptoms were more than twice as likely to emerge during the menopausal transition than premenopausally.<sup>6,7</sup> Depression occurred in the context of the changing hormonal milieu. A recent meta-analysis<sup>8</sup> found an inverse association between age at menopause and the risk of postmenopausal depression. *Table 3*<sup>1,2,4,8-12</sup> describes risk factors for developing depressive symptoms in menopause.

However, one should keep in mind that new-onset mania in menopause is rare and should trigger a medical work-up and a dementia evaluation.<sup>13</sup> *Table 4*<sup>14</sup> (*page 14*) provides recommendations for evaluation of women undergoing menopause.

### Menopause and serious mental illnesses

A study of 91 perimenopausal and postmenopausal women (age 45 to 55) who were diagnosed with schizophrenia/schizoaffective disorder, bipolar disorder, or major depressive disorder (MDD) found that women with severe mental illness experienced significant vasomotor, physical, sexual, and psychosocial symptoms related to menopause.<sup>15</sup> Furthermore, on 7 of 29 items on the Menopause Specific Quality of Life Scale, including hot flashes, women diagnosed with MDD reported problems significantly more often than women with other serious mental illnesses.<sup>15</sup>

Women with serious mental illness often have deficits in their knowledge about menopause.<sup>3</sup> More than half of the 91 women in the study diagnosed with schizophrenia/schizoaffective disorder, bipolar disorder, or MDD felt more stressed related to menopause, and reported that menopause had a negative effect on their mental health.<sup>3</sup> These women rated their top 5 symptoms potentially related to menopause as feeling depressed, anxious, or tired; lacking energy; and experiencing poor memory.<sup>3</sup>

### Role of estrogen on mood and psychosis

Women are at higher risk throughout their reproductive life than are men for MDD,

**Table 3**

### Risk factors for developing depressive symptoms in menopause

History of depression (especially in other reproductive periods)
Vasomotor symptoms
Sleep disturbances
Surgical menopause
Young at menopause
Negative attitudes about menopause/aging
Life stressors
<b>Source:</b> References 1,2,4,8-12

anxiety disorders, and trauma-related disorders.<sup>12</sup> Factors associated with depression during the menopause transition are reproductive hormonal changes (rise of follicle-stimulating hormone [FSH] and luteinizing hormone levels, and variability in estrogen [E2] and FSH levels); menopausal symptoms, particularly vasomotor symptoms; prior depression; psychosocial factors (adverse life events, financial strain, poor social supports); high body mass index, smoking, and poor physical health.<sup>6,7</sup> Decreasing estrogen in the menopause transition may increase susceptibility to depression in some women.<sup>16</sup> *The Box*<sup>17,18</sup> (*page 15*) provides more information on the relationship between estrogen and brain function. Depressive disorders, including premenstrual dysphoric disorder, postpartum depression, and perimenopausal depression, have been linked to changes in hormonal status in women. Symptomatic menopause transition occurs in at least 20% of women, and a retrospective cohort study suggests that symptomatic menopause transition might increase the risk of new-onset depressive disorders, bipolar disorders, anxiety disorders, and sleep disorders.<sup>19</sup> Symptomatic menopause transition also is a vulnerable time for relapse of MDD. Among women experiencing menopausal symptoms, including hot flashes, one-third also report depression—which correlates with a poorer quality of life, less work productivity, and greater use of health care services.<sup>9</sup>

### Clinical Point

**Factors associated with depression during menopause include hormonal changes and menopausal symptoms**

continued



## Psychiatric illness during menopause

### Clinical Point

Some enzymes that metabolize medications are estrogen-dependent and their levels decline after menopause

Table 4

## Evaluation of women undergoing menopause

Symptom	Key areas to explore	Comments
Menstruation	Changes in characteristics, including timeframe	In absence of any menstrual irregularities with other perimenopausal symptoms, serum levels of FSH and estradiol may be helpful to identify perimenopausal status. Don't miss amenorrhea caused by antipsychotics
Sleep	Consider patterns of sleep: related to physical or emotional symptoms?	Depression can be associated with either hypersomnia or insomnia
Mood	Explore variations in mood as well as timeframe and recent significant stressors	Mental state examination is crucial for identifying clinical signs of depression. New-onset bipolar disorder in the perimenopausal period merits a complete work-up, including for dementia
Vasomotor (hot flashes, cold sweats)	Frequency and duration of symptoms	Underlying chronic health conditions or health anxiety may contribute to symptoms
Libido	A decrease in sexual desire or pleasure related to vaginal dryness or atrophy (due to hormonal changes)	Explore emotional reasons for any difficulties, such as relationship stress

**Source:** Reference 14  
FSH: follicle-stimulating hormone

Women who undergo surgical menopause are at greater risk for depression.<sup>8,10,11</sup> This may be due to abrupt deprivation of estrogen—or related to a psychological reaction to the loss of fertility.

The observation that hormonal fluctuations related to women's reproductive cycle have a significant impact on psychotic symptomatology has resulted in the "hypo-estrogenism hypothesis," which proposes that gonadal dysfunction may increase vulnerability to schizophrenia, or that schizophrenia may lead to gonadal dysfunction.<sup>20</sup> The "estrogen protection hypothesis" proposes that estrogen may protect women from schizophrenia, and may be a factor in the delayed onset of schizophrenia compared with men, less severe psychopathology, better outcomes, and premenstrual and postmenopausal deterioration in women. Many women of reproductive age with schizophrenia experience improvement in symptoms during the high estrogen phase of their menstrual cycle.

Pope et al<sup>21</sup> have suggested that a hormone sensitivity syndrome may underlie why some women experience physical, psychological, and emotional symptoms at times of hormonal shifts such as menopause.

This may represent a critical window of vulnerability, and also an opportunity to consider E2 as a therapeutic intervention.

### Treating mental illness in menopause

Changes to drug pharmacokinetics occur because some metabolizing enzymes are estrogen-dependent and their levels decline after menopause, which leads to greater variability in drug response, particularly for oral medications. Other factors that can contribute to variability in medication response are polypharmacy, alcohol, illicit drugs, liver mass, smoking, caffeine, and nutritional intake.

While antidepressants are the first-line treatment for MDD and anxiety disorders, some patients remain unresponsive or inadequately responsive to currently available medications. In perimenopausal women with MDD, there may be an indication for adjunctive therapy with transdermal E2 in refractory cases; estrogen may augment the effects of selective serotonin reuptake inhibitor (SSRI) antidepressants as well as hasten the onset of antidepressant action.<sup>22</sup> Estrogen also may be worth considering in



women with mild depressive symptoms. For MDD, SSRIs plus estrogen may be more beneficial in improving mood than either agent alone. The effectiveness of E2 is less certain in postmenopausal depression.

Hormonal therapy for mental health disorders has equivocal evidence. The individual's history and risk factors (eg, cardiovascular and osteoporosis risks) must be considered. A recent trial found that treatment with either venlafaxine or low-dose estrogen improved quality of life in menopausal women with vasomotor symptoms.<sup>23</sup> Venlafaxine improved the psychosocial domain, while estrogen improved quality of life in other domains. Escitalopram, duloxetine, and citalopram have also been identified as having a possible positive impact on menopausal symptoms.<sup>22</sup> SSRIs and serotonin-norepinephrine reuptake inhibitors may help reduce hot flashes and improve sleep.<sup>11</sup>

Regarding schizophrenia and estrogen, there may be improved symptoms during the high estrogen phase of the menstrual cycle, followed by a premenstrual aggravation of symptoms. Recall that women have a second peak of onset of schizophrenia after age 45, around the age of the onset of menopause.<sup>24</sup> In a study of geropsychiatric hospital admissions, women were overrepresented among those with schizophrenia and schizoaffective disorder, compared with other psychiatric disorders.<sup>25</sup> Postmenopausally, some women experience a decreased responsiveness to antipsychotics and worsening symptoms. In menopausal women with schizophrenia, check prolactin levels to help determine whether they are experiencing a natural menopause or medication-induced amenorrhea. Gender differences in pharmacotherapy responses and the decreasing response to antipsychotics in women older than age 50 have been observed<sup>26</sup> and have led to exploration of the role of estrogen for treating schizophrenia in menopausal women. There have been contradictory results regarding use of estrogen as an adjunct to antipsychotics, with some reports finding this approach is effective and results in lower average doses of antipsychotics. Kulkarni et al<sup>27,28</sup> have reported improvements in

#### Box

### Estrogen and brain function

Numerous molecular and clinical studies have established the role of 17-beta estradiol in modulating brain functions via alterations in neurotransmission.<sup>17</sup> Estrogen increases serotonin availability in the synapse by various pathways. It increases the rate of degradation of monoamine oxidase; monoamine oxidase enzymes are responsible for catabolizing serotonin, dopamine, and norepinephrine. Estrogen also increases tryptophan hydroxylase expression (rate-limiting enzyme in serotonin synthesis) and promotes intraneuronal serotonin transport in brain regions associated with affect regulation by increasing gene expression of the serotonin reuptake transporter. Studies have linked brain-derived neurotrophic factor (BDNF) to increased serotonin turnover and proposed that estrogen may influence depression by increasing BDNF levels within the brain.<sup>18</sup>

positive symptoms of treatment-resistant schizophrenia with transdermal use of E2, 200 mcg, as an adjunct to antipsychotics in women of childbearing age. However, they expressed caution regarding the health risks associated with prolonged use of E2. Long-term risks of high-dose estrogen therapies include thromboembolism, endometrial hyperplasia, and breast cancer, and individual factors should be considered before starting any form of hormone therapy. Selective estrogen receptor modulators (SERMs), such as raloxifene, which can cause activation of E2 receptors in a tissue-specific fashion and have less estrogen-related adverse effects, offer hope for future development in this field.<sup>27,28</sup> While the use of adjunctive hormone therapy to manage psychotic symptoms in menopause is not routinely advised, the dosages of previously effective antipsychotics may need to be reviewed, or long-acting depot routes considered.<sup>29</sup> Increased risk of prolonged QTc interval and tardive dyskinesia in geriatric women also should be considered in decisions regarding changes to antipsychotics or dosages.<sup>30</sup>

There are no guidelines regarding change in dosage of either individual antidepressants or antipsychotics in women at the time of menopause for managing

#### Clinical Point

**Hormonal therapy for mental health disorders has equivocal evidence**



## Psychiatric illness during menopause

### Clinical Point

Cognitive-behavioral therapy may be helpful for menopausal symptoms as well as depressive symptoms

### Related Resource

- The North American Menopause Society. Depression & menopause. <https://www.menopause.org/for-women/menopauseflashes/mental-health-at-menopause/depression-menopause>.

#### Drug Brand Names

Citalopram • Celexa  
Duloxetine • Cymbalta  
Escitalopram • Lexapro

Raloxifene • Evista  
Venlafaxine • Effexor

pre-existing conditions. This may be due to the high variability in the effect of menopause on mental health and recognition that menopause is also a time for deterioration in physical health, as well as psychosocial changes for women, and thus other forms of intervention need to be considered.

The biopsychosocial approach to treatment is particularly important in menopause.<sup>11</sup> Common transitions in midlife include changes in relationships, employment, and financial status, and illness or death of family and friends.<sup>31</sup> Therapy may focus on accepting a role transition and coping with loss of fertility. Cognitive-behavioral therapy may be helpful for menopausal symptoms, including hot flashes,<sup>4</sup> as well as depressive symptoms.<sup>11</sup>

Although there are overlapping symptoms with both MDD and the perimenopause, these are typically restricted to impaired energy, sleep, and concentration, or changes in libido and weight.<sup>32</sup> Therefore, it is vital to obtain a clear history and explore these symptoms in greater depth, as well as collect further information related to additional criteria such as appetite, agitation, feelings of worthlessness or guilt, and suicidal ideation.

#### CASE CONTINUED

### Starting an antidepressant

On evaluation, Mrs. J discloses that she had experienced thoughts of wanting to end her

life by overdose, although she had not acted on these thoughts. She appears subdued with poor eye contact, latency of response, and a slowed thought process. Mrs. J has blood tests to rule out thyroid abnormality or anemia. FSH and LH levels also are measured; these could provide a useful reference for later.

After a discussion with Mrs. J, she agrees to start an antidepressant. She also plans to speak to her gynecologist about the possibility of hormone replacement therapy. She is referred for psychotherapy to help support her with current life stressors. Mrs. J is started on escitalopram, 10 mg/d, and, after a month, she notices some improvement in her mood, psychomotor symptoms, sleep, and energy levels.

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## Bottom Line

Menopause is an important transition in our patients' lives—both biologically and psychosocially. Women's symptom patterns and medication needs may change during menopause.

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