

Vasomotor Symptoms and Depression in Women, Part 1

Role of Vasomotor Symptoms in Signaling the Onset or Relapse of a Major Depressive Episode

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Issue: *Vasomotor symptoms may be harbingers of oncoming depression or signs of incomplete recovery from a major depressive episode in some women.*

Perimenopause can be a time of chaotic change for a woman's body and mind.¹⁻³ Some changes are easily observed: starting around age 47, a woman's menstrual period changes in length, then whole cycles are skipped. Vasomotor symptoms, such as hot flashes (also called hot flushes) plus night sweats, often with sleep disturbances, mark the transitional years of late perimenopause into early postmenopause. Around age 51, a woman's final menstrual period occurs. The actual age at onset and duration of each stage are different for each woman, but every stage is characterized by differences in the fluctuation of estrogen levels.¹⁻³

Linking Estrogen Fluctuations to Depression

Fluctuations in estrogen levels are thought to drive the physiologic changes associated with different stages of the female lifecycle and are increasingly considered to put some

women at greater risk than others for the onset or relapse of a major depressive episode (MDE), including women in midlife with a history of depression, postpartum depression, or premenstrual syndrome.⁴ However, even a woman with no history of depression is almost twice as likely to experience onset of an MDE when she enters perimenopause than women of the same age who remain premenopausal.⁵

Perimenopause, Depression, or Both?

The diagnosis of a perimenopausal MDE can be complicated due to the high degree of symptom overlap between perimenopause and depression (Figure 1)—vasomotor symptoms and depression are linked both clinically and neurobiologically. Clinically, perimenopausal women with vasomotor symptoms are 4 times more likely to be depressed than perimenopausal women without vasomotor symptoms.⁶ The elevated risk seems to subside in postmenopause, when estrogen levels are low and when vasomotor symptoms also subside,³ which agrees with observations that risk for depression and vasomotor symptoms correlate with hormonal fluctuations, not absolute levels.³

Neurobiologically, both vasomotor symptoms and depression are regulated by the monoamine neurotransmitters serotonin, norepinephrine, and dopamine.³ Thus, dysregulation of these

systems can lead to depression when that dysregulation occurs within mood-related circuits (theoretically, such as ventromedial prefrontal cortex and amygdala; Figure 2A) and can hypothetically lead to vasomotor symptoms when it occurs within the hypothalamic thermoregulatory centers (Figure 2B),¹ where homeostatic control sites regulate internal core body temperature and integrate peripheral signals with vascular and neurochemical signals³ and are particularly affected by noradrenergic and serotonergic input. For example, injecting serotonin into the hypothalamus causes core body temperature to rise, and injecting norepinephrine causes internal body temperature to fall.³ Since estrogen fluctuations can cause dysregulation of both noradrenergic and serotonergic circuits, it is not surprising that estrogen fluctuations can lead to both vasomotor symptoms and depression, with substantial overlap in presentation.

Should Vasomotor Symptoms Be Considered Symptoms of Depression and Treated as Such?

Since vasomotor symptoms are associated with onset or recurrence of an MDE, experts now debate whether clinicians should identify and treat vasomotor symptoms as well as the traditional symptoms of depression in perimenopausal women. Many unanswered questions remain:

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TAKE-HOME POINTS

- ◆ Compared with men, women are at increased risk of depression, especially at several reproductive-related lifecycle points, e.g., postpartum and perimenopausal periods.
- ◆ This higher risk may partially be due to changing levels of estrogen, a hormone that can affect levels of neurotransmitters and neural proteins that in turn may modulate the risk of depression in some women.
- ◆ Vasomotor symptoms, including hot flashes with night sweats or sleep disturbances, may signal the dysregulation of not only estrogen but also the monoamine neurotransmitters serotonin, norepinephrine, and dopamine, especially in the hypothalamus, which may in turn increase the risk for major depressive episodes in some women.

Figure 1. Symptoms of Depression and Perimenopause Often Overlap Due to Similar Neurobiological Links Between These 2 Conditions^a



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Do vasomotor symptoms represent hormone and neurotransmitter dysregulation in the hypothalamus, thus indicating potential risk for other hypothalamic disturbances commonly linked to other symptoms of depression such as sleep disturbance, sexual dysfunction, lack of motivation, and changes in appetite?

Do vasomotor symptoms represent a potential proxy for hormone and neurotransmitter disturbances in other brain circuits?

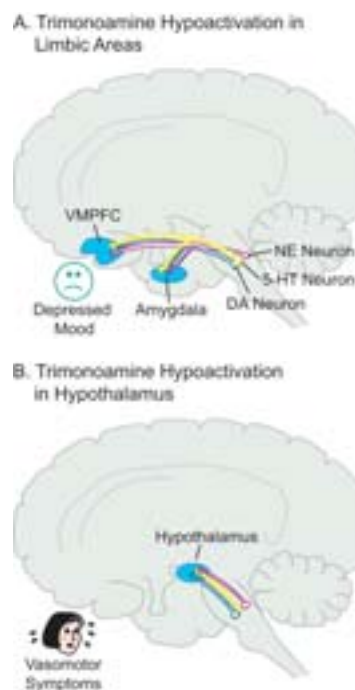
Would treatment of vasomotor symptoms prevent the onset of an MDE?

Are continuing vasomotor symptoms following resolution of the classical symptoms of depression a sign that full remission has not been achieved and that relapse is a risk?

Answers to these questions, which will be discussed in Part 2 in the March BRAINSTORMS, will hopefully emerge from future research, but it is already interesting to note that vasomotor and classical MDE symptoms are both linked to monoamine neurotransmitter dysfunction in different areas of the brain, and it may not be an accident that treatments for vasomotor symptoms (e.g., estrogen) and treatments for MDEs (e.g., some antidepressants) are increasingly interchangeable.³ The efficacies of these approaches and especially their risk-benefit evaluations require much further investigation.

Nevertheless, it is theoretically possible that treating vasomotor symptoms could potentially prevent MDEs in vulnerable women. Furthermore, failure to treat vasomotor symptoms in perimenopausal women who also have an MDE could theoretically stand in the way of full remission of the MDE or of sustaining that remission in the long run. Remission of the classic symptoms of depression while vasomotor symptoms persist is a likely signal that fluctuating estrogen levels are still affecting the brain and could potentially continue to create vulnerability for relapse. Ongoing research seeks to determine whether targeting vasomotor symptoms in women with depression or who are at risk for depression will achieve better outcomes. ◆

Figure 2. Fluctuating Levels of Estrogen Can Lead to Dysregulation of Monoamines, Which Can Lead to Depressive Symptoms Via Mood Circuits (A) and Vasomotor Symptoms Via Hypothalamic Circuits (B)^a



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Abbreviations: DA = dopamine, 5-HT = serotonin, NE = norepinephrine, VMPFC = ventromedial prefrontal cortex.

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