

# NAMS PRACTICE PEARL

## ***Tailoring Strategies for the Management of Depression in Midlife Years***

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***Depression affects one in every five adults in North America. Women are more affected than men, possibly because of genetics, coping strategies, and hormone variations. The concept of a menopause-associated depression, however, remains a complex and controversial topic. Although hormone therapy is not recommended as first-line therapy for depression in midlife women, estrogen-based hormone therapy may minimize the need for or enhance the response to antidepressant or behavior-based therapies in select perimenopausal women.***

One paradigm of depression in women suggests that some (but not all) women experience greater vulnerability for depression at certain stages (or *windows*) of their reproductive life cycles.<sup>1</sup> As such, reproductive-related depressive episodes would likely be associated with an increased sensitivity to changes in the hormone milieu—premenstrually, during the postpartum period, or during the menopause transition.

A myriad of conditions may adversely affect functioning throughout the midlife years, although certain factors seem to more directly modulate the risk for depression (comorbid medical conditions, vasomotor symptoms, sleep problems, stressful life events). Yet, few large clinical trials have focused on midlife depression in women.<sup>2</sup>

On the basis of our current knowledge, what principles could guide more accurate diagnosis and treatment for depression in midlife women or even contribute to its prevention?

***Take into consideration depressive symptoms and clinical depression.*** The burden associated with a major depressive disorder (MDD) is undeniable; yet, depressive symptoms (eg, low mood, reduced enjoyment with usual activities) that don't fully meet diagnostic criteria for depression based on duration and/or severity should also be addressed because they affect overall health and cause psychosocial impairment.

***Look into the right window.*** Cross-sectional and prospective studies have investigated the link between distinct menopause staging and depressive symptoms and MDD (new onset or recurrent). Cross-sectional studies found depressive symptoms in up to 70% of women during perimenopause compared with 30% in the premenopausal years. Longitudinal studies have also confirmed an increased risk for depressive symptoms and MDD during the perimenopause and early postmenopause years, even in women without previous depressive episodes.<sup>3,4</sup>

**Look for continuum of risk factors.** Longitudinal studies have identified risk factors for midlife depression that seemed pervasive throughout the lifespan; they might act as moderators and represent a *continuum* of risk for depression. They include *demographic/socioeconomic characteristics* (unemployment, low education, being black or Hispanic); *health-related factors* (greater body mass index, smoking, poor health caused by chronic conditions); and *psychosocial factors* (low social support, history of anxiety, multiple life stressors). Among all, a previous depressive episode, with or without a hormone component (previous premenstrual syndrome or postpartum depression), is a strong predictor for midlife depression.<sup>3-6</sup>

**Look also for window of risk-related factors.** In addition to lifetime risk factors, researchers have investigated timing-related, context-related factors for midlife depression. Again, cross-sectional and longitudinal studies have been valuable sources to identify mediating or precipitating factors. These include hormone variations (wider fluctuations in follicle-stimulating hormone and estradiol levels over time, rather than hormone depletion), somatic symptoms (vasomotor symptoms, sleep problems), overall health (poor functioning), and psychosocial stressors (loss of social support, stressful life events—not only the magnitude and number of events but also the timing of their occurrences).<sup>3-6</sup>

**Keep an eye on the long run.** Two prospective studies have elegantly examined the trajectories of depressive symptoms throughout the menopause transition and beyond: The Study of Women Across the Nation (SWAN)<sup>7</sup> and the Australian Longitudinal Study on Women's Health.<sup>8</sup> The SWAN investigators examined the course of depression over a 13-year follow-up and confirmed the progression in some women toward a more persistent or recurrent condition, even for *new cases of depression*. Sleep problems and distressing life events were linked to more persistent/recurrent depression. In the Australian study, distinct patterns for depressive symptoms over a 15-year follow-up were identified: those with *stable high* or *increasing* depressive symptoms over time (around 10%) were likely to present with a *continuum* of risk factors (previous diagnosis or treatment for depression, challenging socioeconomic issues) and/or context-related risk factors (prolonged perimenopause or a surgically induced menopause). Depressive symptoms or MDD in midlife women could be a result of the compounded exposure to both long-term and short-term (context-related) risk factors. Such information could help engage patients and colleagues on discussions regarding risk factors and prevention of depression before and during midlife years.

#### **What are the evidence-based treatment options for depression in midlife years?**

- *Antidepressants remain the first-line treatment for depression during midlife years*, particularly for those with previous episodes and those reporting severe symptoms, significant functional impairment, and/or expressing suicidal ideation. For recurrent episodes, a previous response to a specific antidepressant agent or class should guide clinicians on what to try first. For new cases or for treatment-naïve patients, existing data support the use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including fluoxetine, sertraline, venlafaxine, citalopram, escitalopram, duloxetine, and desvenlafaxine.
- *When choosing an antidepressant for midlife depression, look beyond efficacy.* Published reports do not support the superiority of any particular antidepressant agent or class for midlife depression. Still, there are important points to be considered when choosing an antidepressant for this population. First, look for data available on efficacy *and* tolerability; despite some methodologic limitations, there are published reports on paroxetine, citalopram,

escitalopram, venlafaxine, duloxetine, and desvenlafaxine that could inform discussions with your patients. Second, greater tolerability and reduced adverse events (sexual functioning, weight changes) could be strong assets and facilitate treatment adherence to agents such as escitalopram or desvenlafaxine. Third, consider additional benefits because of the improvement of menopause-related symptoms such as hot flashes, pain (citalopram, escitalopram, duloxetine, venlafaxine, paroxetine, desvenlafaxine), and sleep (paroxetine, escitalopram, mirtazapine). Last, evaluate the risk of drug-drug interactions for each of your options, particularly in light of multiple medications often prescribed to midlife women.<sup>2</sup>

- *What about estrogen-based therapies?* Estrogen could be considered a mood enhancer, acting via distinct pathways to regulate synthesis, metabolism, and overall activity of neurotransmitters (dopamine and norepinephrine) that are crucial for mood regulation.<sup>9</sup> Randomized trials have documented the antidepressant efficacy of transdermal 17 $\beta$  estradiol during perimenopause for new-onset and recurrent depression, with or without concomitant vasomotor symptoms.<sup>10</sup> A randomized trial of women in early postmenopause found oral conjugated estrogen (but not transdermal estradiol) to be helpful in improving mood symptoms in nondepressed women.<sup>11</sup> However, hormone interventions seem ineffective for the management of clinical depression in postmenopausal women. Taken together, these findings suggest that the menopause transition might not only be a critical window of risk for depression (similar to windows of vulnerability for cardiovascular and cognitive events) but also a *window of opportunity* to leverage estrogen-based therapies for their antidepressant effects.
- *Is there a preferred treatment sequence or algorithm?* Given the scarcity of data on their efficacy and long-term safety, estrogen-based therapies are not recommended as primary options for depression in midlife women. Other options, including antidepressants and cognitive-behavior therapies, remain as front-line treatments at any given time in life. Notwithstanding, clinicians should consider tailoring treatment strategies to address multiple symptom domains. An argument can be made for a brief trial (2-4 wk) of estrogen-based hormone management for perimenopausal women experiencing significant depressive symptoms or clinical depression and concurrent, bothersome vasomotor symptoms. If helpful and well tolerated, such therapy could minimize the need for or potentially prime the response to antidepressants or behavioral-based techniques. When estrogen therapy is used in perimenopausal women, it should be combined with a dose of progestin that is sufficient to suppress ovulation (eg, low-dose estrogen-progestin oral contraceptives, if no contraindications, or formulations with lower estrogen doses: ethinyl estradiol 5  $\mu$ g/norethindrone acetate 1 mg or estradiol 1 mg/0.5 mg norethindrone acetate).

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## Disclosures

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