



Diagnosis and management of mood disorders during the menopausal transition

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Recent census data indicate that, in the United States, an increasing number of women—almost 1.5 million each year—are reaching menopause. The menopausal transition is marked by intense hormonal fluctuations, and may be accompanied by vasomotor complaints, sleep disturbances, changes in sexual function, and increased risk for osteoporosis and cardiovascular disease. In addition, there is evidence of increased risk for developing depression, even among women who never experienced depressive symptoms before. Thus depression during the perimenopause may have a substantial impact on personal, family, and professional spheres of life. A challenge to clinicians and health professionals lies in the identification of the most tolerable treatments to manage depression and improve quality of life in an aging population. Any treatment strategy should take into account not only the spectrum of side effects that may complicate treatment but also other menopause-related factors (e.g., vasomotor symptoms, psychosocial stressors) that may modulate risk for the development of mood disturbance. This article reviews the current literature on the prevalence and risk factors associated with depression during the menopausal transition. The benefits and risks of using hormonal and nonhormonal strategies for the management of depression and other menopause-related somatic symptoms are critically reviewed.

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Major depressive disorder is a highly prevalent illness that is associated with significant morbidity and mortality. Women are more commonly affected than men, with several studies supporting a 2-fold increase in

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lifetime risk for major depression in women compared with men.¹ The peak period of risk for depression in women occurs between the ages of menarche and menopause,^{1,2} suggesting that hormonal changes occurring during the reproductive years may play a role in the risk for mood disorders in women.³

Periods of reproductive hormonal change,^{4–6} i.e., the premenstrual period, the puerperium, and the menopausal transition, may constitute times of particular risk for the development of depression in women. The extent to which the menopausal transition is associated specifically with increased risk for depression has considerable public health consequences. Recent US census data describe the significant pace of growth of the female versus male population, with approximately 1.5 million women reaching menopause each year in the United States—an estimate arrived at using age as a proxy.⁷ Given that the menopausal transition lasts several years

on average, a large number of women may be at increased risk for depression for an extended time. Thus depression during the menopausal transition may have a substantial impact on personal, family, and professional spheres of life.

The extent to which the transition to menopause is associated with a frank depressive syndrome has been the subject of some controversy. Inconsistent findings in the literature may derive from the heterogeneity of studies in which subject samples have included women from a spectrum of settings, such as specialized menopause clinics, other clinical facilities, and community-based research.^{4,8-11} Most studies define depression based on self-report measures that indicate distress or depressive symptoms but do not conclusively indicate a clinical diagnosis of depression. These scales were designed to be used to screen for, and not to diagnose, depression. More recently, 2 epidemiologic, prospective studies have systematically documented the onset of mood disorders among women approaching menopause by using standardized diagnostic instruments.^{4,8}

Contradictory findings about the association between depression and the menopausal transition also derive from the fact that menopausal status has been assigned based on varying criteria for the menopausal transition. The recent introduction of the Stages of Reproductive Aging Workshop (STRAW) criteria established consistent parameters for menopausal staging.¹² The proposed distinction between early and late transition of the menopause, for example, will improve consistency between studies and enhance opportunities for comparisons between studies.¹²

Despite these methodologic limitations, a significant association between the menopausal transition and risk for depression seems apparent overall. Several longitudinal studies that follow women across the menopausal transition indicate that risk for significant depressive symptoms increases during the menopausal transition and then decreases in the early postmenopause.^{8,10} In the largest community-based study to date, the Study of Women's Health Across the Nation (SWAN) reported that women in early perimenopause had a higher rate of persistent mood symptoms than premenopausal women. These mood symptoms primarily were irritability, nervousness, and frequent mood changes, but not feeling "blue."¹¹ A recent study by Freeman and colleagues⁸ and a follow-up study to the Harvard Study of Moods and Cycles⁴ (a population-based prospective study of women with and without a lifetime history of major depression) have described increased risk for clinically significant first onset of mood disturbance in perimenopausal versus premenopausal women. In a recent report by Schmidt and colleagues,¹³ 29 women with regular menstrual cycles were monitored (mean follow-up, 5 years) until they experienced ≥ 6 months of amenorrhea. The study revealed that the 24-month period surrounding the menopause carried a 14-fold increased risk for depression,

compared with >30 years of regular cycles (premenopause).¹³

Risk of depressive recurrence during the menopausal transition

Several prior studies have concluded that a history of depression is a strong predictor of depressive recurrence during the menopausal transition.^{9,10} Other factors such as health-related issues, social support, and daily stressors may also contribute to the development of depressive symptoms at this time. It is known that a history of depression increases the risk of recurrent depression. Whether the menopausal transition is a particular period of risk for this population, however, has yet to be determined.

A history of premenstrual syndrome (PMS) also may predict depression during the menopausal transition.⁸ PMS is a disorder that includes both physical and psychological symptoms. PMS studies indicate that the mood symptoms result from a differential susceptibility to hormonal changes in the brain.¹³ The association between depression in the menopausal transition and PMS suggests that both disorders reflect an underlying susceptibility to hormonal changes and the effects of such changes on central nervous system neuromodulation. However, studies also suggest the occurrence of significant lifetime comorbidity between depression and PMS, so PMS may be a proxy for a depression history. Despite the strong association between prior history of depression and depressive symptoms during the menopausal transition, the initial onset of depression also occurs in a subset of women approaching menopause.¹³

Role of hot flashes in depression during the menopausal transition

Hot flashes are the primary symptom of the menopausal transition. Hot flashes are a manifestation of the dysregulation in the thermoregulatory center in the hypothalamus that occurs in the setting of ovarian failure and estrogen withdrawal.¹⁴ Nocturnal hot flashes are associated with brief but repeated awakenings from sleep¹⁵; however, recent evidence suggests that the extent of the sleep disruption is not substantial.¹⁶ Hot flashes occur most frequently in the late stages of the menopausal transition and in the early postmenopausal years,^{17,18} and several studies have shown a strong association between hot flashes and depression.^{10,19} Some have suggested that depression during the menopausal transition is an indirect consequence of sleep disruption that occurs in association with hot flashes. Others have hypothesized that depression during the menopausal transition results from sensitivity to changes in estradiol in the brain and suggest that the association between perimenopausal depression and hot flashes indicates that both are markers of the brain's sensitivity to changing levels of reproductive hormones in some individuals.²⁰

Role of hormonal changes in perimenopausal depression

The mechanism by which menopausal transition–related neuroregulatory changes may affect mood is still largely unknown. It has been established that the menopausal transition interferes with the production and balance of different forms of estrogen present in women. The “estrogen withdrawal theory” proposes that the onset or worsening of mood symptoms in perimenopausal women result from a significant decline in peripheral concentrations of estradiol. However, estrogen levels increase during the early perimenopausal period and then drop again, which contradicts this theory.²¹ On the other hand, women who have undergone bilateral oophorectomy (surgical menopause) appear to have a higher incidence of depressive symptoms compared with those who entered menopause naturally. Although there may be a bias because women who undergo oophorectomy may be at higher risk for depression before surgery, this observation supports the hypothesis that abrupt changes in estrogen levels play some role in the development of depressive symptoms in this subpopulation.

Other hormonal changes may affect mood during the menopausal transition as well as at other times. For example, depressive and anxiety symptoms, as well as decreased libido, have been described among postmenopausal women who present with decreased testosterone, particularly after oophorectomy. Testosterone supplementation has been shown to alleviate these symptoms in some women treated concurrently with estrogen.²²

Psychosocial factors in the menopausal depression

Several studies have examined the association between emotional well-being during the menopausal transition and different demographic characteristics, including socioeconomic status, ethnicity, marital satisfaction, and quality of family relationships.^{17,23} For many decades, the menopausal transition was identified as a disruptive event during which women were at risk of losing a “major role”: maternity. The expression “empty-nest syndrome” (when children leave home) has been extensively used to characterize the psychosocial origin of depressive symptoms manifesting during the menopausal transition. The relative validity of this theory, however, is questionable, and it appears to be restricted to a subgroup of women who have children and who are overly engaged with them. More socially active healthy women, on the other hand, would consider this period an ideal opportunity to return to work or to increase social/leisure activities and to improve several aspects of their romantic partnership or marital relationship. For such individuals, children returning home could in fact become a stressful event.^{24,25}

Management of depression during the menopausal transition

If the menopausal transition is a period of risk for mood disturbance, then appropriate management of such depression is critical, given the morbidity associated with untreated affective disorders. Multiple studies have demonstrated the efficacy of both nonpharmacologic modalities and pharmacologic agents for the treatment of depression in general.²⁶ There is a growing number of studies describing the efficacy of a spectrum of treatments of depression in menopausal women.²⁷ These studies suggest that women with perimenopausal depression may respond to specific interventions, such as estrogen therapy (ET), whereas estrogen is not effective in treating depression in older postmenopausal women.²⁸

ET has been used widely to treat menopausal symptoms and may be the most effective treatment of hot flashes. Randomized placebo-controlled trials of estrogen for perimenopausal depression indicate that it also is an effective treatment in this population. In these studies, the use of transdermal estradiol (50 to 100 $\mu\text{g}/\text{day}$) resulted in partial or total remission of depressive episodes in 60% to 75% of subjects receiving hormonal treatment for 4 to 12 weeks, compared with a response rate of 20% to 30% obtained with placebo.^{29,30} ET works within the first month of its use, but no data are available to guide the clinician in the duration of use required to obtain sustained antidepressant benefits from estrogens. Estrogen trials for the treatment of depression associated with the menopausal transition have not specifically investigated the role of concomitant use of progesterone on mood. Despite clinical evidence that the use of progestogens may lead to increased irritability and fatigue,³¹ few studies suggest that cyclic use of progesterone deteriorates mood in those whose depression responds to ET.³²

Results of the Women’s Health Initiative (WHI) have made women concerned about the use of estrogens for any length of time, although most women who have menopausal symptoms typically do not require ongoing use of estrogen therapy beyond the 4- to 5-year period after which the cumulative risk of breast cancer and cardiovascular disease becomes significant. The use of estrogens remains an important therapeutic option for menopausal women with depression who do not have contraindications for estrogen, particularly if they have concomitant hot flashes. Nonetheless, some women prefer to avoid the use of estrogens and others are unable to take ET because of breast cancer or thromboembolic risks.

In the post-WHI era, many women who historically would have continued ET indefinitely are discontinuing the medication. Rapid reemergence of menopausal symptoms, such as severe hot flashes,^{33,34} sleep disruption, and cognitive difficulties, have been reported in women still in the menopausal transition as well as in those aged >60 years who, based on epidemiologic studies, should not be experiencing such severe symptoms at this time.¹⁸ Many of these women have restarted therapy with estrogens because of the significant improvement in their quality of life or have considered novel alternatives to

hormones (e.g., serotonergic agents) for treatment of menopausal symptoms.²⁷ It is yet to be determined whether the discontinuation of hormone therapy will increase the risk of depression, particularly in those women who initiated the medication for treatment of menopause-associated depression. If this is the case, an increase in mood disturbance among perimenopausal and postmenopausal women due to declining prescriptions of hormone therapy may be anticipated. Data on the appropriate management of depression in the context of hormone therapy discontinuation are lacking.

Extensive data exist, however, regarding the efficacy of antidepressant therapy. Studies of antidepressants for the specific treatment of depression in perimenopausal and postmenopausal women demonstrate the efficacy of conventional antidepressants in this population. Open-label studies show that the serotonergic agents citalopram and escitalopram are effective as monotherapy, and that citalopram and mirtazapine are effective adjuncts to ET when depression symptoms do not respond to ET alone.^{35,36} Such antidepressants are effective within 1 month of use, but the length of time that they should be used has not yet been investigated. Antidepressant treatment studies suggest that relapse into depression is minimized if antidepressants are continued for 6 to 12 months of wellness.

Although serotonergic antidepressants have few serious side effects, the prevalence of treatment-emergent sexual dysfunction³⁷ and weight gain associated with use of some compounds limits their extended use. Other treatments for depression in perimenopausal and postmenopausal women are currently under investigation. One such study is evaluating the use of the hypnotic agent zolpidem.³⁸ Although hypnotic agents are not effective treatments of depression in the general population, the putative explanation for depression as a consequence of sleep disruption from hot flashes raises the possibility that hypnotic agents may have specific efficacy in the treatment of depression in this population.

Nonpharmacologic interventions such as specific psychotherapies have not been systematically evaluated as a treatment for depression during the menopausal transition. Few reports indicate that measures such as relaxation response training and exercise^{39,40} can help in preventing or ameliorating symptoms of depression during the menopausal transition or postmenopause. Given the impact of psychosocial factors on the risk for developing depressive symptoms in some women during the menopausal transition, the efficacy of psychotherapeutic interventions warrants further investigation.

Management of depression in women by age and menopausal status

With increased public awareness of the efficacy of antidepressants to treat depression, particularly selective serotonergic reuptake inhibitors (SSRIs), such as fluoxetine and citalopram, and dual-action antidepressants (serotonin/norepinephrine reuptake inhibitors [SNRIs]), such as venlafaxine and duloxetine, it is critical to delineate populations of men and women

who appear more or less responsive to treatment with these compounds. Older agents such as tricyclic antidepressants (TCA) are used less widely now because of their side-effect profile and overdose risks, but they may be particularly effective in certain populations.

Several studies have examined whether menopausal status influences responsiveness to SSRIs and SNRIs.^{41–43} Most have used age cut-offs (older vs. younger than age 45, 50, 52, or 56 years) as proxies for postmenopausal status.^{41–44} One study concluded that in the older age groups, depression in women is more responsive to TCAs than in younger women, who are more responsive to SSRIs.³⁸ In contrast, other studies have found no age-related differences in women in their response to SSRIs, SNRIs, or TCAs.^{43,44} Another study that examined the efficacy of an SSRI according to menopausal status—defined by menstrual cycle patterns and vasomotor symptoms—found no significant difference in antidepressant response in premenopausal, perimenopausal, and postmenopausal women treated with the SSRI.⁴³

Summary and recommendations

What is the ideal algorithm for managing depression in perimenopausal women? The clinical evidence supporting the antidepressant effects of ET for this population is clear, but effectiveness and patient and clinician willingness to use such an intervention as a primary treatment for depression has been complicated by issues raised regarding safety of longer-term use of hormonal interventions. Clearly, the well-documented safety and efficacy of antidepressants may make these agents the treatment of choice for individuals experiencing depression during the menopausal transition. However, the significant prevalence of treatment-emergent sexual dysfunction and weight gain associated with use of some of these compounds are factors that must be considered when managing depression in this population. A challenge to the field lies in the identification of the most tolerable treatments to manage depression in an aging population while taking into account the spectrum of side effects that may complicate treatment as well as associated symptoms (e.g., vasomotor symptoms) and other psychosocial factors that also may modulate risk for the development of mood disturbance.

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