Narrative Review

A Review of Cognitive, Sleep, and Mood Changes in the Menopausal Transition

Beyond Vasomotor Symptoms

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Complaints of brain fog, mood changes, and sleep disruption are common in the menopause transition. These symptoms can negatively affect overall health, quality of life, productivity, and relationships. This narrative review addresses the epidemiology, underlying mechanisms, and treatment options associated with changes in cognition, mood, and sleep during the menopause transition. The goal is to help health care professionals recognize these symptoms, provide information and support to their patients, and use an evidence-based approach to managing these symptoms.

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Vasomotor symptoms (VMS), hot flushes and night sweats, are widely considered the cardinal symptom of the menopause transition. Vasomotor symptoms affect about 80% of individuals with a median duration of 7–9 years and with greatest severity in early postmenopause.[1] Other menopause symptoms such as cognitive complaints, mood disturbance, and sleep disruptions also can affect quality of life, productivity, relationships, and overall health. Helping patients to understand, manage, and improve these symptoms often presents a challenge to health care professionals because of limited training opportunities and uncertainty about the evidence, guidance, and management options. The effects of menopausal hormone therapy (HT) on cognitive, mood, and sleep symptoms have been studied in clinical trials, but menopausal HT is not approved by the U.S. Food and Drug Administration to treat those symptoms. This review addresses the epidemiology, underlying mechanisms, and treatment options associated with changes in cognition, mood, and sleep during the menopause transition.

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COGNITIVE CHANGES

Epidemiology

During the menopause transition, 40–60% of patients report cognitive changes or "brain fog," a constellation of symptoms including difficulty concentrating and remembering words, names, anecdotes, and numbers.[2] These symptoms cause distress to women because many fear that they signal development of dementia. Longitudinal studies using neuropsychological testing show small but reliable declines in verbal learning and memory during perimenopause, with less reproducible declines observed in working memory, attention, and processing speed.[3–6] These changes occur independently of advancing age. Executive functions such as planning and task switching do not appear to change.[2,7] Data from SWAN (Study of Women's Health Across the Nation)[4] suggest that cognitive symptoms do not persist for most women beyond perimenopause, whereas POAS (Penn Ovarian Aging Study)[3] found that declines in verbal learning do persist in postmenopause; data were limited for late postmenopausal women. A diverse sample of low-income women with and without human immunodeficiency virus (HIV) showed declines in verbal memory and learning and working memory that persisted

from perimenopause into the postmenopause period.[7] Of those women, 8–10% showed a level of decline consistent with cognitive impairment. Thus, for the large majority of women, cognitive performance remains well within normal limits and rebounds in postmenopause, but vulnerable populations of women may experience persistent and significant declines.

In a systematic review and meta-analysis, oophorectomy before menopause and before age 46 years was associated with higher prevalence of clinically diagnosed mild cognitive impairment and poorer cognitive performance on a battery of cognitive tests.[8] Oophorectomy performed before age 46 years was associated with a 70% increased risk of cognitive impairment or dementia compared with no oophorectomy?[9] Estrogen replacement can mitigate this risk.[10–12] Individuals with primary ovarian insufficiency and early and premature menopause have a higher risk of cognitive disorders and dementia compared with individuals with menopause at a typical age.[13]

Underlying Mechanisms

Menopause-related cognitive declines are correlated with changes in ovarian hormones and co-occurring menopause-related sleep disturbances, mood changes, VMS, and psychosocial factors.[14] Changes in estrogen activity in the hippocampus and prefrontal cortex, areas of the brain associated with verbal memory and executive functioning, play an important role.[15,16] Reduced estradiol levels after oophorectomy and gonadotropin-releasing hormone suppression of ovarian function lead to declines in verbal learning and memory.[17]

The role of VMS in cognition and as a biomarker for Alzheimer disease is under investigation. Vasomotor symptoms have been associated with declines in memory and poorer brain health.[18–21] Objectively measured physiologic VMS, not self-reported VMS, were associated with decreased verbal memory performance.[18,21,22] Treatment of VMS with a nonhormonal intervention, stellate ganglion blockade, led to improvements in memory that were independent of improvements in sleep, suggesting a possible causal association between hot flushes and memory problems.[23] Neuroimaging studies indicate increased activity in the hippocampus, parahippocampus, and multiple regions of the prefrontal cortex associated with VMS.[18] Nocturnal VMS were found to be associated with brain structural abnormalities as measured by white matter hyperintensities, again with effects independent of sleep.[19]

Clinical Guidance

Educating and reassuring that cognitive changes are expected during the menopause transition are important (Table 1). Menopausal HT is generally not indicated or recommended to treat cognitive changes for those who experience natural menopause because high-quality randomized clinical trial (RCT) data reliably show no benefit.[24–27] Critically, none of those trials focused on women with VMS, and given the association of VMS with poorer memory and markers of brain health, use of menopausal HT or non-HT may provide cognitive benefits in women with VMS.[1] Clinicians should counsel patients about the potential effect of surgical menopause on cognitive function and discuss HT treatment to mitigate the risks.[11] To prevent cognitive decline, The Menopause Society and other medical organizations recommend menopausal HT for women with early menopause and primary ovarian insufficiency until the typical age at menopause.[28]

Risk-modifying and -optimizing behaviors during the menopause transition may improve cognitive reserve and brain health (Table 1).[2] These include moderate-intensity physical exercise, healthy eating (ie, Mediterranean diet), body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) lower than 25.0, social engagement, and avoiding smoking, *excessive alcohol consumption* (defined by the National Institute on Alcohol Abuse and Alcoholism for women as consuming four or more drinks on any day or eight or more drinks per week), and head injuries.[29–31] Disturbed sleep, increased anxiety, and depressive symptoms experienced during the menopause transition are risk factors for impaired cognitive performance; thus, optimizing sleep and psychological well-being may also reduce cognitive impairment.

MOOD CHANGES

Epidemiology

The menopause transition is considered a "window of vulnerability" for the development of depressive symptoms, major depressive episodes, and anxiety symptoms.[32] A meta-analysis and systematic analysis of prospective cohort studies from across the globe found a 40% increased risk of depression in perimenopause compared with premenopause but no increased risk in postmenopause compared with premenopause.[33,34] When we consider only prospective cohort studies from the United States, risk of depression is higher for those in the menopause transition. In SWAN, the odds of developing a major depressive episode was 2.17 times higher in perimenopausal and 3.43 times higher in postmenopausal women compared with premenopausal women. Similarly high risks of perimenopausal depression were found

Table 1. Symptom Management and Clinical Guidance

Symptom	Symptoms That Worsen in the Menopause Transition	Pharmaceuticals		Clinical Guidance
		HT	Non-HT	
Brain fog–cognition	Verbal learning and memory "I am so forgetful…When I am introduced to someone, I immediately forget their name. Or I see a neighbor and can't remember her name." Attention–working memory "I have a difficult time paying attention and doing mental math." Processing speed "I just feel mentally slow."	Recommended for premature surgical menopause, early menopause, or POI May confer benefit in women with bothersome VMS Not recommended to prevent or address cognitive issues in naturally menopausal women		Treat comorbid VMS and sleep disruption Slow midlife weight gain Maintain a healthy BMI of 18.5–25 Balanced Mediterranean-style diet Engage in at least 150 min/wk of moderate-intensity aerobic physical activity Learn (new skills, languages, read) Engage socially Avoid tobacco and excessive alcohol Optimize heart health (prevent or treat hypertension, dyslipidemia, diabetes mellitus)
Mood and anxiety	Depressive symptoms "I just don't get the same pleasure out of my work and relationships as I used to." "I have little interest in the activities that I used to enjoy." Anxiety symptoms "I have been feeling more nervous/anxious lately."	Not approved for depressive symptoms or MDD May be effective to treat MDD, minor depression, and dysthymia in perimenopause No benefit for MDD in postmenopause	Antidepressants are first-line treatment for MDD in perimenopause and postmenopause For recurrent MDD, use antidepressant that was effective in premenopause SSRIs and SNRIs may offer synergistic treatment of VMS Neurokinin B receptor antagonists may improve mood symptoms associated with VMS	Screen for MDD, particularly in women with a history of MDD, and manage appropriately Treat comorbid VMS and sleep symptoms Identify and monitor modifiable risk factors CBT has proven clinical efficacy for depression, anxiety, and VMS Prevent symptoms with Mindfulness-Based Stress Reduction and other stress-reducing interventions Aerobic exercise has antidepressant effects
Sleep disruption	Sleep latency "It takes me longer to fall asleep." WASO "I am waking up more frequently during the night." Sleep duration "I am not able to sleep as long as I have in the past." Sleep efficacy "I lie in bed but I can't sleep."	May offer benefit in those with bothersome VMS Oral micronized progesterone may improve sleep and decrease VMS and be used off label for menopause-related sleep disruption	Neurokinin B receptor antagonists may improve sleep symptoms associated with VMS Paroxetine 7.5 mg approved for VMS also has been shown to improve sleep latency and WASO Mixed data for other SSRI and SNRIs (some improve sleep, others do not) GABA-A receptor antagonists and agonists (benzodiazepines and nonbenzodiazepine sedative–hypnotic medications) should generally be avoided because of adverse side effects and potential for abuse Dietary supplements (ie, magnesium and melatonin): limited and conflicting evidence for efficacy	CBT for insomnia is the recommended first-line therapy for menopause-related sleep disruption and has proven clinical efficacy in perimenopausal and postmenopausal women Treat comorbid mood symptoms

HT, hormone therapy; POI, primary ovarian insufficiency; VMS, vasomotor symptoms; BMI, body mass index; MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; CBT, cognitive behavioral therapy; WASO, wake after sleep onset; GABA-A, γ-aminobutyric acid A.

in POAS[35] and the Harvard Study of Moods and Cycles,[36] although those studies did not find an elevated risk of depression in postmenopause compared with premenopause. Thus, there is reliable evidence that perimenopause is a period of increased risk of depression (Table 1). Women who experience premature or early menopause also appear to be at increased risk of depression.[32,33,37–40]

The most significant risk factor for developing depression during the menopause transition is a history of depressive symptoms and anxiety.[39,41–43] In POAS, a history of depression increased the risk of elevated depressive symptoms eightfold.[39] In SWAN, 59% of women with a history of depression developed depression in perimenopause compared with 28% of women without depression.[42] Depression is more prevalent in midlife women with financial problems, low education levels, bothersome menopause symptoms (VMS, sleep problems), health issues, obesity, major stressful life event, chronic stressors (eg, caregiving), negative attitudes toward aging and menopause, daily hassles, low social support, and high trait anxiety.[32] Reproductive-related mood changes, premenstrual dysphoric disorder, and perinatal depression are also associated with elevated risk for mood changes in the menopause transition.[40,43,44]

In the POA study, Black women had twice the risk of high depressive symptoms compared with White women.[45] In contrast, SWAN found similar risks of depression for Black and White women,[33] although the risk of chronic depression was higher in Black women.[46] SWAN also found that Hispanic ethnicity was associated with increased risk of depressive symptoms during the menopause transition compared with White women.[33]

The SWAN study found an increased risk of anxiety during perimenopause and postmenopause compared with premenopause, but this effect did not persist after controlling for VMS. Vasomotor symptoms were a strong predictor of anxiety, with frequent VMS associated with a threefold increased odds of elevated anxiety.[47] Risk of anxiety was lower in Black and Chinese women compared with White women. Women with high anxiety at entry in SWAN had persistent high anxiety across menopause stages, whereas women with low anxiety at entry experienced elevated anxiety in late perimenopause and postmenopause.

Pathophysiology

Estrogen loss plays a critical role in the development of perimenopausal depression and anxiety. *BRCA* carriers undergoing risk-reducing bilateral salpingo-oophorectomy showed a 2.3 times higher rate of incident depression in the 12 months after surgery compared with controls and were three times more likely to show chronic depression during that time.[48] Clinically significant anxiety was present at 3 months after surgery but dissipated over the remaining 9 months of follow-up.

Fluctuations in estradiol, particularly for certain women, appears to be a key factor for mood disturbance in the perimenopause.[49–51] Fluctuations in estradiol secretion during the menopause transition are postulated to drive neurotransmitter (dopamine, serotonin, and norepinephrine) dysregulation and contribute to depressed mood in the menopause transition.[52] Fluctuations in estradiol and progesterone lead to fluctuations in allopregnanolone, a metabolite of progesterone that acts on the γ-aminobutyric acid A receptor to influence the hypothalamic–pituitary–adrenal axis.[51] Dysregulation of this system appears to be a common mechanism underlying reproductive mood disorders. Estradiol fluctuations are also predictive of greater anxiety symptoms.[53,54] Experimental evidence shows that women who experience new-onset depression during perimenopause have an individual sensitivity to mood changes after withdrawal of estrogen.[55]

Clinical Guidance

First-line therapy for treating midlife depressive symptoms includes behavioral and pharmacologic therapies such as cognitive behavioral therapy, selective serotonin reuptake inhibitors (SSRIs), and serotonin–norepinephrine reuptake inhibitors.[32] These therapies improve other symptoms that present during the menopause transition.[1] Cognitive behavioral therapy has demonstrated efficacy for menopause-related VMS and sleep disturbance. SSRIs and serotonin–norepinephrine reuptake inhibitors have been shown to reduce VMS. Shared decision making and individualization are critical when exploring treatment options because some treatments are associated with weight gain and sexual side effects. Treating bothersome VMS in midlife women with depression is highly recommended because nocturnal VMS and sleep disturbance can exacerbate depressive symptoms.

Combined hormonal contraception is frequently used to reduce mood changes, abnormal uterine bleeding, VMS, and dysmenorrhea during the menopause transition. Combined hormonal contraception minimizes estradiol variability and may reduce mood changes associated with hormonal fluctuations. However, the efficacy of combined hormonal

contraception to prevent or treat depression in the menopausal transition has not been evaluated in RCTs.

Few RCTs have evaluated the efficacy of estrogen therapy to treat depression in menopause. Estradiol has been shown to be effective in perimenopause but not postmenopause, suggesting that perimenopause may be a window of opportunity to use estradiol to treat depressive symptoms. Based on two RCTs demonstrating the efficacy of transdermal estradiol to treat major depressive disorder, the 2016 Clinical Guidelines of the Canadian Network for Mood and Anxiety Treatments included estradiol as a second-line treatment for the management of major depressive disorder during perimenopause.[56] Limited evidence suggests that estrogen used as an adjunct to antidepressant therapy may have a greater effect in alleviating perimenopausal depression than either estrogen or antidepressant alone.[32] Estradiol augments the response to SSRIs, but not venlafaxine, in perimenopausal and postmenopausal women.[32] Transdermal estradiol has been effective in improving anxiety and anhedonia symptoms.[54] Consensus guidelines and expert opinion suggest that it is reasonable to use transdermal estradiol for 2 to 6 weeks in perimenopausal women with bothersome VMS and concomitant depressive symptoms and those who may be resistant to first-line antidepressant therapies.[57]

More trials have evaluated mood effects of menopausal HT in asymptomatic or mildly affected women. Estradiol does not have a reliable positive mood benefit in asymptomatic nondepressed perimenopausal or postmenopausal women.[28] Depression and anxiety symptoms among euthymic postmenopausal women improved with conjugated equine estrogen (0.45 mg) and micronized progesterone (200 mg, 12 d/mo) relative to placebo in KEEPS (Kronos Early Estrogen Prevention Study). Transdermal estradiol (50 mg/wk) did not yield similar benefits.[25] In a 12-month randomized, placebo-controlled trial, transdermal estradiol (0.1 mg/d) and micronized progesterone (200 mg/d for 12 days every 3 months) were more effective than placebo in preventing clinically significant depressive symptoms among early perimenopausal euthymic women and those with stressful life events.[58] According to current evidence, estrogen should not be used to prevent or alleviate symptoms in nondepressed, asymptomatic perimenopausal or postmenopausal women.[59]

Hormone therapy does not appear to mitigate the risk of depression associated with premature or early menopause,[48,60,61] although HT is recommended for those women for other health outcomes (eg, bone), unless contraindicated, at least until the typical age at menopause.

Given the elevated risk of a recurrent major depressive episode in the menopause transition, screening for depression in perimenopausal and postmenopausal women with a history of depression is highly recommended.[32] First-line treatment for those who experience recurrent depression is the antidepressant or psychotherapeutic treatment that previously worked.[32]

SLEEP

Epidemiology

Globally, 40–69% of women experience sleep disturbances during the menopause transition.[62] In SWAN, the cross-sectional age-adjusted rate of sleep difficulty was 31% in premenopausal women, 40% in early perimenopausal women, 45% in late perimenopausal women, 43% in postmenopausal women, and 48% in surgically menopausal women.[63] Sleep disturbance increases during the transition from premenopause to postmenopause (Table 1).[64] In longitudinal analyses in SWAN, reports of difficulty falling asleep and staying asleep increased with advancing menopause stage; early morning awakenings became less frequent in the transition to postmenopause.[64] The most common sleep complaint across all stages was difficulty staying asleep, reported by 40% of late perimenopausal and postmenopausal women. In contrast, difficulty falling asleep was reported by fewer than 20% of women across stages. In SWAN, reports of sleep disturbance were highest in White and Hispanic women, followed by Black women and then Japanese and Chinese women.[63]

The effect of menopause on objective sleep measures (ie, polysomnography, actigraphy) is not well understood because of small sample sizes and sampling periods, poorly controlled confounding variables, and other methodologic factors.[65] Analysis of longitudinal actigraphy data from SWAN indicated that sleep duration decreased in the late perimenopause, wake after sleep onset increased in postmenopause, and sleep latency increased in the late perimenopause and postmenopause stage but that generally sleep difficulties improved over time.[66]

Distinguishing menopause-related sleep disturbance from sleep-related breathing disorders (obstructive and central sleep apnea), restless leg syndrome, and insomnia is important. Initial differentiation occurs after evaluation of the patient's history and a review of the clinical features of sleep diagnoses. Menopause-related sleep disturbances are

characterized by increased wake after sleep onset and sleep onset latency and decreased satisfaction with sleep quality, sleep duration, and maintenance of sleep.[67] Insomnia is a *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) diagnosis characterized by difficulty initiating sleep, difficulty maintaining sleep, or early morning awakenings occurring at least 3 nights per week for at least 3 months and affecting quality of life. The onset of restless leg syndrome is not associated with menopausal status, although postmenopausal women are more likely to screen positive for obstructive sleep apnea.[68]

Underlying Mechanisms

Multiple factors influence menopause-related sleep disturbance (Fig. 1), including hormonal changes, VMS, mood changes, and aging.[64,69,70] It is postulated that sleep disturbance associated with menopause reflects a disruption of the function of the hypothalamic pituitary ovarian axis and sleep–wake regulatory systems.[71] Increases in nighttime awakenings are significantly associated with higher postmenopausal-range follicle-stimulating hormone and lower estradiol levels independently of nocturnal VMS.[72] This finding validates the concern of women who complain of sleep disturbance in the absence of VMS. Several studies demonstrate a relationship between lower estradiol levels and difficulties falling and staying asleep.[64,72,73] Progesterone metabolites, pregnanolone, and allopregnanolone acting on the γ-aminobutyric acid pathways may improve sleep and mood regulation by inducing somnolent, sedative, and anxiolytic effects.[74–76]

Vasomotor symptoms play an important role in sleep disruption in midlife women. The decline of estrogen at menopause alters the function of estrogen-sensitive hypothalamic kisspeptin/neurokinin B/dynorphin neurons implicated in maintaining core body temperature and triggering hot flushes. Kisspeptin/neurokinin B/dynorphin neurons may also play a role in sleep disruption at menopause.[67] Aging is associated with declines in circadian rhythm and sleep disruptive conditions such as obesity, nocturia, pain syndromes, and psychosocial stressors and events. Difficulty sleeping because of "feeling too hot" may herald the menopause transition.[77] There is strong empirical evidence that VMS disrupt sleep; 78% of objectively measured nocturnal VMS are associated with awakenings.[78] However, VMS accounts for only one-third of nighttime awakening, which suggests that other factors may be more influential in menopause sleep disturbance.[78–80] In a prospective study following up patients undergoing risk-reducing bilateral salpingo-oophorectomy, reported sleep quality was significantly reduced and was largely attributable to severe VMS.[73]

There is a complex, bidirectional relationship between depressed mood and sleep disturbances; mood changes are a risk factor for poor sleep, and poor sleep is a risk factor for mood changes.[32] Some evidence suggests that anxiety and depression may in part account for the relationship between VMS and sleep disturbance.

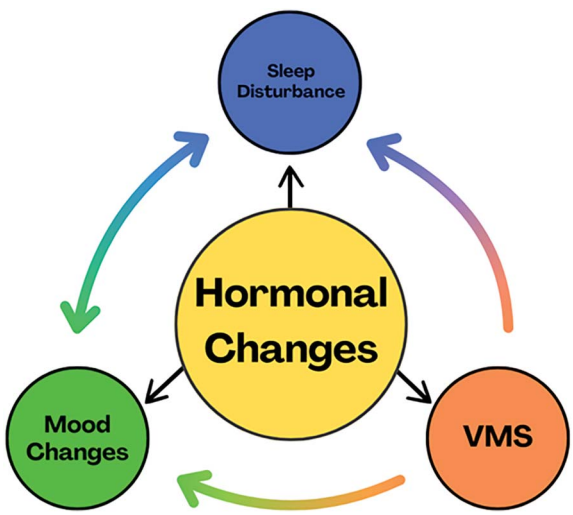

Fig. 1. Complex interactions among vasomotor symptoms (VMS), sleep, mood, and hormonal changes in menopause. *Williams. Non–Vasomotor Symptoms of Menopause. Obstet Gynecol 2025.*

Clinical Guidance

Treatment of menopause-related sleep disturbance often requires a multidisciplinary approach including optimizing sleep hygiene, nonpharmacotherapies, pharmacotherapy, and behavioral therapies. An initial step is treating co-occurring conditions that may affect sleep. Cognitive behavioral therapy for insomnia is recommended as first-line treatment for chronic insomnia by the American College of Physicians and is supported as a treatment for menopause-related sleep disturbance.[81,82] In a systematic review, menopausal HT was moderately effective at improving sleep quality in those whose sleep is disrupted by VMS.[83] For individuals experiencing surgical menopause and VMS-related sleep disturbance, menopausal HT leads to significantly improved sleep quality.[48] On the basis of limited data, The Menopause Society suggests that low-dose estrogen or micronized progesterone 300 mg nightly decreases VMS and improves sleep and may be used to

improve sleep independently of VMS.[28] Non-HTs used to treat VMS such as neurokinin B receptor antagonists and SSRIs have been shown to improve sleep symptoms associated with VMS.[84–88] Hypnotic medications should be used with caution because of their potential for overuse and abuse and their increased risk of falls, fractures, and osteoporosis in postmenopausal women.[89,90]

In a recent systematic review and meta-analysis, behavioral interventions, cognitive behavioral therapy, physical exercise, and mindfulness-based relaxation techniques significantly improve subjective and objective measures of sleep.[82] Low- and moderate-intensity exercise, including yoga, Pilates, strength training, and walking, was associated with improved sleep outcomes.

CONCLUSION

The intersection of numerous factors such as VMS, the changing hormonal milieu, and psychosocial stressors may affect cognition, mood, and sleep changes during the menopause transition. To optimize the health, quality of life, and well-being of patients, it is important for clinicians to recognize these symptoms and address them with an individualized, multidisciplinary approach. This may include HT for those undergoing premature menopause or those with concomitant VMS symptoms. Others may benefit from non-HTs, including pharmaceuticals, lifestyle, behavioral, and dietary modifications.

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