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The Impact of Perimenopause on Mood and Cognition: A Review of Neuroendocrine Mechanisms and Treatment Strategies

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Abstract

The menopausal transition represents a critical neuroendocrine window during which fluctuating ovarian hormones significantly impact mood and cognition, yet the underlying mechanisms and optimal management strategies remain informatively understood. This review synthesizes current evidence on the neuroendocrine pathways-including hormonal fluctuations, receptor dynamics, and neurotransmitter alterations—that contribute to perimenopausal mood disorders and cognitive decline. It further evaluates both hormonal and non-hormonal interventions, highlighting the need for integrated, personalized treatment approaches to address these complex symptoms. Key topics include the role of estrogen and progesterone in modulating serotonergic and dopaminergic systems, the impact of hypothalamic-pituitary-adrenal axis dysregulation, and structural and functional brain changes observed during perimenopause. The review also examines the efficacy of hormone therapy, antidepressants, cognitive behavioral therapy, and complementary treatments such as acupuncture and herbal medicine. Clinical insights are drawn from recent trials assessing transdermal estradiol, micronized progesterone, and traditional formulations, offering a comparative perspective on their benefits and limitations. Additionally, the influence of genetic factors, lifestyle, and psychosocial stressors on symptom severity is discussed, emphasizing the heterogeneity of perimenopausal experiences. The relationship between vasomotor symptoms, sleep disturbances, and cognitive impairment is explored, alongside emerging evidence linking perimenopausal symptoms to long-term neurological risks. Future research should prioritize longitudinal studies to clarify the timing and duration of hormone therapy for cognitive protection and explore the mechanisms of non-hormonal interventions. There is also a critical need to develop biomarker-guided, personalized treatment frameworks that integrate biological, psychological, and social dimensions of perimenopausal health.

Keywords: Cognitive decline, Hormone therapy, Menopausal transition, Mood disorders, Neuroendocrine mechanisms, Perimenopause, Treatment strategies

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Introduction

The impact of perimenopause on mood and cognition has garnered significant scientific interest, primarily due to the profound neuroendocrine changes that occur during this transitional period [1-5]. The fluctuating levels of sex hormones, particularly estrogen and progesterone, are central to understanding the neurobiological mechanisms underlying mood disturbances and cognitive alterations in perimenopausal women [6-10]. One of the key neuroendocrine mechanisms involves the fluctuations of estrogen and progesterone during the menopausal transition [11-15]. As documented in recent reviews, these hormonal variations exert a profound influence on the central nervous system, affecting mood regulation and cognitive functions [16]. Estrogen, especially estradiol, plays a pivotal role in modulating neurotransmitter systems, including serotonergic, dopaminergic, and cholinergic pathways, which are integral to mood stabilization and cognitive processes [17, 18]. The decline in estrogen levels of post-menopause is associated with increased vulnerability to mood disorders such as depression and anxiety, highlighting the hormone's neuroprotective and neuromodulatory roles [16].

Further elucidating these mechanisms, neuroendocrine changes during menopause include alterations in hypothalamic-pituitary-adrenal axis activity, which can influence stress responses and mood regulation [19-23]. The neuroendocrine system's adaptation to declining ovarian hormones may contribute to the onset of mood disturbances, with hot flashes and sleep disruptions serving as both symptoms and potential mediators of mood and cognitive impairment [24, 25]. The neuroendocrine alterations are not only limited to hormonal fluctuations but also involve changes in receptor density and sensitivity within the brain, impacting neural plasticity and cognitive resilience [26]. The relationship between estrogen and cognitive function has been extensively studied, with evidence suggesting that estrogen exerts neuroprotective effects that support memory,

attention, and executive functions. Estrogen's modulation of synaptic plasticity and neurogenesis is believed to underpin these cognitive benefits. Consequently, the decline in estrogen during perimenopause correlates with reports of cognitive decline, including memory lapses and decreased processing speed [27]. Systematic reviews and meta-analyses have reinforced the notion that hormone therapy, particularly estrogen-based regimens, can mitigate some of these cognitive deficits, although results vary depending on timing, formulation, and individual factors [26].

In addition to cognitive effects, mood disturbances during perimenopause are closely linked to neuroendocrine dysregulation [28-32]. The fluctuations in estrogen and progesterone influence serotonergic pathways, which are critical in the pathophysiology of depression [33-37]. Estrogen's ability to enhance serotonergic transmission and receptor sensitivity suggests that hormonal fluctuations can precipitate or exacerbate depressive symptoms [31]. Moreover, stress-related mechanisms, including dysregulation of the hypothalamic-pituitary-adrenal axis, further compound mood disturbances, indicating a complex interplay between neuroendocrine factors and psychological stressors [38].

Treatment strategies aimed at alleviating mood and cognitive symptoms during perimenopause often involve hormone therapy, which has shown promise in improving both domains [39-43]. Hormone therapy, typically involving estrogen with or without progestogen, has been demonstrated to improve mood stability and cognitive performance in menopausal women [27]. The neuroprotective effects of estrogen are thought to be mediated through multiple pathways, including antioxidant properties, modulation of neurotrophic factors, and enhancement of synaptic connectivity [17]. However, the efficacy of hormone therapy is influenced by factors such as timing of initiation, duration, and individual health status, with some studies indicating potential risks that necessitate careful consideration [44]. Beyond hormone therapy, non-pharmacological interventions such as cognitive behavioral therapy and stress management techniques have been explored to address mood and cognitive issues. These approaches aim to mitigate the impact of neuroendocrine dysregulation by reducing psychological stress, which can further disrupt ovarian function and exacerbate neuropsychiatric symptoms [38]. The integration of psychological and hormonal treatments may offer a comprehensive approach to managing perimenopausal mood and cognitive disturbances.

Overall, the neuroendocrine mechanisms underlying mood and cognitive changes during perimenopause are complex and multifaceted. Fluctuations in estrogen and progesterone levels significantly influence neurotransmitter systems, receptor sensitivities, and neural plasticity, thereby affecting mood regulation and cognitive functions. Hormone therapy remains a cornerstone of treatment, with evidence supporting its benefits in mitigating neuropsychiatric symptoms, although individual factors must be considered. Future research continues to explore the nuanced interactions between neuroendocrine changes and psychological factors, aiming to optimize therapeutic strategies for women navigating this transitional phase.

Neuroendocrine Mechanisms

Perimenopausal depression is a significant concern, with hormonal fluctuations triggering neuroinflammation and oxidative stress, leading to neuronal damage (Table 1). This highlights the need for targeted treatments that address these specific pathologies [45]. The neuroendocrine system plays a crucial role in regulating mood and cognition during perimenopause. A significant decline in ovarian hormones, particularly 17β-estradiol, has been linked to cognitive decline and mood disorders. Estradiol is known to influence neurophysiological processes that support cognitive function, and its reduction during perimenopause may contribute to the increased prevalence of mood disorders and cognitive impairments in this population [46]. Research indicates that up to 80% of perimenopausal and postmenopausal women report neurological symptoms, including mood changes and cognitive difficulties [46]. The interplay between hormonal changes and neurobiological factors is complex, with evidence suggesting that alterations in neurotransmitter systems, particularly those involving serotonin and dopamine, may exacerbate mood disturbances during this transition [47].

Estrogen influences cognitive functions through its action on estrogen receptors in the brain [48-51]. Studies using advanced neuroimaging techniques, such as 18F-fluoroestradiol positron emission tomography, have shown that estrogen receptor density increases during menopause, which may be a compensatory response to declining estrogen levels. However, higher estrogen receptor density is paradoxically associated with poor memory performance and mood symptoms, suggesting a complex relationship between estrogen signaling and cognitive outcomes [26, 52]. Cognitive complaints during perimenopause, such as memory issues, are common, but objective evidence of cognitive decline is inconclusive. Some studies suggest that cognitive deficits are mild and transient, with within-person changes in estradiol levels being positively associated with attention and memory performance [53].

The decline in estrogen and progesterone during perimenopause affects neurotransmitter systems, including serotonin, norepinephrine,

Table 1: Key neuroendocrine changes and their impact during perimenopause.

System/component	Change during perimenopause	Potential impact on mood and cognition
Estrogen	Significant fluctuation and eventual decline	Reduced neuroprotection, altered serotonin/dopamine signaling, decreased synaptic plasticity, leading to low mood and memory issues
Progesterone	Fluctuation and decline	Altered GABAergic function (affecting anxiety, sleep), loss of neuroprotective effects
Hypothalamic-pituitary-gonadal axis	Increased follicle-stimulating hormone/luteinizing hormone due to loss of ovarian feedback	Menstrual irregularity: serves as a biomarker of transition, indirectly linked to symptoms
Hypothalamic-pituitary-adrenal axis	Often dysregulated, increased reactivity	Heightened stress response, increased cortisol, exacerbating anxiety and depressive symptoms
Neurotransmitters (serotonin, norepinephrine)	Altered synthesis, release, and receptor sensitivity	Directly contributes to depression, anxiety, irritability, and impaired attention
Neuroinflammation	Increased glial cell activation, inflammatory markers	This contributes to neuronal damage, brain fog, and may increase long-term risk for neurodegeneration
KNDy neurons (hypothalamus)	Altered signaling due to loss of estrogen feedback	Primarily drives vasomotor symptoms (hot flashes), which disrupt sleep and secondarily impair cognition

and dopamine, which are crucial for mood regulation. These hormonal changes can lead to mood disturbances, such as depression and anxiety, which are prevalent during this transition [28, 54]. Perimenopausal symptoms like mood changes and brain fog have been linked to later-life cognitive and behavioral symptoms, potentially increasing dementia risk. Estrogen-based hormone therapy may mitigate some of these symptoms, although its effectiveness varies [55]. Hormone replacement therapy can help alleviate some cognitive and mood symptoms by prolonging the neuroprotective effects of estrogens. It has been shown to positively affect mood and cognitive efficiency by modulating neurotransmitter systems and neural activity. However, the benefits of hormone replacement therapy are not uniform across all women, and its use should be carefully considered based on individual health profiles [12]. The uncoupling of the estrogen receptor network from the brain's bioenergetic system during perimenopause can lead to a hypometabolic state, contributing to neurological dysfunction and potentially increasing the risk of neurodegenerative diseases [56, 57]. Estrogen's role as a master regulator of brain metabolism underscores its importance in maintaining cognitive and mood stability. The perimenopausal transition represents a critical period where these regulatory mechanisms are disrupted [56, 57].

The perimenopausal transition involves significant changes in the hypothalamic-pituitary-gonadal axis, with fluctuating and often elevated levels of follicle-stimulating hormone and luteinizing hormone due to decreased ovarian sensitivity and feedback inhibition from estradiol and inhibin B [58, 59]. These hormonal changes are associated with menstrual irregularities and can lead to increased bone turnover and alterations in lipid profiles, impacting overall health [58]. The perimenopausal period is marked by changes in monoamine neurotransmitter systems, including serotonin and norepinephrine, which are crucial for mood regulation and cognitive function. These changes may contribute to the increased incidence of perimenopausal depression [28]. Alterations in the function of GABAergic and opioid systems in the central nervous system are also observed, potentially leading to mood and cognitive dysfunctions during this transition [59]. Glial cell-induced neuroinflammation is another aspect of the neuroendocrine changes during perimenopause. This inflammation can exacerbate neurological symptoms and may increase the risk of neurodegenerative diseases later in life [28]. The perimenopausal transition is considered a critical period for the emergence of neurological diseases, with some women experiencing increased amyloid-beta deposition, a risk factor for Alzheimer's disease, particularly in those carrying the APOE-4 genotype [60].

Genetic polymorphisms in estrogen receptor genes, such as ESR1 and ESR2, influence the variability in menopausal symptoms among women. These polymorphisms modulate the effects of fluctuating estradiol levels, impacting symptom trajectories during perimenopause [61]. Perimenopause is associated with significant changes in brain structure, connectivity, and energy metabolism. These changes are specific to menopausal endocrine aging and involve brain regions responsible for higher-order cognitive processes [60]. The hypothalamus, a critical brain region for neuroendocrine regulation, undergoes transcriptomic changes during perimenopause. These include alterations in inflammatory pathways and kisspeptin/neurokinin B/dynorphin (KNDy) neuron signaling, which are crucial for thermoregulation and reproductive hormone regulation [62]. The perimenopausal transition is marked by increased neuroinflammation, primarily due to estrogen depletion. This inflammation is linked to the activation of glial cells and altered KNDy neuron activity, which can exacerbate neurological symptoms and increase the risk of neurodegenerative diseases like Alzheimer's disease [59, 63]. The loss of ovarian steroid feedback during perimenopause significantly impacts the activity of KNDy circuits in the hypothalamus, which are essential for regulating reproductive hormones and maintaining neuroendocrine homeostasis [63].

While the decline in estrogen is a central factor in perimenopausal mood and cognitive changes, other factors such as social stressors, lifestyle, and individual health conditions also play a role. The interaction between the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis, as well as epigenetic changes, contribute to the complexity of perimenopausal depression and cognitive issues. Additionally, the brain's ability to produce neurosteroids independently suggests alternative pathways for addressing mood and cognitive changes during menopause. These insights highlight the need for personalized approaches in managing perimenopausal symptoms, considering both hormonal and non-hormonal factors.

Cognitive Impairments in Perimenopause

Cognitive problems are prevalent during perimenopause, with studies indicating that verbal learning and memory are particularly affected. Recent findings suggest that deficits in processing speed, attention, and working memory may also emerge during this period. The heterogeneity of cognitive profiles among women in perimenopause indicates that while some may experience significant cognitive decline, others may retain cognitive strengths. Factors such as depression, sleep disturbances, and vasomotor symptoms have been associated with cognitive difficulties during perimenopause. Neuroimaging studies have begun to identify changes in brain activity patterns that correlate with cognitive performance, highlighting the need for further research to elucidate the underlying neural mechanisms [43].

Nearly two-thirds of women report subjective cognitive difficulties, including memory problems and attention deficits, during the menopausal transition. These symptoms are often referred to as 'brain fog' and can include issues with language and executive function [64, 65]. Mood changes, such as increased anxiety and depression, are common during perimenopause and are associated with cognitive decline. These symptoms can exacerbate cognitive difficulties and are linked to the risk of dementia [55]. Hot flashes and night sweats, common vasomotor symptoms, can disrupt sleep and contribute to cognitive difficulties by affecting attention and memory [53, 64]. The decline in estrogen levels during perimenopause is a primary factor affecting cognitive function. Estrogen has a neuroprotective role, and its reduction can lead to cognitive and mood symptoms. Hormone replacement therapy has been suggested as a potential intervention to mitigate these effects [52].

Neuroimaging studies have shown that estrogen receptor density in the brain increases during menopause, which may be a compensatory response to declining estrogen levels. This increase is associated with poor memory performance and mood symptoms [52]. Perimenopause is characterized as a neurological transition state, where the uncoupling of the estrogen receptor network from the brain's bioenergetic system can lead to a hypometabolic state. This state is associated with neurological dysfunction and may increase the risk of neurodegenerative diseases [56, 57]. Differentiating between cognitive decline due to perimenopause and other conditions like adult attention deficit hyperactivity disorder (ADHD) is crucial for effective management. Neuropsychological assessments and screening tools can help in distinguishing these conditions [65]. The perimenopausal

transition may offer a window of opportunity for interventions aimed at preventing age-related neurological diseases. Understanding the role of estrogen and its receptors in brain metabolism is key to developing such interventions [57].

Memory issues are one of the most commonly reported cognitive symptoms during perimenopause, with many women experiencing forgetfulness and difficulty recalling information [64]. Studies have shown that these memory problems are not solely due to aging but are linked to hormonal changes during the menopausal transition. The prevalence of memory complaints peaks during the menopausal transition, with a significant number of women reporting severe memory issues [66]. Attention deficits, including difficulties in maintaining focus and processing information, are also prevalent during perimenopause [64]. These deficits can affect daily tasks that require sustained concentration, such as work-related activities and managing household responsibilities [67]. Some women report language-related issues, such as finding the right words or following conversations, which can be frustrating and impact communication [64]. These difficulties are often transient but can be distressing and affect social interactions and professional communication [68]. Cognitive symptoms during perimenopause can lead to decreased productivity at work and challenges in managing daily tasks at home [55, 69]. The combination of cognitive and other menopausal symptoms, such as mood swings and sleep disturbances, can exacerbate the impact on daily life, leading to increased stress and reduced quality of life [70, 71].

The CAN-PROTECT study by Crockford et al. [55] investigated the relationship between perimenopausal symptoms and later-life cognitive and behavioral changes, revealing several significant associations. Brain fog, weight changes, and mood changes, these perimenopausal symptoms were significantly associated with poorer subjective cognitive function, as measured by the everyday cognition (ECog-II) scale. Specifically, brain fog (b = 74.8, 95% confidence interval (CI) [47.2, 108.0], $p < 0.001$), weight changes (b = 24.4, 95% CI [8.9, 42.2], $p = 0.001$), and mood changes (b = 36.2, 95% CI [17.3, 58.3], $p < 0.001$) all predicted higher (worse) ECog-II scores. The use of either estrogen-based or non-estrogen-based menopausal hormone therapy during menopause was not found to be significantly associated with current ECog-II scores. Weight changes (b = 24.4, 95% CI [2.4, 51.1], $p = 0.03$) and mood symptoms (b = 68.4%, 95% CI [36.3, 108.1], $p < 0.001$) experienced during perimenopause were significantly linked to poorer current scores on the mild behavioral impairment checklist (MBI-C), indicating more emergent and persistent neuropsychiatric symptoms. MBI-C scores varied depending on the type of menopausal hormone therapy used. Estrogen-based menopausal hormone therapy was associated with a statistically significant 26.9% lower MBI-C score (95% CI [−43.3, −5.7], $p = 0.02$), suggesting a mitigating effect. In contrast, non-estrogen-based menopausal hormone therapy did not show a significant difference in MBI-C scores (b = -19.1, 95% CI [−44.6, 18.1], $p = 0.3$). In summary, the study indicates that certain perimenopausal symptoms, particularly brain fog, weight changes, and mood changes, may predict a greater risk for cognitive and behavioral decline later in life. Furthermore, estrogen-based menopausal hormone therapy appears to potentially mitigate the relationship between perimenopausal symptoms and neuropsychiatric symptoms, though longitudinal research is needed to explore the underlying mechanisms.

A study by Hayashi et al. [66], conducted as a cross-sectional analysis of the Japan Nurses' Health Study, provides several key findings regarding complaints of reduced cognitive functioning during perimenopause. Out of 15,019 participants, 12,507 responded to the 4-year survey, resulting in an 83.3% response rate. The mean age of respondents at the time of the 4-year survey was 46.5 years, with a range of 27 to 82 years. Approximately 38.2% of the women in the study population were within the menopausal transition age range (45 to 54 years). The subjective complaint of 'poor memory or forgetfulness' showed its highest prevalence (81.7%) in the 50 to 54 age group. This included 27.9% reporting severe complaints and 53.8% reporting slight complaints. After 55 years of age, the prevalence of these complaints gradually decreased. 'Poor memory or forgetfulness' was identified as the most common complaint among the 21-item subjective symptoms for women aged 50 to 54 years. For women aged 45 to 54 years, principal component analysis identified six factors accounting for 56.4% of the common variance among the 21 subjective symptoms. 'Poor memory or forgetfulness' primarily belonged to the somatic symptoms group (factor 2) and was also closely associated with the psychological symptoms group (factor 1). Multivariable modified Poisson regression analysis revealed that severe complaints of reduced cognitive functioning were significantly associated with uncertain or postmenopausal status, shorter sleeping hours (less than 5 h or 5 to less than 6 h), night-shift work, and severe vasomotor symptoms. Severe complaints of reduced cognitive functioning were significantly linked to severe vasomotor symptoms, hot flashes, and sweats. Specifically, the adjusted prevalence ratio was 1.77 for hot flashes and 1.67 for sweats, indicating a higher likelihood of cognitive complaints in their presence. In summary, the study highlights that 'poor memory or forgetfulness' is a highly prevalent complaint during the perimenopausal transition, peaking in the early 50 s. It is closely linked to both somatic and psychological symptoms, and its severity is significantly associated with menopausal status, sleep patterns, night-shift work, and vasomotor symptoms.

While the cognitive symptoms associated with perimenopause are well-documented, the exact mechanisms remain partially understood. The interplay between hormonal changes and cognitive function is complex, and further research is needed to fully elucidate these relationships. Additionally, while hormone replacement therapy shows promise, its long-term effects and efficacy require more investigation. Understanding these dynamics is crucial for developing effective strategies to support cognitive health in perimenopausal women.

Treatment Strategies

Given the impact of perimenopause on mood and cognition, various treatment strategies have been explored (Table 2). Hormone therapy has been a traditional approach, but current guidelines from the North American Menopause Society do not support its use for cognitive problems due to insufficient evidence [43]. However, some animal studies suggest that combined hormone treatments may alleviate working memory issues [43]. Non-pharmacological interventions, such as mindfulness and cognitive training, have gained attention for their potential to improve mood and cognitive function in women experiencing mild cognitive impairment [72]. These approaches may offer safe and feasible options, particularly in populations where pharmacological treatments are contraindicated or poorly tolerated. Acupuncture has also emerged as a promising treatment for comorbid depression and insomnia during perimenopause, with studies indicating its efficacy in alleviating symptoms with minimal adverse effects [73]. The mechanisms by which acupuncture exerts its effects may involve neuroendocrine modulation, suggesting a multifaceted approach to treatment [73].

Table 2: Overview of treatment strategies for perimenopausal mood and cognitive symptoms.

Intervention category	Examples	Primary indication and notes
Hormone therapy	Transdermal estradiol, OMP4	First-line for vasomotor symptoms; can improve mood and sleep, which may secondarily help cognition. Timing is critical (window of opportunity hypothesis)
Non-hormonal pharmacotherapy	Selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (e.g., escitalopram), gabapentinoids	First-line for depression/anxiety; also effective for vasomotor symptoms. Alternative for women who cannot use hormone therapy
Psychological interventions	Cognitive behavioral therapy and mindfulness	Effective for low mood, anxiety, and coping with vasomotor symptoms/sleep issues. Low risk, high patient acceptance
Lifestyle modifications	Regular aerobic exercise, balanced diet, sleep hygiene	Foundation of management. Improves overall well-being, reduces cardiovascular/bone risk, can mitigate symptoms
Complementary and alternative medicine	Acupuncture, black cohosh, remifemin®, Chinese herbal formulas (e.g., Huanglian Wendan Tang)	Mixed evidence: some show promise for mood, anxiety, and vasomotor symptoms in clinical studies. Safety and standardization can be concerns

Lifestyle modifications

- Diet and exercise: A balanced diet and regular physical activity are crucial in managing perimenopausal symptoms. These lifestyle changes can help control weight, reduce cardiovascular and bone health risks, and improve overall well-being. However, achieving permanent dietary changes can be challenging, and evidence on their long-term benefits is still emerging [74].

- Sleep hygiene: Educating women about good sleep practices is essential, as poor sleep quality is common during perimenopause. Addressing primary sleep disorders and vasomotor symptoms can significantly improve sleep quality [75].

Hormonal therapies

- Menopausal hormone therapy: Menopausal hormone therapy is the most effective treatment for vasomotor symptoms and can be safely initiated in women without contraindications. It involves estrogen-progestogen therapy or estrogen alone for women who have had a hysterectomy [76]. Hormonal contraceptives also offer non-contraceptive benefits, such as relief from vasomotor symptoms and mood stabilization [77].

- Progesterone therapy: Oral micronized progesterone (OMP4) is a physiological therapy that can alleviate vasomotor symptoms, improve sleep, and treat menorrhagia. It is particularly beneficial for women with higher estradiol and lower progesterone levels [78].

Non-hormonal therapies

- Antidepressants and psychotherapy: Antidepressants and cognitive behavioral therapy are first-line treatments for perimenopausal depression. Hormone therapy may also have antidepressant effects, particularly in women with vasomotor symptoms [79].

- Alternative therapies: Non-hormonal prescription therapies, such as gabapentinoids and clonidine, can offer relief from hot flashes. However, the effectiveness of natural health products like isoflavones and black cohosh remains inconclusive [76].

Psychological and cognitive interventions

- Cognitive behavioral therapy: Cognitive behavioral therapy has shown positive effects on vasomotor symptoms and can be an effective non-pharmacological treatment option [76].

- Cognitive health: Lifestyle modifications, including increased aerobic exercise and a diet rich in vegetables, can help reduce the risk of cognitive decline during perimenopause [75].

While these strategies provide a comprehensive approach to managing perimenopausal symptoms, it is important to consider individual patient preferences and medical histories. Some women may choose not to pursue treatment, and healthcare providers should respect these decisions while offering support and information. Additionally, cultural and traditional therapies may be integrated into treatment plans, ensuring cultural sensitivity and safety [76].

Clinical Studies

Perimenopause is a transitional phase around menopause characterized by various physical and psychological symptoms. Treatment strategies for perimenopause aim to optimize women's health during this period, but clinical trial data are limited, making it challenging to establish evidence-based treatment standards. The North American Menopause Society has developed consensus opinions to guide clinicians in managing perimenopausal symptoms, emphasizing individualized care and the inclusion of women in decision-making processes. Various treatment strategies, including hormonal therapies, herbal remedies, and lifestyle modifications, have been explored to address the diverse symptoms associated with perimenopause.

A study by Gao et al. [80] investigating the effectiveness of modified Huanglian Wendan Tang for treating perimenopausal emotional disorders yielded several key results. The treatment group, which received modified Huanglian Wendan Tang, showed a significantly higher total effective rate compared to the control group, which was treated with Shugan Jieyu capsule. This difference was statistically significant ($p < 0.05$). Both the treatment group and the control group experienced significant decreases in their Hamilton depression scale (HAMD-17) scores after treatment. Similarly, both groups also saw significant reductions in their Hamilton anxiety scale scores post-treatment. Crucially, the HAMD-17 and Hamilton anxiety scale scores in the treatment group were significantly lower than those in the control group after treatment, indicating a superior improvement in depression and anxiety symptoms with modified Huanglian Wendan Tang ($p < 0.05$). In summary, the results suggest that modified Huanglian Wendan Tang is more effective than Shugan Jieyu capsule in improving clinical efficacy and reducing symptoms of depression and anxiety in patients with perimenopausal emotional disorders.

The primary aim of a study by Wang et al. [81] was to determine whether Guilu Erxian Jiao helps relieve perimenopausal syndrome, especially given that many women in Taiwan prefer Guilu Erxian Jiao over hormonal replacement therapy for these symptoms. Perimenopausal women experiencing symptoms were divided into three groups: (i) high-dose Guilu Erxian Jiao: 200 mg per day, (ii) low-dose Guilu Erxian Jiao: 100 mg per day, and (iii) placebo: Guilu Erxian Jiao-free starch powder. All treatments were administered in the same capsule form, one capsule per day, for a duration of two months. Serum estradiol and follicle-stimulating hormone levels were

tested at pre-treatment, 1-month post-treatment, and 2-month post-treatment. Clinical symptoms were assessed using a questionnaire before and after two months of treatment. After two months, serum estradiol levels significantly increased in the high-dose Guilu Erxian Jiao group (200 mg/day). High-dose Guilu Erxian Jiao elevated serum estradiol levels more than the low dose. No significant differences in serum follicle-stimulating hormone levels were observed among the groups after Guilu Erxian Jiao treatment. Improvements in clinical symptoms were noted in both the high-dose and low-dose Guilu Erxian Jiao groups. However, a significant amelioration of clinical symptoms, particularly for hectic sweats and palpitation, was observed in the low-dose group (100 mg/day) compared to the high-dose group. The study concluded that Guilu Erxian Jiao is effective for relieving perimenopausal syndrome. Despite the high-dose elevating estradiol more, the low-dose showed better improvement in specific clinical symptoms, indicating that Guilu Erxian Jiao is beneficial for treating perimenopausal syndrome

A study by Jie and Chunquan [82] investigated the clinical efficacy and safety of remifemin in treating perimenopause syndrome, yielding several significant results. Three months after remifemin treatment, symptoms of perimenopause syndrome were significantly relieved. Specifically, sweat, hot flashes, and sleep disorders disappeared in some patients. The clinical total effective rate reached 92.3%. Clinical trials demonstrated that scores for both Kupperman menopausal index and the menopause rating scale and (likely symptom assessment scales) showed great statistical significance when compared to the control group and to the values before treatment ($p < 0.001$). In the therapy group, the levels of female serum follicle-stimulating hormone, luteinizing hormone, and estradiol after treatment showed no significant changes compared to pre-treatment levels ($p > 0.05$). Fasting blood glucose levels also showed no significant changes after treatment compared to before treatment ($p > 0.05$). Lipid metabolism levels exhibited significant changes after treatment ($p < 0.05$). Specifically, triglyceride, total cholesterol, and low-density lipoprotein levels decreased, while high-density lipoprotein levels increased ($p < 0.05$ for all). Liver and kidney function, as well as endometrial thickness, showed no significant variance before and after treatment. Atypical hyperplasia and malignant cells were not detected in cervical smears both before and after treatment. The study reported a low incidence of side effects. Six patients experienced stomach upset, four felt breast tenderness (which disappeared without discontinuing remifemin), and only one patient reported a slight headache. No serious adverse effects such as abnormal vaginal bleeding, bellyache, edema, or breast nodules were observed. In summary, the study concluded that remifemin demonstrates significant clinical curative effects in improving perimenopausal symptoms, with a high safety profile and low incidence of side effects, making it well-accepted by patients.

The primary objective of a study by Lingzhi [83] was to investigate the effect and safety of hormone replacement therapy in patients diagnosed with perimenopausal syndrome. A total of 112 patients with perimenopausal syndrome from Jiaozuo Second People's Hospital (China) were included in the study. Patients were randomly divided into two groups, A and B, with 56 cases in each group. Group A received oryzanol tablets (30 mg per dose, three times a day) and group B received hormone replacement therapy. Clinical efficacy was assessed using Kupperman scores. Various parameters were recorded both before and after treatment, including Kupperman scores, follicle-stimulating hormone, estradiol, corpus luteum surviving levels, and endometrial thickness. Adverse reactions were also monitored in both groups. After treatment, both groups showed significant reductions in Kupperman scores, follicle-stimulating hormone, and corpus luteum surviving levels (all $p < 0.05$). Conversely, estradiol and endometrial thickness significantly increased in both groups after treatment (all $p < 0.05$). Group B (hormone replacement therapy) demonstrated significantly lower Kupperman scores, follicle-stimulating hormone, and corpus luteum surviving levels compared to group A (oryzanol tablets) (all $p < 0.05$). Additionally, estradiol and endometrial thickness were significantly higher in group B than in group A (all $p < 0.10$). No obvious adverse drug reactions were observed in any of the patients after treatment. The study concluded that hormone replacement therapy is both effective and safe for patients with perimenopausal syndrome. It can effectively alleviate clinical symptoms and improve the quality of life for these patients. This study highlights the beneficial role of hormone replacement therapy in managing perimenopausal syndrome, showing superior efficacy compared to oryzanol tablets while maintaining a good safety profile.

A study by Cao et al. [84] aimed to evaluate the effectiveness of Chinese herbal medicine granules combined with traditional Chinese medicine-based psychotherapy (TBP) for perimenopausal depression. A multicenter, randomized, placebo-controlled clinical trial. Conducted in nine hospitals in China between August 2015 and June 2017. Included 307 women diagnosed with perimenopausal depression. Participants were randomly assigned to two groups: (i) Bushen Tiaogan formula plus TBP (n = 156) and (ii) placebo plus TBP (n = 151). All participants received 8 weeks of treatment and were followed up for an additional 4 weeks. Scores on the Greene climacteric scale (GCS), self-rating depression scale (SDS), and self-rating anxiety scale (SAS). Serum levels of sex hormones and lipids, as well as adverse events. The Bushen Tiaogan formula-plus-TBP group showed significantly lower average GCS, SDS, and SAS scores after treatment compared to the placebo-plus-TBP group, with the greatest differences observed at the end of the 12th week (all $p < 0.001$). GCS scores 10.8 (Bushen Tiaogan formula + TBP) vs 18.5 (placebo + TBP). SDS scores, 30.7 (Bushen Tiaogan formula + TBP) vs 45.4 (placebo + TBP). SAS scores, 28.6 (Bushen Tiaogan formula + TBP) vs 42.6 (placebo + TBP). Bushen Tiaogan formula + TBP significantly reduced basal follicle-stimulating hormone levels ($p = 0.045$) and triglycerides ($p = 0.039$), while increasing high-density lipoprotein cholesterol levels ($p < 0.001$) compared to placebo treatments with TBP. No serious adverse events were reported, and safety indices (complete blood counts, renal function, and liver function) remained within normal ranges before and after treatments. The study concluded that treatment with the Bushen Tiaogan formula combined with TBP was more effective than TBP alone in improving perimenopausal depression symptoms, sexual hormone levels, and blood lipid conditions in women with mild perimenopausal depression.

A study by Zhou et al. [85] investigated the relationship between hormone levels, quality of life, and depression symptoms in perimenopausal women, as well as the effects of electroacupuncture. It compared electroacupuncture with escitalopram as interventions. A total of 242 participants with mild to moderate perimenopausal depression were enrolled from six hospitals in China. Each participant underwent a 12-week intervention period followed by a 12-week follow-up period. Primary outcome, the HAMD-17. Secondary outcomes, the menopause-specific quality of life scale (MENQOL), and serum levels of follicle-stimulating hormone, luteinizing hormone, and estrogen. The structural equation model revealed that hormone levels were not directly associated with HAMD-17 scores ($p = 0.852$). MENQOL was statistically correlated with HAMD-17 and acted as an intermediary variable ($p < 0.001$). Electroacupuncture progressively

showed positive impacts on both MENQOL and HAMD-17 during the follow-up period ($p < 0.05$) (Figure 1). Cognitive impairment was identified as the dominant dimension of perimenopausal depression. The study concluded that hormonal shock might indirectly lead to perimenopausal depression by affecting clinical symptoms and poor quality of life, which in turn induces cognitive impairment. This impact on cognition is considered embodied. Electroacupuncture was found to have a positive effect on perimenopausal depression and overall quality of life.

A study by Gordon et al. [86] investigated the efficacy of transdermal estradiol plus intermittent micronized progesterone (TE+IMP) in preventing depressive symptoms during the menopause transition. The study included 172 participants, with 130 (76%) being white and 70 (19%) African American. The mean age of participants was 51 years, and the average household income ranged from 50,000 to 79,999. At baseline, women randomized to TE+IMP and placebo groups did not significantly differ in demographic or psychosocial variables. By visit 12, the reproductive stage distribution in the placebo group was 17% early perimenopausal, 49% late perimenopausal, and 32% early postmenopausal. Overall, 25% of participants (43 out of 172) developed clinically significant depressive symptoms (CES-D score of at least 16) at least once during the study. Women assigned to the placebo group were significantly more likely to develop CES-D score (≥16) at least once during the intervention phase compared to those receiving TE+IMP. Specifically, 32.3% of the placebo group reached this threshold versus 17.3% of the TE+IMP group, with an odds ratio of 2.5 (95% CI, 1.1 to 5.7; $p = 0.03$). The placebo group also exhibited a significantly higher mean CES-D score across the 12-month intervention period ($p = 0.03$). TE+IMP was associated with a decrease in CES-D scores compared to placebo, and this effect remained significant even after removing outliers. The beneficial mood effects of TE+IMP were significantly moderated by baseline reproductive stage. Benefits were evident among women in the early menopause transition (β, −4.2; standard error of the mean (SEM), 1.2; $p < 0.001$). No significant mood benefits were observed for women in the late menopause transition (β, −0.9; SEM, 0.3; $p = 0.23$) or among postmenopausal women (β, −0.3; SEM, 1.1; $p = 0.92$). Stressful life events experienced in the 6 months prior to enrollment also moderate the treatment effect (Figure 2). The mood benefits of TE+IMP increased with a greater number of stressful life events (β, 1.22; SEM, 0.40; $p = 0.003$). For women with two or more stressful life events, TE+IMP was associated with one fewer instance of CES-D compared to placebo. Baseline estradiol levels, baseline vasomotor symptoms, history of depression, and history of abuse were not found to significantly moderate the effects of TE+IMP on depressive symptoms. Adverse effects such as spotting, mild or moderate bleeding, heavy bleeding, and prolonged bleeding were more commonly reported by participants in the TE+IMP group compared to the placebo group. The treatment groups did not differ in the reporting of other adverse effects like breast tenderness, bloating, headache, or weight gain. Three severe adverse events led to study termination: two cases of major depressive disorder in the placebo group and one case of acute deep vein thrombosis in the TE+IMP group. In summary, the study demonstrates that 12 months of TE+IMP effectively prevented the development of CES-D in initially euthymic perimenopausal and early postmenopausal women, particularly benefiting those in early menopause transition and those with a higher number of recent stressful life events. While some adverse effects like bleeding were more common with TE+IMP, the overall findings support its prophylactic use for mood symptoms in this population.

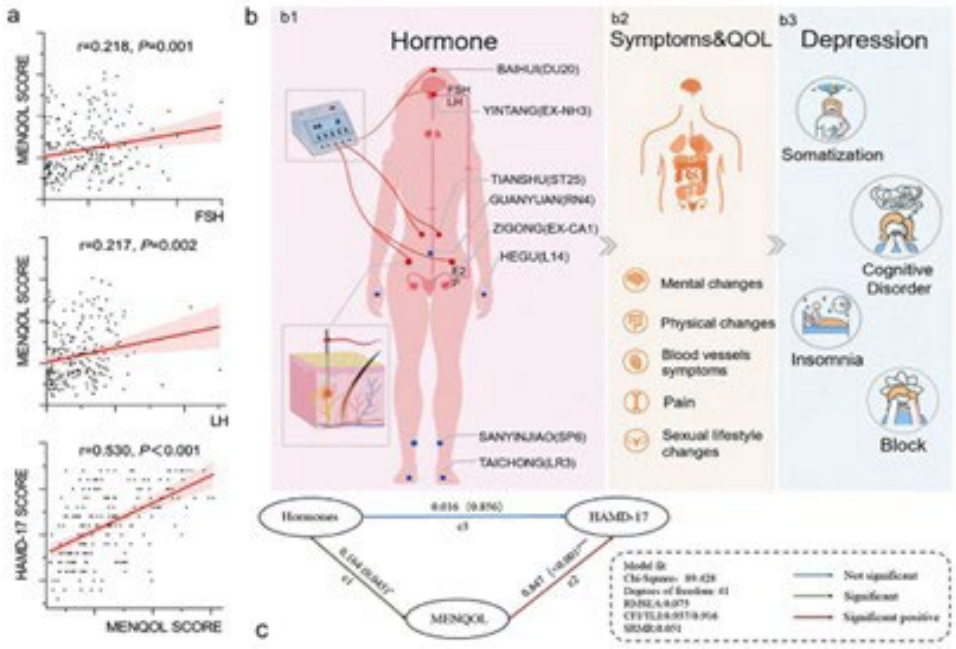

Figure 1: (a) Correlation analysis, a significant positive correlation was found between the hormone levels (follicle-stimulating hormone and luteinizing hormone) and the severity of MENQOL. Furthermore, a higher MENQOL score was positively correlated with a higher score on the depression scale (HAMD). **(b)** Conceptual framework, **(b1)** Hormonal factors (follicle-stimulating hormone, luteinizing hormone, estrogen, and overall hormonal fluctuation) are the primary drivers of the various symptoms experienced during perimenopause, **(b2)** These clinical symptoms collectively impact the patient's overall quality of life, and **(b3)** This decline in quality of life is associated with depression, with cognitive impairment being a particularly prominent feature of the depressive symptoms. **(c)** Structural equation model, a mediation model was constructed where 'hormones' (a latent variable indicated by follicle-stimulating hormone and luteinizing hormone) directly influence the mediator variable 'MENQOL' (representing symptoms and quality of life). MENQOL, in turn, has a direct effect on 'HAMD-17' (depression). This confirms that the effect of hormones on depression is indirectly mediated through the patient's experience of symptoms and quality of life [85].

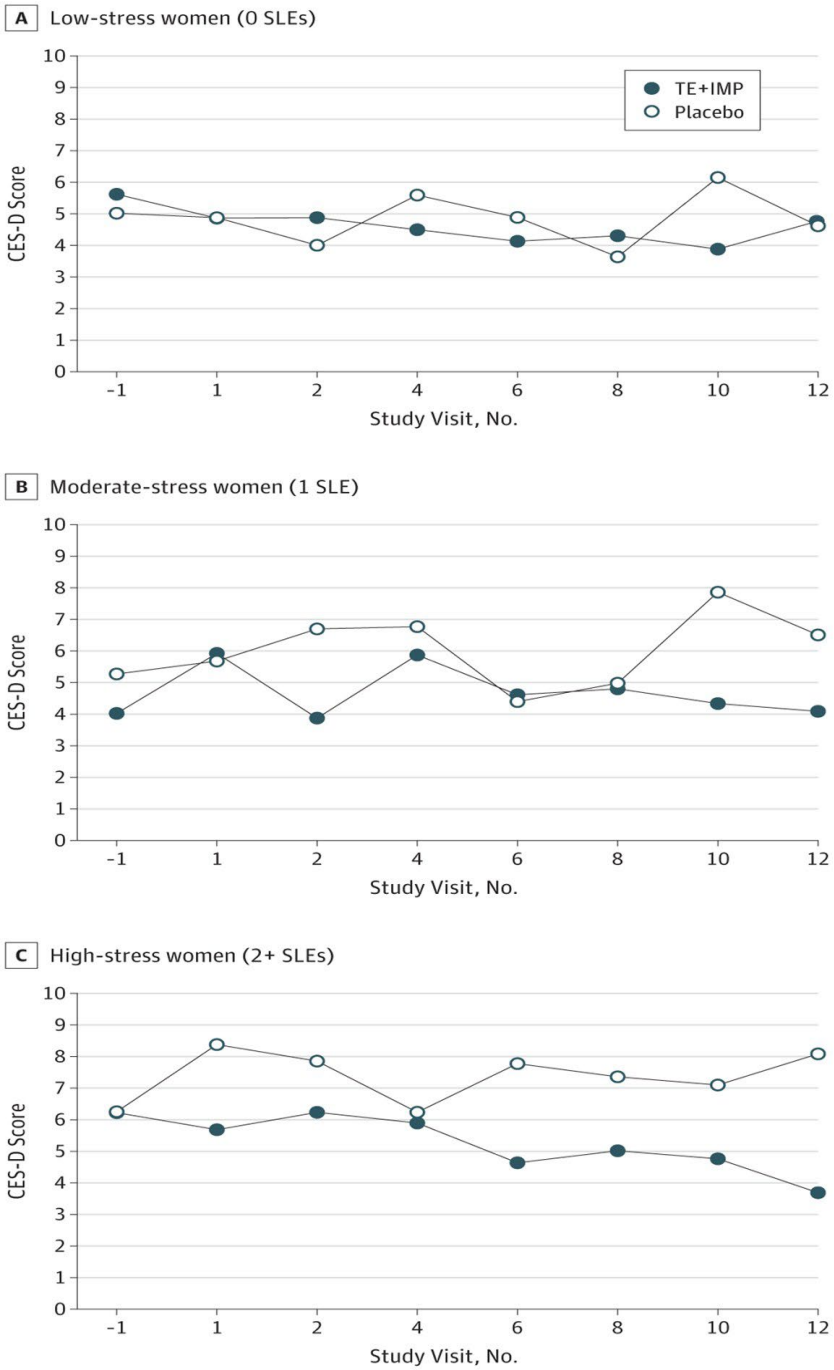

Figure 2: The model-based analysis revealed that the effect of the treatment (TE+IMP) on depression scores (CES-D) was dependent on the number of stressful life events. A statistically significant reduction in depression scores was observed specifically in the **(a)** high-stress group (55 women; p = 0.005). In contrast, the treatment did not produce a significant effect for women with **(b)** moderate (46 women; p = 0.70) or **(c)** low levels of stress (72 women; p = 0.53) [86].

While these studies provide valuable insights into the treatment of perimenopausal syndrome, they also highlight the need for further research to establish evidence-based guidelines. The diversity of treatment options reflects the complexity of perimenopausal symptoms and the necessity for personalized care. Additionally, the potential for non-hormonal treatments to offer relief with fewer side effects presents an attractive alternative for many women. However, the choice of treatment should be guided by individual patient needs, preferences, and risk factors, ensuring a holistic approach to managing this transitional phase.

Conclusion

The literature collectively underscores the significant impact of hormonal fluctuations during perimenopause on mood and cognitive function, with neuroendocrine mechanisms playing a central role. Estrogen and progesterone level variations critically influence neurobiological pathways involving neurotransmitters such as serotonin, dopamine, as well as neurosteroidogenesis processes, which together modulate mood regulation and cognitive performance. Estrogen receptor subtypes, notably estrogen receptor-α and estrogen

receptor-β, demonstrate differential effects on neural circuits implicated in affective and cognitive domains, with emerging evidence indicating receptor density changes during neuroendocrine aging that may reflect compensatory or pathological adaptations. Moreover, dysregulation of the hypothalamic-pituitary-adrenal axis interacts with ovarian hormone fluctuations, amplifying vulnerability to stress and depressive symptoms, especially in women with histories of psychosocial stress or early life trauma. These complex interactions highlight the necessity of integrating biological and psychosocial factors in understanding perimenopausal mood disorders.

Regarding treatment strategies, hormone replacement therapy, particularly transdermal estrogen formulations, appears effective in alleviating depressive symptoms and improving sleep quality for many women during perimenopause. However, the long-term cognitive benefits of hormone therapy remain inconclusive, and concerns about safety, including risks of thrombosis and stroke, necessitate cautious, individualized clinical decision-making. Selective estrogen receptor modulators present promising alternatives with potentially favorable side effect profiles but require more rigorous clinical evaluation. Psychosocial interventions such as cognitive behavioral therapy and mindfulness-based approaches have demonstrated efficacy in improving mood and cognitive complaints, yet their integration into routine care is limited, highlighting a critical gap in service provision and multidisciplinary management. The heterogeneity of clinical presentations and symptoms overlap with menopausal vasomotor and sleep disturbances complicate diagnosis and treatment, underscoring the need for validated screening tools and personalized therapeutic approaches.

In conclusion, the literature advocates for a biopsychosocial model that considers hormonal sensitivity, receptor dynamics, and psychosocial stressors to tailor interventions effectively. Advances in neuroimaging and neurochemical studies provide promising avenues for biomarker development to guide treatment selection. Nevertheless, substantial gaps remain in longitudinal research, mechanistic clarity of receptor subtype functions, and the development of integrated care models that combine hormone therapy with psychosocial support. Addressing these limitations is essential to optimize outcomes for women experiencing mood and cognitive disturbances during perimenopause.

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None.

Conflict of Interest

None.

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