

Hormone Replacement Therapy and Mood Disorders During Menopause

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Abstract

Background: Menopause is a significant transitional phase for women, marked by hormonal changes that profoundly affect physical and mental health. This paper examines the intricate relationship between menopause, hormonal fluctuations, and mood disorders, emphasizing the challenges of treatment. The depletion of ovarian follicles and the resulting decline in estrogen, progesterone, and other hormones disrupt the hypothalamic-pituitary-gonadal axis and neurotransmitter pathways, leading to increased rates of depression, anxiety, and other mood disorders in middle-aged women. Conventional treatments, such as selective serotonin reuptake inhibitors (SSRIs), are often less effective for menopausal-related mood disorders, underscoring the need for alternative approaches.

Methodology: A targeted review of current literature explores conventional and alternative treatment approaches for menopausal mood disorders. This includes a review of pharmacological therapies, such as selective serotonin reuptake inhibitors (SSRIs), and the potential efficacy of hormone replacement therapy (HRT) in mitigating mood-related symptoms.

Results: Conventional treatments like SSRIs are often less effective for menopausal mood disorders, underscoring the need for alternative approaches. HRT emerges as a viable option, offering symptom relief from vasomotor and genitourinary syndromes, improved cardiovascular and bone health, and potential mitigation of mood disorders. However, the controversial results of the 2002 Women’s Health Initiative (WHI) study raised concerns about risks, resulting in reduced usage. Recent studies support the “critical window” hypothesis, suggesting that initiating HRT early in menopause enhances safety and efficacy.

Conclusion: This paper highlights the importance of personalized and integrative strategies for managing menopause and mood disorders. Although HRT shows promise, further research is essential to clarify its influence on inflammatory pathways and neuroinflammatory mechanisms. Understanding the long-term effects of HRT and addressing the unique hormonal and neurobiological dynamics of menopausal women are critical for developing targeted interventions and improving outcomes for this underserved demographic.

Keywords: Estrogen, Progesterone, Reproductive Hormones, Hormone Replacement Therapy, Mood Disorders, Depression, Anxiety.

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All human females with ovaries who reach puberty will ultimately experience menopause, provided they live long enough. Menopause consists of three main stages: perimenopause, menopause, and post menopause, generally occurring between the ages of 40 and 60. At this stage, the ovaries begin to atrophy, decreasing the production of the main hormones that regulate the menstrual cycle: estrogen and progesterone. Most women experience vasomotor (hot flashes, excessive sweating, sleep disturbance) and genitourinary (vaginal dryness, pain during intercourse, urinary incontinence, decreased libido) symptoms during this period (Jin, 2017). Middle-aged women also experience significant increases in depression, anxiety, post-traumatic stress disorder, and substance abuse compared to other age groups. As a demographic cohort, women in this age range have a high suicide rate (Maki et al., 2019, as cited by Kulkarni et al., 2024). Cultural, genetic, and environmental factors influence the menopause journey and subsequent treatment efficacy.

During the feminist movement of the 1960s, there was a significant shift in the promotion of menopausal therapy, especially in European countries, with the concept of "feminine forever" (Wilson, 1968). A book by the same title became a bestseller, claiming that "menopause is a hormone deficiency disease, curable and totally preventable, just take estrogen" (Wilson, 1968, as cited in Cagnacci & Venier, 2019, p. 602). Since that time, women have had a complex relationship with hormone replacement, alternately viewing it as a panacea or risk too hazardous to employ.

Menopause is a complex biological process characterized by hormonal changes that can significantly impact mental health, creating challenges for effective treatment. Pre-menopausal women without a history of mood disorders are nearly twice as likely to develop symptoms of anxiety and depression during menopause compared to those with no prior mood disorder history (Cohen et al., 2006, as cited in Alblooshi et al., 2023). As ovarian follicles deplete, ovarian function declines, leading to a reduction in mood-regulating hormones. This shift disrupts the hypothalamic-pituitary-gonadal axis, influencing mood regulation and stress responses. Life stages with low estrogen levels (premenstrual, postpartum, menopause) are linked to increased depressive symptoms. Additionally, between 15% to 50% of women report experiencing depression during the menopause transition (Toffol et al., 2015, as cited by Wiczorek et al., 2023). Fluctuations in estrogen, progesterone, testosterone, cortisol, triiodothyronine (T3), thyroxine (T4), dehydroepiandrosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) affect multiple systems, with estrogen, progesterone, and cortisol playing key roles in mood regulation. Understanding these hormonal changes is critical for addressing menopausal mood disorders effectively.

Standard mental health interventions, such as lifestyle modification and antidepressants, are often insufficient in addressing menopausal mood disorders. Healthcare providers often

recommend stress reduction techniques and psychotherapies, like cognitive-behavioral therapy, as the first intervention. Antidepressants, particularly SSRIs, are usually the next treatment option. However, many medications that had previously helped are no longer effective, or a much higher dose is required to have the same effect (Worley et al., 2012; Grigoriadis et al., 2006, as cited by Behrman & Crockett, 2023). Current guidelines are to treat menopausal depression as any other depressive episode. However, it is known that peri- and postmenopausal people do not respond to SSRIs as effectively as other demographics, and rates of discontinuation due to adverse events are significant (Wu et al., 2020, as cited by Behrman & Crockett, 2023). Hormonal therapies may be more effective but remain underutilized due to safety concerns and a lack of sufficient knowledge among mental health professionals about their use in treating mood disorders (Behrman & Crockett, 2023). The interplay between hormonal shifts and mental health challenges underscores the necessity for a nuanced understanding of menopause in clinical settings. Conventional mental health treatments fail to account for the unique physiological changes during menopause, highlighting a critical gap in care. Integrative approaches and targeted interventions are needed to support women during this critical stage of life.

Neuroscience of Hormonal Influence on Mental Health During Menopause

Neurotransmitters such as serotonin, norepinephrine, and dopamine play a crucial role in modulating both vasomotor and mood disorders. Dysregulation of these pathways, particularly in the prefrontal cortex and limbic system, key regions of the central nervous system involved in mood control, can contribute to the onset of depression (Giannini et al., 2021). Estrogen has a role in the modulation of serotonin and the serotonergic pathways, considered a root neurobiological cause of depression (Herson & Kulkarni, 2022, as cited in Behrman & Crockett, 2023). Estrogen affects the concentration of serotonin by increasing the rate of monoamine oxidase (MAO), an enzyme responsible for serotonin catabolism. Estrogen is also linked to neuron activity due to its ability to affect cerebral blood flow, glucose levels, neuronal growth, and synaptic activity (Giannini et al., 2021). Other neurotransmitter pathways linked to changes in mood, such as dehydroepiandrosterone sulfate and gamma-aminobutyric acid (GABA), are also affected by the menopausal transition (Behrman & Crockett, 2023). Estrogen significantly affects mood-regulating brain areas such as the hippocampus and amygdala by enhancing synaptic plasticity, promoting neuronal growth, and modulating neurotransmitter systems, collectively contributing to improved mood regulation and stress resilience (Behrman & Crockett, 2023). The progesterone derivative allopregnanolone “interacts with gamma-aminobutyric acid type A (GABA-A) receptors even at nanomolar concentrations and induces significant anti-depressant, anti-stress, sedative, and anxiolytic effects” (Stefaniak et al., 2023, p. 520). Low to moderate concentrations of allopregnanolone increase amygdala activity as measured by functional magnetic resonance imaging (fMRI), similar to changes experienced during heightened anxiety. When concentrations increased, amygdala activity slowed, resembling the effect of sedatives like benzodiazepines (Stefaniak et al., 2023).

Hormone Replacement Therapy

HRT is an effective treatment for various adverse symptoms associated with menopause, including vasomotor symptoms (such as intense heat, sweating, and flushing) and genitourinary syndrome (characterized by vaginal dryness, irritation, burning, painful intercourse, recurrent urinary tract infections, and urinary incontinence). Additionally, multiple randomized trials have demonstrated HRT's positive effects on cardiovascular, endocrine, and bone health, with evidence suggesting a reduction in all-cause mortality among recently menopausal women (Flores et al., 2021). However, the 2002 WHI report delivered transformative findings into HRT risks of breast cancer and cardiovascular disease in older postmenopausal women, driving a “seismic shift” in menopause management and influencing perspectives that persist today (Flores et al., 2021, p. 720). The WHI study included a large population of older postmenopausal women more than 10 years after the cessation of menses. These women were more likely to have pre-existing conditions, such as cardiovascular disease, making them more prone to adverse outcomes. The study also used a combination of estrogen and medroxyprogesterone acetate (MPA), a synthetic progestin. Unlike natural progesterone, MPA has been associated with an increased risk of breast cancer and cardiovascular disease (Manson et al., 2024). These issues led to misunderstandings about the safety of HRT, resulting in significant declines in prescribing, even for women not at significant risk. New formulations and updated research have clarified these findings, highlighting the significance of bio-identical progesterone, personalized treatment, and timing in hormone therapy choices. Although HRT is safe for many women, it still poses certain risks. Prolonged use can increase the chances of breast and endometrial cancer, blood clots, and stroke and may impair cognitive function (Marsden, 2022). The benefits and risks of taking HRT depend on an individual's age, menopause stage, and any pre-existing risk factors they may have.

The aftermath of the WHI study has led to the “critical window” or “timing hypothesis,” which states estrogen can be neuroprotective only if HRT is started shortly after the onset of menopause. Some studies indicate that using HRT in the early postmenopausal phase is associated with improved well-being, while its use at later stages does not show the same benefits. According to Flores et al. (2021), HRT is a valuable option for symptomatic, healthy menopausal women who are under 60 years old and have been menopausal for less than 10 years. This applies as long as they do not have any contraindications, such as cardiovascular disease, poorly controlled diabetes, or high blood pressure, as well as no risk factors for venous thromboembolism, including obesity, smoking, or clotting disorders.

While the number of hormones that shift during menopause is significant, only estrogen and progesterone are used in HRT for this cohort. Estrogen-only formulations for HRT include conjugated equine estrogens, 17 β -E₂, and esterified estrogens; they are typically used for women without a uterus (Flores et al., 2021). In addition to oral routes of administration, estrogen-only formulations such as injection, subdermal implant, and transdermal formulations are available.

Progesterone can be used alone or in combination with estrogen. Available routes of administration include oral, injection, implants, transdermal (via vaginal application), and intrauterine systems. Formulations containing progesterone are used more commonly in women with a uterus. Selective estrogen receptor modulators are a newer treatment option that targets specific estrogen receptors to exert agonist or antagonist actions on the estrogen receptors in various estrogen-target tissues (Flores et al., 2021).

Women randomized to oral estrogen in the Kronos Early Estrogen Prevention Cognitive and Affective Ancillary Study showed greater benefit on affective mood states than women randomized to transdermal 17 β -estradiol or placebo (Raz et al., 2016). However, after a systematic review of the literature comparing the transdermal and oral administration routes of estrogens for menopausal women, Goldštajn et al. (2023) determined that available evidence is limited and low quality. The authors indicate that until more research is available, the main clinical difference between the two administration routes is the reduced risk of venous thromboembolism, which suggests that transdermal HRT is safer than the oral administration route.

Perceived and Actual Risk Factors of HRT

Similarly, like all pharmaceutical interventions, HRT is not without risk. Depending on formulation and individual patient profile, physical risks include increased prevalence of breast and uterine cancer, cardiovascular disease, gallbladder disease, and urinary incontinence. While research does not indicate that HRT directly decreases emotional well-being, there may be indirect risk. Even in the absence of physical risk factors, there is the possibility of a toll on mental health. Hearing about others experiencing negative outcomes can amplify concerns and lead to anxiety or worsening mental health. According to Bagarić et al. (2022), the phenomenon known as the vicarious nocebo effect refers to the psychological impact of learning about the adverse effects experienced by others who are using the same medical intervention. This may decrease as erroneous media reports about the WHI study claiming that hormone therapy causes breast cancer and cardiovascular disease fade from the memories of healthcare providers and the general public.

Emerging Research on HRT's Role in Inflammatory Pathways

In recent years, researchers have hypothesized that mood disorders may result from an inflammatory response. Evidence supporting this hypothesis was presented by Ye et al. (2023), who identified low-grade systemic inflammation in patients with depression. Their findings included elevated concentrations of C-reactive protein in 21% to 34% of patients, as well as increased levels of interleukin-6 (IL-6) and other inflammatory cytokines in both blood and cerebrospinal fluid. This inflammatory activity is believed to impact neural circuits in the brain related to mood regulation, such as the hippocampus and the prefrontal cortex (Ye et al., 2023). Autoimmune diseases often worsen during menopause due to increased inflammation, highlighting the complex interplay between physical health and mood disorders during this

transition. These links suggest that targeting inflammation could be a viable approach to managing mental health symptoms.

HRT, particularly estrogen-based therapies, may help modulate inflammatory responses in menopausal women. Estrogen has anti-inflammatory properties that can reduce levels of pro-inflammatory cytokines like IL-6. By potentially lowering systemic inflammation, HRT could alleviate some of the depressive and anxiety symptoms that are exacerbated by these inflammatory processes. Slavich and Sacher (2019) describe how estrogen modulates the hypothalamic-pituitary-adrenal (HPA) axis and its implications for stress-related disorders. Researchers note that estrogen can attenuate HPA axis responses to stress, which may be beneficial in reducing anxiety and depression symptoms (Slavich & Sacher, 2019). These findings suggest a promising role for HRT not only in alleviating physical symptoms of menopause but also in addressing the neuroinflammatory mechanisms that contribute to mood disorders. While these studies are promising, they are limited in scope, and more research is needed to determine the underlying mechanisms of HRT in relation to inflammation-related mental health outcomes. Large-scale, randomized controlled trials are necessary to confirm conclusions and identify the most effective treatment protocols.

Conclusion

Given the complex interplay between hormones and mental health, there is a need for personalized treatment approaches when it comes to treatment. There is an understanding that HRT may mitigate mood disorders. However, it may be most efficacious for a narrow subset of individuals during a specific stage of menopause or used in conjunction with antidepressants. All women, but especially older women, do not have equal representation in health research. Further investigation is needed to deepen our understanding of the complex relationship between hormonal transitions and mood disorders in women.

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