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Postmenopausal Review

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ABSTRACT

Postmenopausal depression (PMD) is a prevalent yet often overlooked condition influenced by neuroendocrine changes, neurotransmitter imbalances, and inflammatory processes. Declining estrogen levels disrupt serotonin and dopamine systems, impair neurotrophic support, and exacerbate neuroinflammation, increasing susceptibility to mood disorders. While hormonal therapy (HT) and antidepressants remain primary treatment options, concerns over adverse effects highlight the need for alternative strategies. Emerging approaches such as selective estrogen receptor modulators (SERMs), gut-brain axis modulation, exosome therapy, and AI-driven personalized interventions offer promising solutions. Non-pharmacological approaches such as cognitive behavioral therapy (CBT), regular physical activity, and mindfulness, have proven effective in managing menopausal symptoms. Future research should focus on refining these interventions, evaluating their long-term efficacy, and tailoring individualized treatment plans to enhance the overall well-being of postmenopausal women globally.

Keywords: Postmenopausal depression, Estrogen, Serotonin and Dopamine system, Neurotransmitter.

INTRODUCTION

Menopause is a natural biological process that signifies the end of a woman's reproductive years [1]. It is preceded by perimenopause, a transitional phase marked by hormonal fluctuations, and followed by post-menopause, during which the menstrual cycle ceases permanently [2]. The onset and severity of menopausal symptoms largely depend on an individual's lifestyle, impacting their quality of life [2,3]. Aging-associated ovarian dysfunction, coupled with menopause, contributes to various health conditions such as vasomotor disturbances, urogenital atrophy, osteoporosis, cardiovascular disease, cancer, mental health disorders, cognitive decline, and sexual dysfunction [2].

Depression is a significant concern among postmenopausal women, with studies indicating a high prevalence rate. Cross-sectional studies have reported that depression in postmenopausal women ranges between 24% and 28% [4, 5]. A meta-analysis published in 2024 encompassing 76,817 postmenopausal women across 55 studies estimated the global prevalence of postmenopausal depression at 34.9% [6]. In India, another meta-analysis indicated that 42.47% (95% CI: 28.73-22.73%) of peri- and postmenopausal women experience depression [7]. Among Indian postmenopausal women aged ≥ 50 years, depression affects almost one each in a dozen individuals, with a prevalence of 21.76% (95% CI: 20.81-22.73). For women under 50 years, the prevalence is slightly lower at (17.60%, 95% CI: 16.33, 18.94) [8].

Neurobiological Mechanisms Underlying Postmenopausal Depression: The Role of Estrogen, Neurotransmitters, and Inflammatory Pathways

Estrogen primarily produced by the ovaries, is reproductive health and plays a significant role in the regulation of neurotransmitter systems [9]. Estrogen receptors, ERα and Erβ, are widely distributed in brain regions like the hippocampus and amygdala, which are key areas involved in emotional processing and regulation [10].

Serotonin and Dopamine Systems

Estrogen (E2) influences serotonin levels by reducing serotonin transporter (SERT) activity, thereby increasing serotonin availability in the central nervous system. It also affects the synthesis of serotonin by regulating tryptophan hydroxylase-2 (TPH-2), a key enzyme in serotonin production. Mice lacking Erβ exhibit significant serotonin depletion, highlighting the critical role of this receptor in mood regulation. Additionally, estrogen modulates serotonin receptor activity by inhibiting 5-HT1A receptors while promoting 5-HT2A receptors, enhancing serotonergic signaling [11,12, 13, 14]. Serotonin: Efferent Signal for Dopaminergic

Function The complex interaction of various hormones and chemicals in the central nervous system makes up the signaling pathway that is responsible for the communication and sometimes conflict of many of these transmitters, including dopamine, serotonin, GABA, etc. [12]

Estrogen also plays a bi-directional role in dopamine regulation, impacting dopamine synthesis, release, and receptor sensitivity. Estrogen regulates the expression of tyrosine hydroxylase, the key enzyme responsible for controlling the rate of dopamine synthesis. While estrogen enhances dopamine release, its decline during menopause contributes to mood disturbances. This means the production of tyrosine hydroxylase is mediated by estradiol, while the reuptake of dopamine keeps pace at a fast rate even with progesterone being present. Under the influence of estradiol, the levels of tyrosine hydroxylase, the primary rate-limiting enzyme in dopamine synthesis, increase [15].

HPA axis dysregulation

Estrogen plays a key role in regulating the hypothalamic-pituitary-adrenal (HPA) axis, which controls the body's response to stress. It influences the expression of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), helping to moderate the release of stress hormones like cortisol [16]. During menopause, estrogen depletion leads to HPA axis overactivity, increasing vulnerability to mood disorders. Clinical studies suggest that estrogen enhances the efficacy of selective serotonin reuptake inhibitors (SSRIs), underscoring its role in mood stabilization. It is clear that estrogen is a key hormone in treating affective disorders, and if it is necessarily taken away, then the person is likely not to use the antidepressants [17].

Neurotrophic Factor Deficiency

Brain-derived neurotrophic factor (BDNF) is essential for neuronal growth, survival, and synaptic plasticity. Estrogen directly regulates BDNF expression, particularly in the hippocampus, a brain region associated with mood and memory (18). Erβ knockout models show a significant reduction in BDNF levels, weakening synaptic plasticity and increasing susceptibility to stress and depression. Moreover, BDNF interacts with serotonin pathways, and disruptions in Erβ signaling lead to an upregulation of 5-HT2A receptors, exacerbating mood disorders [19,20]. The knowledge of these mechanisms leads to the development of targeted treatments like ERβ-specific modulators, which diminish neurotrophic deficiencies and relieve depressive symptoms in postmenopausal women.

Neuroinflammation

Postmenopausal depression (PMD) is associated with increased neuroinflammation. Estrogen possesses anti-inflammatory properties that suppress pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α [21,23]. A decline in estrogen disrupts this balance, triggering neuroimmune dysfunction and depressive symptoms. Elevated levels of IL-18 and TNF-α are observed in postmenopausal women with depression, and menopausal hormone therapy (MHT) has been shown to reduce these inflammatory markers. Estradiol's interaction with estrogen receptors supports synaptic plasticity and brain-derived neurotrophic factor (BDNF), counteracting neuroinflammation [21,22]. Neuroinflammation's role in PMD is the fact that it is the cause for the need to target therapies such as MHT, which can re-establish and maintain the balance between the immune system and mood. Investigations should concentrate on solutions that will work for the lasting management of PMD.

Oxidative Stress:

Oxidative stress also contributes to postmenopausal depression by disrupting the balance between reactive oxygen species (ROS) and antioxidant defenses. Postmenopausal women exhibit lower levels of antioxidant enzymes such as superoxide dismutase (SOD) and higher markers of lipid peroxidation, such as malondialdehyde (MDA), leading to increased neuronal damage and susceptibility to depression [24-27]. Treating oxidative stress may be a solution for better mental health through dietary and therapeutic interventions.

Clinical Manifestations of Postmenopausal Depression

Postmenopausal depression is a multifactorial disorder influenced by hormonal shifts, psychological factors, and medical comorbidities. Women in the postmenopausal phase exhibit higher rates of depressive symptoms than premenopausal women whose incidence rates can differ according to their race and economic status [28,29]. The SWAN study found that women in their early perimenopause had a 1.3-fold higher risk of depression, while postmenopausal women had a 1.79-fold higher risk [29]. The STAR*D study further revealed that postmenopausal women experience a later onset of depression, prolonged illness duration, and greater medical comorbidities [30].

Vasomotor symptoms, such as hot flashes and night sweats, contribute significantly to mood disorders. The 'domino hypothesis' suggests that vasomotor symptoms disrupt sleep, leading to mood disturbances. While antidepressants are commonly used for symptom management, their effectiveness varies, necessitating individualized treatment approaches [28]. Early diagnosis and individualized treatment methods are significantly important in the management of postmenopausal depression.

Treatment Approaches

Pharmacological Treatment

The menopausal transition is often associated with an increase in depressive symptoms, though these symptoms may decline in postmenopausal women [31]. Traditionally, antidepressants have been the preferred treatment for menopause-related depression: however, substantial evidence highlights the role of estrogen in the central nervous system, making hormonal therapy (HT) with estrogen an experimental approach for managing depressive symptoms during menopause [32, 33]. Despite its potential benefits, HT is not recommended for breast cancer survivors, as it increases breast density, which can elevate the risk of cancer. Additionally, the combination of estrogen and progesterone has been linked to a higher likelihood of developing breast cancer [34]. On the other hand, HT may also interact with selective serotonin reuptake inhibitors (SSRIs) in postmenopausal women, affecting their efficacy. Research indicates that postmenopausal women undergoing HT respond more favorably to antidepressant treatments compared to those not receiving HT [35].

Isoflavones, naturally occurring compounds found in plant extracts used for menopause treatment, offer various benefits, including enhanced bone mineralization, regulation of lipid metabolism, and support for protective brain receptors. Unlike HT, isoflavones provide a greater degree of uterine protection while mimicking the effects of female sex hormones [32]. Another alternative to HT is selective estrogen receptor modulators (SERMs), a class of drugs that selectively block estrogen's effect on bones, fat, and the brain while reducing its impact on the uterus and breasts. By doing so, SERMs not only improve the overall quality of life during menopause but may also help alleviate psychological, and cognitive challenges while lowering the risk of cancers affecting the ovaries, uterus, and breasts tissues [32].

Tibolone, a commonly used SERM, has been recognized for its potential to promote neurological health and overall well-being. Studies suggest that tibolone significantly reduces depressive symptoms in postmenopausal women, making it a promising option for managing menopause-related depression [36].

Antidepressants	Fluoxetine [37]	When combined with oral estrogen-progesterone therapy, it can be effective in reducing depression.
	Desvenlafaxine and venlafaxine [38]	These SNRIs are non-hormonal treatment options that can relieve hot flashes.
Hormonal therapies	Estradiol [39]	It can be effective in reducing depressive symptoms in women experiencing perimenopause.
	Tibolone [36]	It can be effective in treating menopausal depression.
Agomelatine [40]		It can be effective in treating depression and insomnia It can help break the cycle between insomnia and depression

Non-pharmacological treatments

Beyond pharmaceutical treatments, various non-pharmacological interventions have bben explored for managing depression. These include cognitive behavioral therapy (CBT), exercise, sleep hygiene, mindfulness meditation, yoga, acupuncture, aromatherapy, and physiotherapy. Research highlights the effectiveness of holistic and natural approaches in helping postmenopausal women cope with depression without relying on medication [41-44].

Experimental and Emerging Therapies:

Gut-Brain Axis Modulation and Probiotic Interventions

The gut-brain axis plays a crucial role in mood regulation, as disruptions in gut microbiota due to dysbiosis contribute to postmenopausal depression. Estrogen loss affects microbial diversity, influencing mental well-being. Probiotic interventions with Lactobacillus and Bifidobacterium strains help restore gut balance and enhance neurotransmitter function, and reduce inflammation. Additionally, YYNS has shown potential in modulating gut microbiota and improving depressive symptoms, offering a promising herbal approach for managing postmenopausal depression through gut-brain axis regulation [45].

Exosome therapy

Exosome therapy is a promising new approach for managing perimenopausal and postmenopausal symptoms by promoting natural estrogen production. Derived from mesenchymal stem cells, exosomes support cellular communication and stimulate ovarian tissue to enhance estrogen synthesis. Research indicates that exosome treatment boosts estrogen levels, upregulates estrogen receptor expression, promotes cell growth, and reduces apoptosis markers. This innovative non-hormonal therapy offers a potentially safer and more effective alternative to traditional hormone replacement therapy (HRT) for menopause symptom management [46].

Personalized medicine and AI-based mental health monitoring:

Advancements in AI and personalized interventions are transforming the management of postmenopausal depression. AI-driven precision medicine tailors interventions based on individual factors such as genetics, hormone levels, and lifestyle, enhancing effectiveness while reducing side effects. AI-enabled mental health apps offer customized support through cognitive behavioral therapy and mindfulness training, helping women navigate emotional challenges during menopause. Additionally, AI-integrated wearables monitor physiological parameters in real time, providing valuable feedback to guide lifestyle choices, optimize symptom management, and promote overall-well-being [47].

Plant-Based Therapies for Postmenopausal Depression

Postmenopausal depression is a very general concern associated with hormonal changes and is often treated with antidepressants and hormones that may induce side effects. Plant-based treatments with bioactive compounds are a steady way forward.

Objective	Bioactive Compounds	Methods	Results	Ref
Red Clover Isoflavones - Test on mood	Isoflavones	109 women received 80 mg or placebo for 90 days.	Reduced anxiety and depression scores.	48
Phytoestrogens - Evaluate for depression	Phytoestrogens	Meta-analysis of 10 studies (1248 participants).	Reduced symptoms with low doses.	49
Pomegranate Juice and Seed Extract - Test in OVX mice	Polyphenols, Flavonoids	Mice received juice and seed extract for 2 weeks.	Reduced depression and improved bone density.	50
Asparagus cochinchinensis Extract - ameliorates menopausal depression	Saponins	OVX rats under stress treated with AC extract.	Reduced depression, and cytokines; restored BDNF.	51
Echium amoenum Extract - Compare with fluoxetine	Flavonoids, Anthocyanins	72 women were treated for 8 weeks.	Faster improvement by week 4.	52
Pterocarpus soyauxii Extract - Investigate neuroprotective potential	Isoflavones, Polyphenols, Tannins	Phytochemical profiling, 84-day OVX rat model.	Reduced anxiety, depression, and neuronal death.	53

Conclusion

Postmenopausal depression (PMD) is a significant yet often overlooked health concern influenced by neuroendocrine and psychological factors. The decline in estrogen disrupts neurotransmitter function, neurotrophic support, and inflammatory balance, increasing susceptibility to mood disorders. While pharmaceutical treatments like hormone therapy and antidepressants are available, their side effects highlight the need for alternative therapeutic strategies. Emerging approaches, including gut-brain axis modulation, exosome therapy, and personalized medicine, show promise in addressing the complex nature of PMD. Future research should focus on refining these innovative treatments, assessing their long-term efficacy, and developing personalized interventions. By understanding the underlying mechanisms of PMD and optimizing therapeutic strategies, we can improve mental health and quality of life for postmenopausal women worldwide.

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