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Review Article

Menopausal Transition Raises Vulnerability for Anxiety and Depression Disorders

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Abstract

Background & Objective: Hormonal instability during the menopausal transition negatively impacts the limbic and prefrontal circuits, heightening women's vulnerability to depressive disorders and anxiety. This narrative review integrates basic-science and clinical evidence to clarify how perimenopausal endocrine disturbances increase vulnerability to depression and anxiety, and whether augmenting first-line antidepressants with hormone replacement therapy (HRT) offers superior relief. ***Methods:*** English-language literature between the years 1990 – 2024 was searched in PubMed and Google Scholar for studies on menopause, estradiol, depression, anxiety, selective-serotonin/-norepinephrine reuptake inhibitors (SSRI/SNRI), and HRT. Preference was given to randomised controlled trials (RCTs), meta-analyses, and extensive cohort studies; mechanistic papers were included when they provided insight into pathophysiology. Findings were collated qualitatively. ***Results & Conclusion:*** Estrogen withdrawal disrupts serotonergic concentration, upregulates HPA-axis reactivity, and alters ERα/ERβ signalling in limbic-cortical circuits, predisposing to mood lability, especially in late perimenopause. Multiple studies and a 2023 network meta-analysis demonstrate that adding systemic estradiol (with or without progesterone) to fluoxetine or similar agents yields higher response and symptomatic remission rates (up to 92% vs. 48%) than either modality alone.
However, systemic HRT also raises breast cancer, thromboembolic, and stroke risk, with the magnitude increasing over prolonged use.

Keywords: ***Neurobiology links estrogen loss to altered brain signaling; Solo Antidepressant therapy often falls short; HRT can increase efficacy; Benefits of HRT must be weighed against patient-specific risks and knowledge gaps; The coupling of estrogen and progesterone can mitigate the turbulent fluctuation of hormones during peri and late-stage menopause.***

Introduction

For females, menopause is a second wave of puberty that reconstructs the brain and the body. Over the last decade, one-third of women report new or worsening depressive or anxiety symptoms as estrogen levels fluctuate in the late reproductive years [4]. Perimenopause, according to the World Health Organization, is defined as the time immediately preceding menopause, characterized by endocrine, biological, and neurological changes, and lasting until a year after the final menstrual period. During the early stages of menopause, the body increasingly relies on the production of E1 (estrogen) in fat tissue, rather than the production of E2 (estradiol), another form of estrogen. Eventually, ovulation ends due to ovarian failure, which is associated with a decrease in the production of E2. Numerous studies have underscored the significance associated with higher risks of mood changes and symptomatic depression as a result of hormonal changes. Recent research has suggested that Hormone Replacement Therapy, in

addition to first-line antidepressants and antianxiety medication, can improve symptoms associated with both premenopausal and menopausal periods [4].

Hormones and Neurobiology

Menopause marks the transition into hypoestrogenism, a chronic state of estrogen deficiency. During perimenopause, estrogen levels, especially E2 levels, fluctuate significantly before they substantially decline [8]. Estradiol (E2) is the most potent type of estrogen and is essential for the facilitation of ovulation and menstruation during a female's reproductive years. Estradiol (E2) circulates in the body at 4 times the concentration of E1 (Estrone), which is the weaker form of estrogen in the body. During peak reproductive years, granulosa cells surround the developing eggs within the follicle and produce E2 and inhibin-B, which play a crucial role in regulating FSH (follicle-stimulating hormone) [5]. The two central estrogen receptor proteins mediate estrogen's actions in the body, contributing to distinctly different physiological processes [12]. ERα (estrogen receptor alpha) is predominantly found in reproductive tissues like the uterus and breast, as well as the bones, liver, and kidneys. ERβ (estrogen receptor beta) is typically found in a wider range of tissues, including the ovaries, central nervous system, cardiovascular system, prostate, and immune system. During the early stages of menopause, the heterogeneous follicle pool is depleted, beginning with a drop in inhibin-B. Due to the lack of inhibin-B, the feedback loop indicating the release of FSH becomes irregular. The hormone cycles ultimately interfere with the limbic and cortical circuits that stabilize estradiol, regulate mood lability, anxiety surges, depressive episodes, and somatic symptoms that characterise the menopausal transition. Estrogen withdrawal reduces serotonin and heightens the HPA-axis (hypothalamic-pituitary-adrenal axis) reactivity and increases vulnerability to major depressive disorder and psychosocial stress [10,14].

Epidemiology

The risk of depression and the severity of depressive symptoms rise during the perimenopausal period of development [9]. The highest risk of a depressive onset occurs in the late stages of the perimenopausal period, leading up to the final menstrual period. While the high risks of depression typically drop during the post menopausal period, some feel lingering depressive symptoms up to two years after their final period. The CES-D (Center for Epidemiologic Studies Depression Scale) is used to determine the significance of present depressive symptoms [10]. Vasomotor symptoms such as severe hot flashes and night sweats, and low estradiol (E2) levels are linked to an increase in depression as well as a history of prior mood disorders or recent stressful life events. While the CES-D is not a diagnostic tool, it can help mental health providers accurately evaluate a patient's risk for clinical depression and inform treatment options [11,12].

SSRI Setbacks

Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors are often prescribed at a low dose to combat the vasomotor symptoms of menopause. A low dose of a medication that is typically used to control anxiety and depression has been proven effective for managing hot flashes and night sweats; however, at the prescribed low dosage, there is little effect on the anxiety or depressive symptoms of menopause [7]. Estradiol typically amplifies the serotonergic tone, which means it controls the synthesis of serotonin inside and outside the central nervous system. It also lowers the MAO-A (monoamine oxidase), a gene and the enzyme that breaks down select neurotransmitters. During perimenopause, estradiol levels spike and crash, often remaining chronically low, which makes the breakdown and synthesis of neurotransmitters more difficult. Recently, studies have indicated that augmenting SSRI/SNRI treatment protocols with hormone replacement therapy (HRT) can significantly increase the efficacy for controlling symptoms of anxiety and depression [11,12].

Use and Effectiveness of HRT in Menopausal and Postmenopausal Women Experiencing Depressive Symptoms in Prior Studies

The first clinical use of Hormone Replacement Therapy (HRT) as a treatment for menopausal and postmenopausal depression began in the late 1990s. As more research on HRT in menopausal women increased in the early 2000s, the popularity of the treatment decreased, particularly with the announcement of results regarding the safety of synthetic estrogen by the Women's Health Initiative in 2002. This study showed that the use of HRTs to treat chronic menopausal conditions had more negative effects than positive effects, and HRT usage decreased. In the last five years, a reanalysis of HRT usage has revealed more favorable results, increasing the demand for reconsideration of HRT to treat chronic menopausal conditions [19].

Several studies regarding HRT use in menopausal women have shown an alleviation of depressive symptoms. A recent study published by ***The Menopause Society*** found that menopausal hormone therapy (MHT) has a significant improvement in depressive symptoms, paired or not paired with antidepressant medications ($P<0.001$) [16]. Additionally, a study from the ***Harvard Medical School*** supported the use of hormone therapy after women with clinical depressive symptoms in the HRT experimental group improved significantly after augmented treatment [15]. Both studies acknowledge the health risks accompanying the use of hormone treatments, such as a greater chance of blood clots, stroke, and ovarian cancer. The treatment of menopausal depression through hormone therapy should be used in addition to low-dose SSRIs or SNRIs [16,15]. Another factor to consider when administering hormone therapy is the effects of withdrawal when discontinuing the treatment. A study published in the journal ***Psychiatric News*** displays an increased likelihood of depressive symptoms when discontinuing transdermal estradiol hormone therapy in women with a history of perimenopausal depression (PMD). While the use of hormone therapy to treat menopausal symptoms should be momentary and in small doses, hormone therapy should be incrementally decreased rather than promptly stopped [18].

Hormone therapy paired with antidepressants has displayed promising results, and a recent meta-analysis published under the ***Psychiatry Research Journal*** showed a significant improvement of depressive symptoms in menopausal women treated with a combination of fluoxetine and oral HRT compared to placebo groups [6]. Additional literature has supported the administration of HRT paired with fluoxetine, as a clinical trial published by the ***Chinese Medical Association*** Publishing House indicated a 92% healing rate in the experimental group treated with fluoxetine plus HRT, compared to the 48% healing rate of the control group treated only with HRT. The study also conducted a chi-square analysis, which revealed that the results of the two groups were significantly different. Before the clinical research, the two groups showed no differences in depressive scores or symptoms [1]. Furthermore, a study published in the ***Psychiatric Times*** has shown that the effectiveness of HRT on mood in menopausal depression often

varies depending on the diagnosis. Despite this varying effectiveness, the study indicated that the HRT treatment, coupled with fluoxetine, showed a significantly greater improvement in depression ratings (40% vs. 17%, respectively) [2,3].

Contradictory to formerly mentioned studies, a study published in the ***Jama Network*** researching the association of HRT With Depression during Menopause in Danish women concluded that the use of systemically administered HRT before and during menopause is associated with a higher risk of depression, whilst locally administered HRT post-menopause has been associated with lower risk of depression. This study has several confounding variables, as the researched population appears to be exceedingly large (800,000 participants) and employed a register-based methodology. The reliability of the survey is questionable due to the lack of control in the experimental group and the potential for self-report bias inherent in the register-based methodology. While the study acknowledged several confounding variables, such as prior health complications, the vast population raises concerns [14].

Biological Interaction of Fluoxetine and HRT

An increase in E2 (estradiol) alters the concentration of serotonin through multiple pathways during the menopausal transition. E2 increases the production of tryptophan hydroxylase (TPH), which increases the concentration of serotonin through serotonin synthesis. The secondary path involves inhibiting the SLC6A4gene, which encodes the serotonin transporter (SERT), responsible for reuptake of serotonin from the synaptic cleft. Inhibition of the serotonin transporter (SERT) increases extracellular serotonin levels by prolonging the time serotonin remains in the synaptic cleft and interstitial space, enhancing serotonergic signaling. An additional mechanism by which estradiol (E2) enhances serotonergic concentration involves the interaction between high estradiol levels and circulating progesterone [6]. This hormonal combination upregulates estrogen receptor beta (ERβ) while downregulating the expression of estrogen receptor alpha (ERα). The upregulation of E2β upregulates 5HT activation and 2A binding; whereas the downregulation of E2α receptors causes a reduction in 5-hydroxytryptamine receptor 1A (5HT 1A) concentration. The binding and increased density of 5-hydroxytryptamine (serotonin) receptor 2A(5-HT2A) activates protein kinase C, which then uncouples 5-HT1A autoreceptors [11]. Following this cellular pathway, the 5HT 1A receptors become unable to reduce serotonin production via negative feedback, subsequently overwhelming the serotonin concentration [20,13].

Risks and Concerns Regarding HRT

While the portrayal of hormone replacement treatment (HRT) has been positive, it is crucial to weigh the potential risks involved in HRT. Side effects of HRT are numerous and include increased risk of breast cancer, blood clots, and stroke [21]. It is essential to note that the risks associated with HRT are more likely to occur when HRT is taken for an extended period. Previous studies reported that estradiol treatment is believed to increase the risk of cardiovascular disease. However, additional reanalysis of this misconception has shown that estradiol (E2) and progesterone (P4) treatment has no harm to cardiovascular health and can potentially delay cardiovascular disease in menopausal and postmenopausal women [23]. Doctors do not usually recommend HRT to a patient who has just undergone a hysterectomy unless their ovaries have been removed or they are experiencing debilitating menopausal symptoms post-hysterectomy [22]. Consequently, estrogen can refuel cancerous cells due to the presence of estrogen-receptor-positive (ER+) cells. HRT increases circulating estradiol (and, in most cases, progestogens), which can promote the growth of dormant cancerous cells [24]. Additionally, while HRT might not be the proper treatment for all patients, those who do not benefit from SSRIs alone could find relief from vasomotor symptoms.

Discussion and Gaps in Current Research

The effects of Fluoxetine (Prozac®) on estrogenic activity have a convoluted history, as many studies support that fluoxetine upregulates estrogenic activity and downregulates estrogenic activity. Studies have concluded that fluoxetine modulates estrogen synthesis and signaling; however, evidence has yielded varying results regarding whether fluoxetine downregulates or upregulates estrogen production and signaling [20,13]. Despite the differing results, several studies indicate that high and low levels of fluoxetine have differing effects on estrogen receptors [20,13]. The combination of the increased serotonin of SSRIs and the increased serotonin from increases in estradiol (E2) levels seems most effective when treating menopausal/perimenopausal depression in women [1]. HRT has been considered an effective treatment option for vasomotor conditions relating to perimenopause, but its use in mood-related conditions has been less studied [17]. In women with treatment-resistant MDD, estrogen supplementation in replacement dosages may have significant additive effects [2]. The higher dosage of estrogen, although associated with less insomnia, was associated with significant adverse effects (lethargy, hypotension, tremor, depersonalization). These findings suggest that there may be a therapeutic window for estrogen treatment; if endogenous levels are already high, additional estrogen supplementation may lead to toxic reactions [16]. Research must be aimed at properly assessing the ideal estrogenic level to combat subsequent depressive symptoms due to fluctuating hormones.

Conclusion

Menopause triggers a transition akin to a second puberty, and the resulting estrogen volatility heightens vulnerability to depression and anxiety. Emerging evidence suggests that combining estradiol replacement with the SSRI fluoxetine can deliver synergistic antidepressant benefits, outperforming either agent alone. While this treatment has shown promise, the profile of this dual therapy remains under-characterised. Rigorous, adequately powered trials that track both efficacy and adverse results are essential before this strategy can be translated into routine clinical care.

Ethics approval and consent to participate

Not Applicable

List of abbreviations

HRT: Hormone Replacement Therapy
RCTs: Randomized Controlled Trials
SSRI: Selective Serotonin Reuptake Inhibitor
SNRI: Serotonin norepinephrine Reuptake Inhibitor

Data Availability

All data contributing to this article was derived exclusively from previously published studied that are accessible through PubMed (https://pubmed.ncbi.nlm.nih.gov) or discoverable on google scholar. The complete search for data and full biography of included studied are available in the ‘References’ section. The summarized

data has been de identified and have been submitted to the repository holding derived datasets, extraction sheets and analysis codes.

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Authors' contributions

ZG analysed and interpreted the data and created a research question and explorative article.

A to discussion contributed: EW MB, SS, HS P, P, M S, S

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