Review paper

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Estrogen Hormonal Therapy, Clinical Picture, and Course of Schizophrenia and Postpartum Disorders: Review of the Current State of Evidence

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Key words

Schizophrenia; estradiol; hormones; depression, postpartum; menopause

Abstract

Aim: The aim of the paper is to evaluate the hormonal influence on mental disorders, especially schizophrenia and postpartum disorders. **Materials and Methods:** The paper consists of a literature review using the databases PubMed, Cochrane Library, clinicaltrials.gov, EMBASE, WHO ICTRP, and research4Life.org, covering the period 2000–2024. To increase the relevance of the results, only original articles based on clinical trials, systematic reviews, and meta-analyses were selected. A cohort study was also included. Particular attention was given to the role of estrogen/estradiol in schizophrenia, postpartum, and menopausal disorders. **Results:** Estrogens, particularly estradiol, show neuroprotective, neuromodulatory, and anti-inflammatory effects, trigger gene expression, and influence dopaminergic neurotransmission. **Conclusion:** Estrogen, as well as progesterone and allopregnanolone, have significant potential in the treatment of schizophrenia and postpartum disorders. This may contribute to a more favourable prognosis and may represent a novel therapeutic option for depressive conditions. Estrogen therapy may also be associated with reduced antipsychotic dosage and fewer side effects. Future research should focus on estrogen and other sex hormones as adjunctive treatments, considering dosage, safety, and treatment duration to optimize therapeutic outcomes and minimize adverse effects.

Introduction

Sex hormones are an important part of the neuroendocrine system. In addition to basic reproductive purposes, they can perform protective and many other functions. In recent years, research on sex hormones and neurosteroids has attracted attention because of growing interest due to their potential influence on the symptoms of schizophrenia. However, their role in the pathogenesis of this disease is not well understood [1]. The functions of all hormones are to bind to the receptors of target cells, and, as a result, that leads to many cellular reactions and effects [2]. Neurosteroids also influence mental processes. Paul and Purdy define neurosteroids as a group of „natural or synthetic steroids that rapidly alter the excitability of neurons by binding to

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membrane-bound receptors such as those for inhibitory and/or excitatory neurotransmitters" [3]. In 2006, Maurice T. and associates reported that neurosteroids exert rapid modulations of neurotransmitter responses through specific interactions with membrane receptors, mainly the gamma-aminobutyric acid type A (GABA-A) receptor and N-methyl-d- aspartate (NMDA) type of glutamate receptor" [4]. Neurosteroids are synthesized in the nervous system, from cholesterol or other blood-borne steroidal precursors, and glial cells and neurons participate in this process [5]. They can perform inhibitory or excitatory functions. For example, progesterone and its metabolite allopregnanolone are inhibitory steroids, and pregnenolone sulfate or dehydroepiandrosterone sulfate are excitatory steroids [4]. Sex hormones are synthesized mainly in reproductive cells, as well as in the adrenal cortex [2].

Materials and Methods

The paper includes a literature review using the databases PubMed, Cochrane Library, clinicaltrials.gov, EMBASE, WHO ICTRP, and research4Life.org for the period 2000-2024. To increase the relevance of the results, only original articles based on clinical trials, systematic reviews and meta-analyses were selected. One cohort study was also included. Particular attention was given to the role of estrogen/estradiol in schizophrenia, postpartum, and menopausal disorders evaluated.

Results

Estrogen implications in schizophrenia and postpartum disorders

Estrogen is synthesized in the body not only by reproductive cells, but also by other organs and tissues, for example, adipose tissue, mammary glands, and the brain [6]. Estrogen promotes cell survival, repair, and protection of neurons from excitotoxic damage, for example, due to seizures and strokes or in neurodegenerative diseases such as Alzheimer's or Parkinson's disease, enhances the expression and release of neuropeptide Y, which has an anti-excitatory effect, protects neurons from glutamate and peptide toxicity Aβ, oxidative stress, glucose deficiency, activates mitochondrial activity, increases the amount of Bcl - 2 and Bcl - xL proteins, preventing apoptosis, promotes increased synaptic transmission, neurogenesis, axonal sprouting, and has neuroprotective and neuromodulatory effects [2]. It is assumed that estrogens stimulate growth factors, regulate genes under the influence of glutamate [2]. Anti - inflammatory mechanisms of estrogen are also known, which activate regenerative and antioxidant activity, suppress the production of microglia, inflammatory cytokines, and free radicals [2,7,8]. Previously, Sommer and van Westrhenen and associates reported about the, mild anti-inflammatory properties" of 17β - estradiol (E2), due to „reduction of TNF-α (tumour necrosis factor - α) and „reduction of antioxidant stress." According to the authors, estrogen also affects dopaminergic neurotransmission [8]. Estrogen and estrogen receptors can trigger the expression of various genes, phosphorylation cascades, and increase the synthesis of DNA, RNA, and various proteins in target tissues [6,9]. 17β - estradiol (E2) is the main estrogen that is involved in reproductive function, is synthesized in both sexes, and affects the central nervous system (CNS), the cardiovascular system, and lipid metabolism [10-12]. Estriol (E3) is maximally synthesized by the placenta during pregnancy, and estrone (E1) predominates in women after menopause [10]. According to Fink, G and associates low levels of estrogen in women are associated with the premenstrual syndrome, postnatal depression, and post-menopausal depression. At the same time, a significant increase in the density of 5 - hydroxytryptamine2A (5 - HT2A) in the anterior cingulate and primary olfactory cortex and in the nucleus accumbens is related to the control of mood, mental state, cognition, emotion, and behaviour [12]. The postpartum period is associated with a sharp drop in estrogen and progesterone levels, which, according to Reilly and associates is associated with a „23-fold increase in the relative risk of affective psychotic episodes" [13]. Similarly, a meta-analysis involving women with psychiatric diagnoses demonstrated worse mental health outcomes associated with decreased estrogen levels during different phases of the menstrual cycle [13]. There is emerging evidence of sex differences in the clinical presentation of schizophrenia, which are partially mediated by estrogen [1,7,14]. It is reported that patients with schizophrenia in untreated prodromal stages have hyperprolactinemia, gonadal dysfunction, estrogen deficiency in women, and testosterone deficiency in men [1]. Mark Weiser and associates reporting about the potential use of transdermal estradiol patches in women over 38 years with schizophrenia, conclude that, estradiol is an effective adjunctive treatment for women of childbearing age with schizophrenia". The authors state that estradiol showed improvement in negative symptoms and that the effect occurred almost entirely in 100 participants over 38.0 years of age (46 in the placebo group and 54 in the estradiol group; difference -1.98 points on the PANSS positive subscale; 95 % CI, –2.94 to –1.02; $P < 0.001$) [15]. According to the meta-analysis combining the results of the current study with all previous studies involving women with schizophrenia who received estradiol patches, the group receiving patches with estradiol had a statistically signifi-

cant improvement in PANSS total scores [15,16]. However, the authors have some concerns" about the quality and design of the studies, noting that „three studies were conducted by a single investigator in Australia, and one study was conducted in Moldova by different investigators." However, the latter study found nonsignificant results for the PANSS total score [15,17]. Estrogens influence „important pathophysiological pathways in schizophrenia, including dopamine activity, mitochondrial function, and the stress system," thereby contributing to elements of pathogenesis [14]. Thus, estrogen can also influence the treatment process and prognosis in schizophrenia. Brand BA and associates state that „premenopausal women require lower doses of antipsychotics than men, since estrogens increase the availability and effectiveness of antipsychotics " [14]. The conclusions drawn by the authors Brand, Willemse and associates according to two meta-analyses related to the study of estrogens in women with schizophrenia, where estrogen and raloxifene improved overall symptoms, deserve serious attention in terms of clinical improvement of symptoms and regulation of hormonal dysfunction both against the background of antipsychotic therapy, and against the background of age-related changes [18]. The same authors recommend three policy options and their combination to improve treatment, outcomes and reduce the risk of side effects in women with schizophrenia-like conditions, suggesting as an alternative the use of the following options: Dosing of antipsychotics for women, hormone replacement therapy with raloxifene for women in the postmenopausal period, and addition of aripiprazole in cases of hyperprolactinemia caused by antipsychotics [18]. Dalton, studying the hormonal influence on the exacerbation of psychotic symptoms, reports that out of 276 women hospitalized in psychiatric institutions, 46 % were patients during or immediately before menstruation when estrogen levels were minimal [19]. Many women with schizophrenia have insufficient estrogen levels. Menstrual cycle dysfunction is also common [7,20]. Thus, sufficiently high levels of estrogen contribute to a favorable, stable mental state. Moreover, according to Sbisa, van den Buuse and associates, estrogens have therapeutic potential in psychotic disorders" [21]. The influence of estrogen extends to other conditions, including risk reduction, delayed onset and progression of Alzheimer's disease and schizophrenia, better rehabilitation after stroke, and performing neuroprotective and neuroendocrine functions [6]. Estrogen regulates dopaminergic neurotransmission, its receptors, and transporters, which can be considered one of the molecular mechanisms of interaction [7,22]. Molecular studies demonstrate the interaction of estradiol with the main brain neurotransmitters that are involved in the pathogenesis of schizophrenia, as well as the clinical improvement of positive, negative, and cognitive symptoms of schizophrenia with adjuvant use of estradiol drugs [7].

Estradiol, the main component of estrogens, may have a protective effect on schizophrenic psychoses. In addition, many patients with schizophrenic psychoses, even in untreated prodromal stages, have hyperprolactinemia and gonadal dysfunction, estrogen deficiency in women, and testosterone deficiency in men. On the other hand, adult-onset schizophrenia is associated with decreased secretion of dehydroepiandrosterone (DHEA) [2,23]. Ritsner and associates concludes that elevated cortisol and cortisol/DHEAS (dehydroepiandrosterone sulphate) ratios in serum can serve as markers of the biological mechanisms of sensitivity of patients with schizophrenia to antipsychotic therapy, and the steroids themselves, DHEA, DHEAS, may be involved in the pathophysiology of schizophrenia [23]. DHEAS is considered to be the precursor for 75 % of estrogens in premenopausal women and almost 100 % of active estrogens during menopause [24]. In addition to their reproductive function, sex hormones can cause neurotransmitter effects through interaction with various types of receptors and have dopamine-like or glutamate-like effects [2]. The influence of estrogens on aspects of social behaviour is studied in animals. Ervin and associates conclude that the effects largely depend on the brain areas involved, the types of estrogens functioning in these areas, and the mechanisms that are involved [25]. Other effects of sex hormones are associated with their influence on the mechanisms of neural plasticity, including participation in the growth of nerve cells, synaptogenesis, myelination, and other possible mechanisms [10]. Both, neurons themselves, and glial cells take part in the biosynthesis and metabolism of neurosteroids [5].

Statistically reliable data were presented by Weis, Hausmann and associates confirming the neuromodulatory effect of estradiol depending on the phases of the menstrual cycle. The authors prove functional cerebral asymmetry, changes in functional connections in the dominant and non-dominant hemispheres depending on the menstrual and follicular phases in women, which is associated with the effects of sex hormones, especially estradiol, in addition to the established role of progesterone [26]. There is enough scientifically based evidence that estrogen performs protective functions in a woman's body, influencing the evolution, and providing a more favourable prognosis for schizophrenia [1,7,10,21]. It is believed that sex differences in schizophrenia are associated with the influence of sex hormones on the severity of symptoms, evolution, and prognosis of this disease. Some clinical studies have demonstrated positive results in patients with schizophrenia using estrogen, and the best effects were observed in the evolution of positive

symptoms [21]. Sezer, Köşger and associates have investigated the levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol, and progesterone in blood plasma in schizophrenia, as well as the severity of symptoms depending on the phase of the menstrual cycle in female patients with schizophrenia [27]. Other authors conducted a systematic review and meta-analysis, which resulted in „strong evidence of increased hospitalizations for perimenstrual psychotic disorders, consistent with the estrogen protection hypothesis" [13]. The same authors state that, the rate of hospitalization during the perimenstrual phase was 1.48 fold higher than expected (95 % CI: 1.31 – 1.67), and the worsening of psychotic symptoms ranged from 20 % to 32.4 %" [13].

As is well known, adverse reactions to antipsychotics often occur in the treatment of patients with schizophrenia, including hormonal and metabolic disorders, namely hyperprolactinemia and metabolic syndrome. These consequences may also depend on the phases of the menstrual cycle. It has been suggested that elevated prolactin levels cause a decrease in estrogen levels, may be a reaction to stress, or can result from exposure to antipsychotics [14]. Other authors also report the effect of hyperprolactinemia on the synthesis of estradiol in the ovaries in patients with schizophrenia and schizoaffective disorder during treatment with classical and non-classical neuroleptics, and thus, the relationship between prolactin and sex hormones [28]. Describing the effect of prolactin on sex hormones, the authors state that „ prolactin, by binding to gonadotropin ovarian receptors, inhibits the effect of gonadotropins on steroidogenesis and reduces the sensitivity of the ovaries to exogenous and endogenous gonadotropins" [28]. Hormonal imbalance and menstrual irregularities, as a manifestation of hyperprolactinemia in response to treatment with antipsychotic drugs, lead to an imbalance in the estradiol/testosterone ratio [28]. Increases in testosterone levels are associated with decreases in estradiol and, to a lesser extent, prolactin levels [28]. Other authors also report worsening of schizophrenia symptoms „during phases of the menstrual cycle with low estradiol levels and during the postmenopausal period when estradiol levels decrease" [29]. The effect of estrogen on the emotional, behavioural and cognitive state of patients with neuropsychiatric disorders in both sexes is also mentioned [7,30].

Clinical findings

Chua, de Izquierdo, Kulkarni and associates in the systematic review of four clinical studies (n = 108), compared estrogen only with placebo and came to the conclusion that short-term scores for general mental state showed no significant difference between groups. Data from all four studies showed that overall loss was low (5 %), with no significant differences between groups (n = 96, 4 RCTs, RR 0.95 CI 0.2 to 6.1) [31]. However, the following studies show results in favour of estrogens as adjunctive therapy to antipsychotics. A comparative analysis of several studies can be seen in Table no. 1.

The results show that the first two studies were not randomized, and the last one was a cohort study. In the study related by Louza MR and associates at the end of the study, only estrone was increased without an increase in estradiol. But is not specified which type of estrogen was given to the patients.

In the meta-analysis performed for studies with estradiol until March 2022 with only randomized, double-blind, placebo-controlled studies with six estradiol versus placebo (n = 724) , adjunctive estradiol outperformed the placebo in terms of the Positive and Negative Syndrome Scale (PANSS) total score (MD = -7.29; 95 % CI = -10.67 to - 3.91; I2 = 59.1 %; $p < 0.001$; k = 9; N = 858), positive symptom score (MD = -1.54; 95% CI = -3.04 to -0.72; I2 = 45.8 %; $p < 0.001$; k = 7; N = 624), negative symptom score (MD = -1.9; 95 % CI = -1.77 to -0.34; I2 = 37.6 %; $p < 0.05$; k = 14; N = 1042), and general psychopathology score (MD = -4.27; 95% CI = -7.14 to -1.41; I2 = 76.3 %; $p < 0.005$; k = 7; N = 624) (37).

The role of other hormones in development of clinical features in schizophrenia

In addition to the study of hormonal profiles and correlations between follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol, and progesterone during the menstrual cycle in schizophrenia, Sezer, Köşger and associates used scales such as Positive and Negative Symptom Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), and Hamilton Anxiety Rating Scale (HAM - A) [27]. In the obtained results, the scores were lower in the luteal phase than in the follicular phase and were statistically significant, which means that clinical symptoms in patients with schizophrenia improve in the luteal phase and worsen in the follicular phase of the menstrual cycle [27]. The authors also statistically proved correlations between steroid hormonal effects and psychopathology, namely negative correlations between follicle stimulating hormone and the PANSS positive symptom subscale (r = -0.393, P = 0.035), as well as between prolactin and the PANSS total score (r = -0.406, P = 0.029). Finally, the authors draw the very important conclusion that dysfunction of sex steroid hormones in patients with schizophrenia leads to changes in mental status, and ultimately, sex hormones may influence the severity of symptoms in schizophrenia [27]. According to the table 2 reported by Baird DT. Fraser IS., the highest level of estradiol and estrone is in the preovulatory

Table 1. Studies on estrogen as adjunctive treatment in schizophrenia (2001-2022)

Study authors	Number of participants	Study duration	Treatment	Results
Kulkarni, et al. (2001)	36 females with schizophrenia	28 days	A double blind, 28 day, placebo-controlled study was conducted with three groups of women of child-bearing age (N = 12 in each group) who received standardized antipsychotic medication plus 50 mcg transdermal estradiol or 100 mcg transdermal estradiol or transdermal placebo.	Analyses show that women receiving 100 mcg of estradiol made greater improvements in the symptoms of schizophrenia than both the 50 mcg estradiol and placebo groups. Women receiving 50 mcg estradiol had more improvement in their symptoms compared with the placebo group.
Louzã MR, et al. (2004)	40 females	28 days	0,625 mg estrogen were added to a fixed dosage of haloperidol (5 mg daily) in a double-blind, placebo-controlled study.	Both groups showed similar clinical improvement during the evaluation, although there was a trend for the CE group to show a better improvement than the placebo group ($p < 0.10$).
Kulkarni, et al., (2008)	102 females with schizophrenia.	28 days Randomized, double-blind study	Patients were randomized to receive 100 µg of transdermal estradiol (n = 56) or transdermal placebo (n = 46) for 28 days.	The addition of 100 µg of transdermal estradiol significantly reduced positive ($P < 0.05$) and general psychopathological ($P < 0.05$) symptoms during the 28-day trial period compared with women receiving antipsychotic medication alone.
Kulkarni, et al. (2015)	183 female participants were aged between 18 and 45 (mean = 35 years), with schizophrenia or schizoaffective disorder and ongoing symptoms of psychosis (Positive and Negative Syndrome Scale, PANSS score>60) despite a stable dose of antipsychotic medication for at least 4 weeks. Mean duration of illness was more than 10 years.	8 week three-arm, double-blind, randomized-controlled trial.	Participants received transdermal estradiol 200 µg, transdermal estradiol 100 µg or an identical placebo patch. Cognition was assessed at baseline and day 56 using the Repeatable Battery of Neuropsychological Status. Data were analysed using latent growth curve modelling.	The largest effect size was for the positive subscale of PANSS in the estradiol 200 µg treatment group (effect size 0.44, $P < 0.01$).

Table 1. (*Continued*)

Study authors	Number of participants	Study duration	Treatment	Results
Weiser, et al. (2019)	andomized, placebo-controlled trial performed in the Republic of Moldova, among 200 premenopausal women aged 19 to 46 years with schizophrenia or schizoaffective disorder.	8 week	Patients were randomized to receive a 200-μg estradiol patch or placebo patch changed twice a week added to their antipsychotic treatment.	Compared with placebo, participants receiving add-on estradiol patches had statistically significant improvements in the primary outcome measure, PANSS positive subscale points (- 0.94; 95 % CI, -1.64 to - 0.24; P = 0.008; effect size = 0.38). Post hoc heterogeneity analyses found that this effect occurred almost entirely in 100 participants older than 38.0 years (46 in placebo group vs 54 in estradiol group; difference, -1.98 points on the PANSS positive subscale; 95 % CI, -2.94 to -1.02; P < 0.001). Younger participants did not benefit from estradiol (difference, 0.08 points on the PANSS positive subscale; 95 % CI, -0.91 to 1.07; P = 0.87).
Sommer, et al. (2023)	The cohort of persons with schizophrenia/ schizoaffective disorder was identified from Finnish nationwide registers (N = 61 889) and stratified by sex and age < 45 vs. ≥ 45 years.	Hospitalizations for psychosis were defined per 5-year age group	Risk of psychosis hospitalization (Adjusted Hazard Ratio, aHR) was assessed using within-individual design, by comparing antipsychotic monotherapy use to nonuse periods in the same individuals for seven dose categories in defined daily doses (DDDs/day)	Starting at age 45–50, women were consistently more often hospitalized for psychosis than their male peers. Women ≥ 45 had significantly higher aHRs than women < 45 at antipsychotic monotherapy > 0.6 DDDs/day, and than men at > 1.1 DDDs/day.

phase and remains high in the mid-luteal phase, and progesterone has an increase in the preovulatory phase and the highest value in the mid-luteal phase.

Similarities to estrogen and progesterone are also seen in the localization of the receptors in the brain. The amygdala, hypothalamus, and hippocampus contain enough estrogen and progesterone-sensitive receptors. Estrogen receptors are located in the cerebellum, ventral tegmentum, hippocampus, amygdala, frontal cortex, midbrain raphe nuclei, and brainstem, and progesterone receptors are located in the amygdala, midbrain, brainstem, hippocampus, cerebellum, and frontal cortex [10]. It is evident that the localization of estrogen and progesterone receptors is basically the same, with the exception of the ventral tegmentum, where only estrogen receptors are located. The result concludes that more research is needed to evaluate the role of follicle-stimulating hormone, luteinizing hormone, prolactin, progesterone, and estrogen and that sex hormones could be used in patients with schizophrenia as an alternative therapy, especially in those who "do not respond adequately to treatment" [27]. Another hormone, namely progesterone, is a natural progestin synthesized by the ovaries in women and the testes and adrenal cortex in men [39]. Allopregnanolone is considered the main metabolite of progesterone, and its levels increase during pregnancy, reaching maximum levels in the third trimester of gestation [40]. Autumn and associates state that because allopregnanolone levels „increase throughout pregnancy and decline sharply to normal levels in the postpartum period," this suggest that altered allopregnanolone level may be involved in the pathogenesis of postpartum depression [41]. According to Luisi, Petraglia and associates allopregnanolone is active in the central nervous system and blood pressure control" and is thought to be „involved in pregnancy-induced adaptive processes"[40]. In addition to the reproductive function, progesterone performs immunomodulatory, cholesterol synthesis inhibitory and neuroprotective functions [39,42]. Progesterone reduces the level of gonadotropin-releasing hormone and the release of gonadotropins during the transition from the luteal phase to the follicular phase [43]. Allopregnanolone also enhances gene expression by promoting mitosis of nerve cells, inhibits gene expression by suppressing cell proliferation, and also induces a rapid increase in intracellular calcium in hippocampal neurons activated by the GABA type A receptor [44]. Another mechanism of action of progesterone and estrogen is their ability to bind to an atypical protein, the sigma 1 (σ1) receptor, triggering neuroprotective activity [4,45]. Sigma 1 receptors are also implicated in release of dopamine and glutamate in the brain. Carcolé, Zamanillo and associates highlight the blockade of sigma-1 receptors that alleviates the nociceptive, cognitive and emotional manifestations associated to chronic osteoarthritis pain [46]. The antidepressant effect of estradiol has been reported previously by other authors. This effect is supposed to be due to the action on dopamine, serotonin, and sigma-1 receptors [47]. For these reasons, antidepressants are frequently used as adjunctive treatment to reduce the negative symptoms in schizophrenia.

Hormonal implications in postpartum disorders

There is a close connection between sex hormones and the main neurotransmitters, such as serotonin, dopamine, GABA, and glutamate, so sex hormones affect mood, behaviour, and cognitive abilities, participate in the pathogenesis of mental diseases [2,10,12,23]. The GABA system is the main inhibitory mediator of the brain and the central nervous system; it participates in the regulation of such brain functions as mood, behaviour, excitement, and cognition [48]. Therefore, antidepressants that belong to the group of positive modulators of GABA receptors (brexanolone, zuranolone) have been developed based on its mechanisms [48,49]. Brexanolone - belongs to the class of GABA - A modulator drugs, was called a "breakthrough therapy" by the FDA, and was approved in March 2019 for the treatment of postpartum depression [50]. According to Azhar and associates, the mechanism of action of brexanolone remains unclear. [50]. However, it is known that brexanolone is the form of allopregnanolone, which is considered the main metabolite of progesterone [50]. In August 2023, the FDA approved the second antidepressant from this class, zuranolone. Both brexanolone and zuranolone are indicated for the treatment of postpartum depression [51]. Moreover, Clauton, Lasser and associates conclude on the basis of a randomized clinical trial that zuranolone, proved its potential in the treatment of adult patients with a major depressive episode" [52]. Based on these data was concluded that, allopregnanolone agonists present a new mechanism of action in the treatment of depressive disorders" [41]. The authors state that clinical trials and preliminary findings, confirm the improvement of the condition of patients with depression symptoms by brexanolone in postpartum depression, and zuranolone in major depressive episode, bipolar and postpartum depression" [41]. The mechanisms of action of brexanolone and zuranolone are not yet fully understood, but appear to be similar. [48,49,53]. Therefore, allopregnanolone is considered a potent endogenous neuroactive steroid that modulates neuronal excitability through GABA-A receptors. [3]. Fink George and associates, in discussing the clinical relevance of treating depressive symptoms with estrogen as a "natural psychoprotective agent," concluded that the effectiveness of estrogen therapy or selective sero-

Table 2. Production Rate of Sex Steroids in Women at Different Stages of the Menstrual Cycle [38]

	Daily Production Rate		
Sex Steroids	Early Follicular	Preovulatory	Mid-luteal
Progesterone (mg)	1	4	25
17α - Hydroxyprogesterone (mg)	0.5	4	4
Dehydroepiandrosterone (mg)	7	7	7
Androstenedione (mg)	2.6	4.7	3.4
Testosterone (μg)	144	171	126
Estrone (μg)	50	350	250
Estradiol (μg)	36	380	250

tonin reuptake inhibitors (SSRIs) in alleviating depressive symptoms associated with premenstrual syndrome supports the hypothesis that sex differences in schizophrenia may be related to estrogen's modulatory effects on 5-HT2A receptors. [12]. The authors argue that estrogen increases the density of serotonin receptors – 5 - hydroxytryptamine 2A (5 - HT2A) in areas of the brain responsible for the control of mental state, emotions, and behaviour, as well as the number of dopamine (D2) receptors in the striatum [12].

Discussion

Scientific evidence highlights the neuroprotective, anti-inflammatory, and neuromodulatory effects of estrogen, as well as its therapeutic potential in psychiatric disorders such as schizophrenia, postpartum depression and menopause. This suggests that estrogen and progesterone, as well as their metabolites, play a critical role in regulating mood and the symptoms of schizophrenia. Therefore, treatment of schizophrenia, postmenopausal, and postpartum depression with estrogens requires a comprehensive understanding of hormonal status and its impact on mental health. Estrogens, especially estradiol, have shown therapeutic effects in several studies. There are also risks associated with the effectiveness and safety of estrogen therapy. There are also some concerns about the quality and design of earlier clinical studies. No clear correlation was established between the dose, duration of therapy, and the occurrence of immediate or delayed side effects. This underscores the need for future well-designed randomized controlled trials.

In conclusion, estrogen, as well as progesterone and allopregnanolone, appears to hold significant potential in the treatment of schizophrenia and postpartum disorders. Their use may contribute to a more favorable prognosis in schizophrenia. Moreover, estrogen therapy could enable a reduction in antipsychotic dosage and help minimize associated side effects. Future research should focus on exploring estrogen and other sex hormones as adjunctive treatments for schizophrenia and postpartum depression, with careful consideration of optimal dosing, safety, treatment duration, and overall therapeutic efficacy.

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Conflict of interest

None to declare.

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