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Review

THE IMPACT OF SEX HORMONE LEVELS ON COGNITIVE FUNCTIONING IN WOMEN WITH SCHIZOPHRENIA - SCOPING REVIEW

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SUMMARY

Background: *Cognitive impairment is a core and disabling feature of schizophrenia, with a profound impact on functional outcomes. Female patients often demonstrate better cognitive profiles than males, suggesting a potential modulatory role of sex hormones. Estrogens, particularly estradiol, have been hypothesized to exert neuroprotective effects via modulation of neurotrophic, neurotransmitter, and inflammatory pathways. However, evidence regarding the relationship between sex hormone levels and cognition in schizophrenia remains scattered and inconclusive.*

Methods: *This scoping review synthesized evidence from clinical and preclinical studies examining the association between endogenous estrogen levels or estrogen-based treatments and cognitive functioning in women with schizophrenia. We included peer-reviewed literature addressing hormonal fluctuations across the menstrual cycle, menopause, and in response to antipsychotic treatment, with specific focus on estradiol and selective estrogen receptor modulators.*

Results: *Findings suggest that low estrogen levels may be linked to more severe negative symptoms and poorer cognitive performance in female patients. Studies investigating menstrual cycle phases report mixed results, while evidence from animal models indicates potential cognitive benefits of estrogenic compounds. Raloxifene has shown promise in mitigating cognitive deficits when administered during sensitive developmental periods. However, large-scale hormonal interventions in postmenopausal women have produced inconsistent results, likely due to differences in timing, dosage, and individual neurobiological context.*

Conclusions: *Sex hormone levels, especially estradiol, appear to influence cognitive outcomes in women with schizophrenia, though findings are heterogeneous. Future research should address methodological inconsistencies and explore phase-specific, personalized hormonal strategies. A deeper understanding of hormonal-cognitive interactions may inform more effective, sex-sensitive treatment approaches in schizophrenia.*

Key words: *schizophrenia - cognitive functions - sex hormones - adjunctive treatment*

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INTRODUCTION

Schizophrenia is a chronic and multifaceted neuropsychiatric disorder characterized not only by positive and negative symptoms but also by profound cognitive deficits, which are critical predictors of long-term functional outcomes. A growing body of research has pointed to sex-based differences in the course and expression of the illness, with women often presenting with later onset, milder symptom severity, and comparatively better cognitive performance than men (Krysta et al. 2013). These findings have sparked interest in the potential protective role of sex hormones, particularly estrogens, in female patients with schizophrenia. Estrogens, especially estradiol, have been proposed to exert neuroprotective effects through multiple mechanisms, including modulation of brain-derived neurotrophic factor (BDNF), neuroinflammation, and neurotransmitter systems such as NMDA and GABAergic pathways (McGregor et al. 2017). These effects are particularly relevant to the cognitive domain, where estrogen may enhance functions such as memory, attention, and executive control - areas that are typically impaired in schizophrenia. Evidence from clinical and preclinical studies supports the notion that fluctuations in estrogen levels may influence the severity of cognitive symptoms. Ko et al. (2006) demonstrated that women with schizophrenia and low estradiol levels during the follicular phase of the menstrual cycle exhibited more pronounced negative symptoms and performed worse in cognitive tasks compared to those with normal hormone levels. These findings were reinforced by the observation that estrogenic agents, including raloxifene, can attenuate cognitive deficits in animal models of schizophrenia when administered during critical developmental windows (Felgel-Farnholz et al. 2023). Despite these promising insights, the literature remains inconclusive, particularly regarding the timing and efficacy of hormonal interventions. Large-scale trials of hormone replacement therapy in aging women, for instance, have failed to show consistent protective effects against cognitive decline, underscoring the complexity of hormonal interactions with brain function (Aloysi et al. 2006). This suggests that the timing, type of hormone, and the neurobiological context are crucial

variables influencing cognitive outcomes. Given the centrality of cognitive impairment in schizophrenia and the growing evidence linking sex hormones to neurocognitive performance, a comprehensive scoping review is warranted. This review aims to synthesize existing findings on the relationship between sex hormone levels - particularly estrogens - and cognitive functioning in women with schizophrenia. By mapping the available evidence, we seek to clarify biological underpinnings, identify gaps in the literature, and inform future research and therapeutic strategies.

METHODS

This study followed the methodological framework for scoping reviews proposed by Arksey and O'Malley (2005), which includes five essential stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; and (5) collating, summarizing, and reporting the results.

The main research question guiding this review was: What is the relationship between sex hormone levels, especially estrogens and progesterone, and cognitive functioning in women with schizophrenia? A comprehensive literature search was conducted in the PubMed, Scopus, and PsycINFO databases. Search terms included combinations of "schizophrenia," "estrogen," "progesterone," "sex hormones," "cognition," "menstrual cycle," and "menopause." Only peer-reviewed English-language publications were included.

Eligible studies were those that (a) involved female participants diagnosed with schizophrenia or schizoaffective disorder, (b) assessed endogenous or pharmacologically modified sex hormone levels, and (c) reported cognitive outcomes. Both clinical and preclinical studies were included when mechanistically informative.

From each study, we extracted data on sample characteristics, hormone levels, cognitive domains tested, methodological approach, and main findings.

The findings were synthesized thematically, organized according to type of hormone, reproductive stage (e.g. menstrual phase, menopause), and nature of intervention (e.g. hormone therapy, selective estrogen receptor modulators). Identified patterns and gaps were narratively summarized to inform future research and treatment strategies.

ESTRADIOL AND COGNITIVE FUNCTIONING

Estradiol has emerged as a key neuroendocrine factor with potential neuroprotective and pro-cognitive effects, particularly relevant to the pathophysiology and treatment of schizophrenia in women. In recent years, an increasing number of clinical trials and case studies have investigated the role of estradiol and selective estrogen receptor modulators (SERMs) in improving cognitive outcomes and reducing psychopathological symptoms in women with schizophrenia. These studies reflect a growing awareness of gender-specific therapeutic needs and the biological interplay between hormonal status and cognitive function. The foundational study by Hoff et al. (2001) demonstrated a clear and significant correlation between serum estradiol levels and neuropsychological performance in women diagnosed with schizophrenia. In a cohort of 22 female inpatients, higher average estrogen levels were strongly associated with improved performance in global cognition, verbal memory, spatial memory, and perceptual-motor speed. Importantly, this effect was independent of changes in psychiatric symptom severity, indicating a specific pro-cognitive influence of estradiol rather than a nonspecific mood-related improvement (Hoff et al. 2001). The relationship between estradiol and cognitive enhancement has been further supported by controlled interventional studies. Bergemann et al. (2007) conducted a double-blind, placebo-controlled crossover trial investigating the effects of 17β-estradiol on cognitive performance in 19 women with schizophrenia. The study revealed a statistically significant improvement in the comprehension of metaphoric speech, a cognitive domain impaired in schizophrenia and closely related to formal thought disorders. Although other verbal tasks (e.g., fluency, word recognition) did not improve significantly, the enhancement in metaphoric abstraction provides evidence that estradiol can target specific higher-order cognitive processes relevant to social functioning and communication (Bergemann et al. 2007). Clinical case reports provide additional support for the efficacy of estrogen-based treatments. Kulkarni et al. (2008) presented three cases drawn from larger clinical trials. One case involved a premenopausal woman treated with adjunctive transdermal estradiol (200 μg/day), resulting in a marked improvement in psychotic symptoms. A second case described a postmenopausal woman who received raloxifene (120 mg/day), which was associated with significant cognitive improvement. These cases illustrate not only symptom reduction but also the capacity of hormone therapy to enhance cognitive domains that are often resistant to standard antipsychotic medications (Kulkarni et al. 2008). Kulkarni et al. (2015) extended these findings in the largest randomized-controlled trial to date involving 183 women of childbearing age with treatment-resistant schizophrenia. Participants received transdermal estradiol (100 μg or 200 μg) or placebo over an eight-week period. Both estradiol groups

exhibited significantly greater reductions in positive and general symptoms on the PANSS scale, with the 200 μg group showing the strongest effects. Cognitive assessments conducted at baseline and at study endpoint also indicated a trend toward improved neuropsychological performance, supporting estradiol's role in symptom modulation and cognitive enhancement (Kulkarni et al. 2015). For postmenopausal women, where traditional estrogen therapy poses risks to breast and uterine tissue, raloxifene offers a safer alternative. In a randomized, placebo-controlled trial, Huerta-Ramos et al. (2014) demonstrated that 60 mg/day of raloxifene significantly improved memory and executive functions over 12 weeks in women with stable schizophrenia. These benefits occurred independently of clinical symptom change, reinforcing the idea that cognitive enhancement through estrogenic mechanisms can be selectively achieved (Huerta-Ramos et al. 2014). Beyond schizophrenia-specific trials, evidence from broader neuropsychological research supports estradiol's role in enhancing working memory - particularly for emotionally salient stimuli. Gasbarri et al. (2008) reviewed studies in humans and non-human primates and reported that estradiol improves performance in tasks such as delayed matching-to-sample (DMTS) and delayed non-matching-to-sample (DNMTS), especially when stimuli involve emotional facial expressions. These findings are consistent with the widespread distribution of estrogen receptors in limbic and prefrontal brain regions and the hormone's modulatory influence on neurotransmitters such as dopamine and serotonin (Gasbarri et al. 2008). This research highlights the relevance of hormonal fluctuations across the menstrual cycle, menopause, and postpartum periods in influencing mood, affect regulation, and memory areas that overlap with cognitive impairments observed in schizophrenia. Gasbarri et al.'s findings suggest that estrogen-sensitive modulation of emotional working memory could be particularly beneficial in clinical settings, where both affect and cognition are compromised (Gasbarri et al. 2008).

PROGESTERONE AND COGNITIVE OUTCOMES IN SCHIZOPHRENIC FEMALE PATIENTS

Progesterone is not only a reproductive hormone but also a neuroactive steroid, meaning it can directly modulate neural activity. It acts primarily via the GABA-A receptor, promoting anxiolytic and sedative effects. In the brain, progesterone also influences neurogenesis, myelination, and neuronal survival. These effects make it a candidate modulator of cognitive function, particularly in contexts of neuropsychiatric illness. In schizophrenia, sex differences in onset, course, and cognitive symptomatology have long been recognized. Women typically exhibit later onset and milder negative symptoms, which has been partly attributed to the protective influence of estrogen. However, recent findings suggest that progesterone may also play a role, either independently or in interaction with other hormones. Sun et al. (2016) conducted a comprehensive review of the interactions between progesterone and dopaminergic systems in the context of schizophrenia. They emphasized that progesterone modulates dopamine neurotransmission, a key pathway involved in both psychosis and cognitive function. Preclinical studies in animal models suggest that progesterone may mitigate dopaminergic hyperactivity, which could help with positive symptoms. However, this same modulation may exacerbate negative or cognitive symptoms depending on timing and dosage (Sun 2016). Progesterone's inhibitory effects on excitatory neurotransmission could impair attention, memory encoding, and executive function in some scenarios. On the other hand, its neuroprotective properties might buffer cognitive decline under neuroinflammatory or oxidetive stress conditions. A study by Huang et al. (2021) investigated serum progesterone levels in schizophrenia patients at various treatment stages. In female patients, no significant elevation in progesterone levels was observed after antipsychotic treatment, unlike in male patients. However, an important finding was a negative correlation between serum progesterone and total PANSS scores, including the positive symptom subscale (Huang 2021). This suggests that higher progesterone levels may be associated with less severe clinical presentation, potentially including better cognitive function, though cognition was not directly assessed in this study. These findings raise the possibility that progesterone levels reflect adaptive stress responses, and that insufficient progesterone may be linked to worse outcomes, particularly in the cognitive-affective domain. Progesterone's action as a positive allosteric modulator of the GABA-A receptor may lead to sedative, anxiolytic, and mood-stabilizing effects, all of which can indirectly influence cognition. For example, reduction of anxiety may enhance working memory or attentional flexibility. However, excessive GABAergic activation may cause cognitive dulling, with reduced processing speed or impairments in short-term memory. Thus, the effects of progesterone on cognition in schizophrenia appear to follow a nonlinear pattern: potentially beneficial at physiological levels and detrimental when imbalanced, whether due to pharmacological, endogenous, or pathological causes.

PROLACTIN, ESTROGEN SUPPRESSION, AND CLINICAL IMPLICATIONS IN WOMEN WITH SCHIZOPHRENIA

Antipsychotics, particularly those that elevate prolactin, may suppress ovarian function, leading to reduced estrogen levels. This hormonal interplay has implications for cognition, mood, menstrual health, and overall treatment outcomes (Bodyl 2024, Caruso 2002). Caruso (2002) conducted a foundational 8-week study on 16 premenopausal women with schizophrenia or schizoaffective disorder. Participants were split into two groups: those receiving prolactin-raising antipsychotics (e.g., typicals, risperidone) and those receiving prolactin-sparing agents (e.g., olanzapine, clozapine). Prolactin levels were significantly higher in the prolactin-elevating group. However, estradiol and progesterone levels were low in both groups, with no statistically significant differences. Importantly, most participants had estradiol levels below normal periovulatory values, regardless of medication type or prolactin status. This suggested that ovarian dysfunction might be partly intrinsic to schizophrenia, not solely a side effect of medication. In a larger cross-sectional study of 79 women, Bodyl (2024) confirmed that prolactin-raising antipsychotics were associated with lower 17β-estradiol levels and greater symptom severity. In women receiving these medications, prolactin correlated negatively with estrogen ($r = –0.42$, $p = 0.03$), and high prolactin predicted slower processing speed, while estrogen positively correlated with verbal fluency. Moreover, in women on prolactin-sparing drugs, higher estrogen levels were linked to lower depression/anxiety symptoms, reinforcing the idea that estrogen plays a regulatory role in psychiatric symptoms and cognition.

MENSTRUAL CYCLE, MENOPAUSE, AND COGNITIVE FLUCTUATION IN WOMEN WITH SCHIZOPHRENIA

Hormonal variability across the female lifespan plays a critical role in shaping cognitive functioning. In women with schizophrenia, this influence is particularly relevant, as both the menstrual cycle and menopausal transition can modulate cognitive performance and symptom severity. Recent research has deepened our understanding of how fluctuations in sex steroid hormones interact with brain systems in schizophrenia, with implications for both diagnosis and treatment strategies. The menstrual cycle is characterized by dynamic hormonal changes, particularly in estradiol and progesterone levels, which modulate neural circuits involved in memory, attention, and executive functioning. Rubin (2015) investigated cognitive performance across the early follicular and midluteal phases in women with schizophrenia. Contrary to initial hypotheses, the study found no significant differences in cognitive function associated with estradiol or progesterone levels. However, oxytocin levels correlated positively with performance on verbal memory tasks, suggesting that non-steroidal hormones may exert a more robust effect on certain cognitive domains in schizophrenia than previously recognized (Rubin 2015). The impact of hormonal variability is further underscored by findings related to menstrual irregularity and menopause. Gurvich (2018) demonstrated that women with schizophrenia who had irregular menstrual cycles showed significantly poorer performance on tasks assessing psychomotor speed, verbal fluency, and memory. This suggests that disruptions in the normal rhythm of reproductive hormones may have deleterious effects on cognition, even in reproductive-aged women. Interestingly, perimenopausal status alone did not predict significant cognitive decline, while postmenopausal status was associated with reduced visuospatial performance. These findings indicate that both the presence and regularity of menstrual cycling may be more influential than the menopausal transition per se, at least in some cognitive domains (Gurvich 2018). The postmenopausal period presents additional complexities. Searles (2018) highlighted the observation that schizophrenia diagnoses in women tend to increase after menopause. This suggests a protective role for estrogen, possibly through its interactions with dopaminergic pathways critical to cognition and emotion regulation. The decline in estradiol may unmask latent vulnerabilities or exacerbate existing cognitive impairments, especially in older women with schizophrenia. Furthermore, Searles emphasized the need to consider estradiol as a potential therapeutic target in postmenopausal patients. While estrogen's cognitive effects in premenopausal women appear modest or variable, its role in older women may be more pronounced due to the loss of gonadal steroids and the neurobiological shifts that accompany aging (Searles 2018).

CONLUSIONS

Collectively, the findings from case studies, clinical trials, and neuroendocrine correlational studies suggest that estradiol exerts a positive effect on cognitive functioning in women with schizophrenia. This effect appears to be particularly pronounced in domains related to memory, abstract reasoning, and language comprehension. While traditional antipsychotics have limited impact on cognition, estradiol and raloxifene represent promising adjunctive options. Given the observed specificity and safety profiles, further long-term, large-scale studies are warranted to establish guidelines for the use of hormone modulation as a

standard component of schizophrenia treatment in women. While estradiol has been the primary focus of sex hormone research in schizophrenia, progesterone represents an underexplored but potentially critical factor in modulating cognition in female patients. Its influence on dopaminergic activity, stress responses, and GABAergic transmission positions it as both a biological signal and a potential therapeutic target. Current evidence suggests that balanced progesterone levels may be linked with milder clinical symptoms and possibly better cognitive outcomes, though further studies are needed to establish causality and optimal treatment implications. Taken together, these studies suggest that sex hormones influence cognition in schizophrenia in a phase- and age-specific manner. While estradiol and progesterone may not uniformly enhance cognitive performance, their absence, particularly in the context of irregular cycles or menopause may contribute to worsening cognitive outcomes. Additionally, the association of oxytocin with verbal performance warrants further exploration, especially given its emerging role in social and cognitive domains. These findings have practical relevance. Clinicians should be aware of menstrual and menopausal status when assessing cognitive symptoms in female patients with schizophrenia. Moreover, hormone-based interventions, including estradiol supplementation or oxytocin modulation, may hold promise but must be tailored to the patient's reproductive status and symptom profile. Further research is needed to delineate the mechanisms by which hormonal fluctuations affect specific cognitive domains, and whether these effects are mediated by genetic factors, brain structure, or neurotransmitter systems. Longitudinal studies that track hormonal profiles and cognition over time would be especially valuable in developing personalized, hormone-informed treatment strategies.

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Krzysztof Krysta: conceptualisation, methodology, data collection, visualisation, writing - original draft, writing - review and editing.

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Agnieszka Koźmin-Burzyńska: writing - review and editing.

Katarzyna Piekarska-Bugiel: methodology, data collection, writing - original draft, writing.

Roman Wojnar: data analysis, writing - review and editing.

Rafał Bieś: data analysis.

Marek Krzystanek: validation, visualisation, project administration.

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