SEX HORMONES AND PSYCHOSIS: A REVIEW

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OBJECTIVES

The aim of this work is to shortly review current knowledge on the topic of **sex hormones in psychotic disorders**.

BACKGROUND

Recent studies have shown that **sex hormones**, such as **estrogens**, **progesterone**, **testosterone**, **dehydroepiandrosterone sulfate (DHEA-S)** and **prolactin**, play an **important role in psychotic disorders** like schizophrenia.

These hormones seem to be related to the **pathophysiology**, **course** and **severity** of disease, **symptomatology** and **gender differences** in psychosis¹⁻⁹.

MATERIALS AND METHODS

A literature search in the *PubMed* database was conducted, using the search terms “sex hormones”, “sex steroids”, “psychosis”, “psychotic disorders” and “schizophrenia”. Relevant articles were also sought from citations.

A non-systematic review was performed, using articles published up to December 2018. Nine relevant articles were selected.

RESULTS

Most of the available studies focus on the **role of sex hormones** in **schizophrenia** and **first-episode psychosis (FEP)**.

▪ **Estrogen hormones** are the best studied^{1,3,7,8}.

Research over the last two decades has established for them a clear neuromodulatory role in the pathogenesis of schizophrenia.

Estrogens seem to have **neuroprotective** properties, protecting the brain from the development and severity of mental disorders like psychosis. On the other hand, states of estrogen deficiency have been frequently reported in women with schizophrenia.

The “**estrogen hypothesis**” can be an explanation to **gender differences** in schizophrenia, such as higher incidence in men, older age of onset and less severe course of illness in women. It is also consistent with the existence of a peak of onset in females after the age of 40, which may be associated with the hormonal decline in menopause.

Clinical studies have shown that women with psychotic disorders demonstrate increased symptom severity, greater relapse rates and more hospital admissions during **phases of low circulating sex hormones**: perimenstrual, postpartum and postmenopause.

An increasing amount of literature has explored estrogen therapy as a **potential adjunct to antipsychotics**, as it might improve cognition and positive symptoms, but this remains controversial.

▪ **Progesterone** ^{1,2,9}

The impact of this hormone has been far less studied.

Existing data suggest that it is a **key modulator** of central systems implicated in schizophrenia, such as the **dopaminergic** system. There is some evidence of **dysregulation of progesterone levels** in patients with schizophrenia, particularly in women during the mid-luteal phase of menstrual cycle.

It can also contribute to **gender differences** in psychosis. Better prognosis and response to medication in women may be related to the combined effects of estrogen and progesterone on functions like cognition and sensorimotor performance.

▪ **Prolactin** is commonly increased in psychotic patients, even in those who are antipsychotic-naïve or with an at-risk mental state. The “**stress-prolactin-dopamine hypothesis**” has been proposed to explain how it acts in the transition to psychosis. Since it suppresses the production of the gonadal estrogens and progesterone, the **hyperprolactinemia** could explain those hormonal deficiencies⁷.

▪ **Testosterone** and **DHEA-S** importantly influence dopaminergic, glutamatergic and GABAergic systems, which act in the **pathophysiology** of psychotic disorders^{2,4,5,6}.

It has also been reported that their levels may impact **psychopathological manifestations of schizophrenia**. Specifically, many studies revealed a **negative correlation** between the levels of **testosterone** and the severity of **negative symptoms** or **cognitive deficits**.

A recent review and meta-analysis⁵ has found significantly **higher levels** of **DHEA-S** in psychotic patients compared to controls, the difference being more significant in men. This might be perceived as a stress response mechanism, since it is produced after the release of ACTH, or related to increased dopaminergic transmission in acute psychosis. Levels of **testosterone** differ in FEP (increased free and unaltered total testosterone) and acute relapses (the opposite pattern).

CONCLUSIONS

There is still much to be discovered on the present topic. Future research is needed, as improved understanding of the role of sex hormones in psychosis and their potential application in treatment would be of significant clinical value.

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