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Gaps or links between hormonal therapy and schizophrenia? (Review)

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Abstract. Schizophrenia is considered the most severe and debilitating psychiatric disorder. During the 80's, first reports on abnormalities of the schizophrenic brain which could be objectively observed on MRI, CT scans and other imagistic techniques were published. This showed that schizophrenia is a disorder that goes beyond the functional aspect of the symptomatology. The ties between psychiatry and endocrinology are easily observed, even empirically, by any mental health practitioner, and mirrored by endocrinology specialists. Disorders related to menstruation phase of the menstrual cycle have a code in DSM-V, people expect women 'to have mental disturbances' during puberty, pregnancy, menopause and other periods of life known to cause a hormonal storm. Leaving aside those simple and common beliefs, any mental health specialist can observe the differences between men and women when it comes to psychopathology, and the differences between male and female patients when it comes to a severe disorder such as schizophrenia. Males present more severe symptoms; their evolution is worse and they tend to have more medico-legal issues. On the contrary, the current available treatments for schizophrenia tend to have some side effects easily observed by endocrinologists: from gynecomastia to breast asymmetry in women, hyperprolactinemia, weight gain and other metabolic disorders, the clinic shows us regularly what the science has already told us; that the impact of hormones on the developing brain, starting *in utero* and going on through life may hold the key to finding better treatments for debilitating disorders such as schizophrenia. This mini-review is focused on the role of estrogen in the evolution of schizophrenia and on reporting trials that showed how hormonal therapy (used mainly for breast cancer and osteoporosis) can improve the outcome of patients with schizophrenia.

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Contents

1. Connecting the dots between schizophrenia and estrogen

Schizophrenia is a disorder associated with different changes in the structure of the brain in which we can observe a progressive decrease of the volume of white and gray matter and also a progressive enlargement of the brain ventricles. As known, the negative cluster of symptoms tend to be more resistant than positive ones to medication. The multitude of neurotransmitter systems which are involved in schizophrenia (e.g., dopaminergic, glutamatergic and serotonergic) makes this disorder so hard to treat effectively (1). In recent years, increasing data have suggested that there is sex-specific differences in schizophrenia, influencing the age of onset, treatment outcome and the prevalence of negative symptoms. Following these data, many scientists have tried to find a correlation between sex hormones and the evolution of patients diagnosed with schizophrenia. From the analysis of many factors (data related to anatomical, neurochemical, epidemiologic and treatment response facts), a theory emerged of 'protection' from schizophrenia stating that estrogens offer protection against this disorder (2). As far as we know, the chronology effects of estrogen add to neural plasticity, the mechanism is via gene expression; there are also receptor sites or post-receptor sites (G proteins) where the estrogen effects may affect the neurotransmitter systems directly. Very important when it comes to schizophrenia (dopamine being the most significant neurotransmitter involved in symptomatology) is that estrogens modulate the dopamine system (3) which predominantly aims at the dopaminergic system (4).

A Canadian researcher named Shijit Kapur, has proposed a theory on how dopamine dysregulation links to symptom formation (5). He used the term 'salience' regarding the roles

of dopamine. He stated that dopamine can provide 'salience', by transforming neutral mental representations into ones with specific importance, this being the first step towards psychosis. His theory adds into discussion the fact that in psychotic episodes, dopamine may somehow 'highlight' otherwise insignificant daily thoughts or perceptions; the delusions develop as a way to find a sense in a world in which this kind of events happen all the time and they end up being processed in a delusional manner. The researcher emphasizes some clinical situations which show the relation between excess dopamine and schizophrenia. For example, the typical antipsychotic drugs which cause extrapyramidal effects by blocking dopamine in the substantia nigra; the fact that the clinical efficacy of typical antipsychotics is correlated to their ability to block dopamine.

Schizophrenia has a later average onset and shows a better prognosis in women than in men (6,7); these facts, as postulated above, are thought to be due also to the antidopaminergic effect of estrogen (8,9). Another peak in the prevalence of schizophrenia in women can be seen in the postmenopausal period, this being another argument sustaining the protective effect of estrogen (10). Also, while female patients with schizophrenia need usually lower doses of antipsychotic treatment than males, their dosage might be increased after reaching menopause (11,12).

Several aspects of the estrogen effect on brain function and structure have been documented: The modulation of neurogenesis, axonal sprouting, plasticity and connectivity. Reviewed in (13) women with schizophrenia, lower circulating estradiol levels (14,15) seem to contribute to the brain pathology associated with the psychiatric disorder, so clinicians expect to see differences between the brains of female and male patients with schizophrenia medical history. There are two MRI studies which showed more severe abnormalities of the schizophrenic brain in males than in females when compared with control groups, especially regarding ventricular enlargement (16) and temporal lobe volume (17). In these patients the enlargement of the brain ventricles is associated with the severity of negative symptoms, low monoamine activity and low cerebral glucose metabolism. Estradiol-17β is the most potent female sex hormone; it influences embryonal, as well fetal growth and development and also the development of the aminergic system (relevant in schizophrenia) (18).

The neuroprotective effects and influence of Estradiol-17β in the morphological aspect of neuronal systems can explain the marked sex differences regarding the progression of schizophrenia. This hormone can be an integrated part of a system that ameliorates the outcome of this debilitating psychiatric disorder. Studies on human induced pluripotent cells (iPSC) also demonstrated positive effects of estradiol-17β. The results of a study performed in 2018 showed its ability to increase the expression of synaptic protein in iPSC-neurons in patients diagnosed with schizophrenia to a similar level found in iPSC-neurons of healthy people (19).

There are also studies which found a correlation between the severity of psychotic outbreaks in women diagnosed with schizophrenia and the phase of their menstrual cycle. The exacerbation of psychosis during the perimenstrual phase of the menstrual cycle was reported by studying the rate of admissions in the psychiatric wards and by studying self-reported exacerbation of psychotic symptoms (20).

The symptomatology of female patients is much more severe in the low estrogen phase of the menstrual cycle. Female patients with schizophrenia have more severe symptoms in the low estrogen phase of their menstrual cycle. Studies that controlled the level of estrogen in plasma also showed a negative correlation between the severity of symptoms and the estradiol-17β levels (21).

In order to define the relation between schizophrenia and sexual hormones, variation within symptoms was observed to be linked with female menstrual cycle (depending on estrogen and progesterone phase). While on estrogen phase, researchers saw an improvement in negative symptoms, on progesterone phase a decrease of positive symptoms was registered (22). In contrast, a prospective study concluded that premenstrual variation of hormones and symptoms in female patients are not defined by a proportional rate (23). So, it is critical, both for the patient and clinician to individualize the treatment.

2. Dissecting the trials

Kraepelin sustained, 100 years ago, that an imbalance of estrogens may be one of the reasons which underlie the structural changes in dementia praecox. At present, various studies have merged, besides estrogen protection hypothesis (sex differences) (24) the clinical benefit of schizophrenia treatment along with hormonal therapy, especially in menopausal and postmenopausal women. In comorbid depression, which is often associated with schizophrenia, administering 17β-estradiol to suffering women may boost their emotional status with an antidepressant effect (25). Further research is needed to provide this aspect.

Regarding the correlation between menstrual cycle and exacerbation of schizophrenia symptoms, we highlight a study that shows a higher hospitalization of women, non-age related, especially three days before and after menstruation starts (26). Clinical implication was revealed also by a higher induced level of prolactin hormone due to antipsychotic drugs (e.g. prolactin-elevated drugs). Observed in the serum of both males and females, there is a cause-effect loop between hyperprolactinemia and low estrogen levels (27) raising questions among schizophrenia treatment. In addition, studies have shown that men with induced antipsychotic-hyperprolactinemia are more prone to develop venous thromboembolism (VTE) (28). Also, by lowering levels of estrogen, antipsychotic medication destabilizes patients with schizophrenia, exacerbating their symptoms (29). Being aware of this, therapy with estrogen shows its efficacy in specifically targeted trials. While symptoms tended to diminish on females who benefited of hormonal therapy, no notable differences were noted on male patients vs. placebo (30).

Although schizophrenia cumulates negative, positive and cognitive symptoms, there are not yet common conclusions that summarize which category of symptoms are improved by hormonal therapy. Several studies sustained particular effects in positive symptoms of premenopausal period, added to schizophrenia treatment (31-33), while others approved improvements in negative ones (34,35).

Regarding women in their menopausal period, positive potential of raloxifene is seen in studies which focus on the cognitive decline present in schizophrenia (36-38).

Management of cognitive function with raloxifene was also reported successful in case of a young patient (39). But given the dose-time related specifics of the cases, further studies are required to see if raloxifene induces improvement by chance or by a dual improvement in cognition and symptoms, clinically revealed depending on specific patterns of the schizophrenic patients.

On the contrary, there are those who claim a non-improvement effect of raloxifene in respect of the cognitive side of patients suffering from schizophrenia (40,41). Supporting this point of view, a randomized, double blind trial, which concluded that adjunctive raloxifene, besides not showing an improvement on severe forms of schizophrenia, worsened the outcome of patients (42).

As the interest in the efficacy of estrogens increased among the researchers, a meta-analysis was performed in order to have an overview on the effects of the therapy. Starting from this, the balance tilted towards a weighted effect for the adjuvant treatment. The superiority was highlighted by Hedge's g=0.66, in correlation with female patients whose manifested disease has a high heterogeneity of symptoms and severity. Although the total aspect of the disease showed an improvement when patients were treated with estrogen, it is necessary to establish from the beginning that estrogen treatment was applied for only 4-8 weeks (30).

It has been demonstrated that long-term use of estrogen is associated with considerable side effects, especially on the sex organs (31). Besides, the changes induced in sex organs, hormonal therapy can also cause complications threatening the life of the patient (e.g. venous thromboembolism, breast and endometrium hyperplasia) (29,43).

Meta-analysis of Begemann *et al* (30) focused also on the significant modulation of estrogen treatment on positive and negative symptoms. Results were correlated to a larger population with a more attention on raloxifene treatment in women in their postmenopausal period (32).

Research postulates that we may save patients from the side-effects by using selective estrogen receptor modulators (SERMs) in estrogen treatment. The theory is sustainable, on the one hand because sex organs are free of these receptors and on the other because their agonist action is released only in brain and bones SERMs. That being said, raloxifene, a SERM-medication, may be used among all schizophrenic patients. The clinical implications are seen especially in male population, in whom we now have the possibility to test and administer the hormonal therapy without worries about a possible feminizing-effect. Among SERMs, it seemed that raloxifene is the only treatment that offer benefits sustainable on long-term and therefore, a history of 10 years of studies have focused on this 'free-risk' adjuvant treatment regarding symptoms and severity of schizophrenia (31,32).

But the 'safety risks' associated with the administration of raloxifene are not exempted from a higher possibility of developing VTE (44). We note that in an extended clinical trial, many potent risks of VTE and stroke were reported in females who were treated with only half of dose required for improvements in schizophrenic symptoms (36,45).

Regarding comorbidities such breast cancer and osteoporosis, a better tolerability is reported by patients treated with raloxifene compared with those treated with estrogen. Positive effects are sustained on a very long period of administration (36,46). Furthermore, raloxifene may be used among schizophrenia men, due to the freedom effect they benefit from in regard of the feminizing-like syndrome they were exposed earlier (47). Besides the provided effects above, patients treated with raloxifene need a lower dose and have fewer side effects associated with antipsychotic therapy (48).

Even if the majority of extended trials targeted post-menopausal women, recent studies were focused on young patients. In the few trials aimed at male patients with schizophrenia, the bundle between schizophrenia symptoms and raloxifene claim an improvement in negative and general PANSS ratings (47). As for estradiol therapy, general symptoms have also improved. A delay of only seven days in placebo group compared with the estradiol group was presented, which suggest a minimal effect of this therapy (49). For young women with resistant schizophrenia, some trials merge to a decrease of general symptoms, but with no significant differences in cognition and positive symptoms (40), while in others there were improvements both in male and female ability to learn, process and recognize emotions (50,51).

Finally, we feel the need to deepen a little the knowledge in clinical expression of schizophrenia in men, who tends to be more exacerbated compared with women. The earlier onset of first episode (52), tendency of substances abuse, social maladjustment (53) aggressiveness (54) and more negative symptoms makes them patients with lower compliance to the treatment. There are few studies highlighting the positive effects of raloxifene treatment in male patients, but possibly this medicine will find its place in therapeutic scheme of schizophrenia, since all trials reviewed connected the effectiveness on the debilitating of symptoms of schizophrenia and side effects associated with the current treatment of this disease (41,47,55).

3. Conclusions

To maintain an objective overview of the improvement on hormonal therapy as an adjuvant treatment in schizophrenia, we included in this mini-review both negative and positive effects of the aspect. Considering this, we hope to bring forward evidence on therapeutic modulation of estrogen therapy, especially raloxifene, SERMs that show, by now, their better side. Besides improving the schizophrenia outcome, raloxifene can be used on long-term treatment, without having the specific side-effects of estrogen therapy.

As regard the lack of a proper treatment for cognitive decline associated with schizophrenia, the positive effect of hormonal therapy on that is crucial, both in men and women. The possibility of earlier on-set administration of estrogen to prevent the neuronal and cognitive decline on younger patients who struggle with this debilitating disequilibrium of their mind. Also, by lowering the negative effects of antipsychotics drugs, we may see an increment in their compliance regarding the treatment.

Even if there are still more to know, the effectiveness of adjunctive therapy with estrogen is highlighted by significant adjustment on the quality life of women and their response to treatment. Further studies are needed to explore more profoundly action and management of these drugs, as well as their efficacy for young, and male patients, who suffer from schizophrenia.

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Availability of data and materials

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Authors' contributions

SCT contributed in all the stages of the article, designed the study and revised the manuscript for important intellectual content. DI and DAM acquired the data by screening the papers identified on PubMed and drafted the manuscript. DAM contributed to the conception of the study and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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