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THE ROLE OF SELECTIVE ESTROGEN RECEPTOR MODULATORS IN THE TREATMENT OF SCHIZOPHRENIA

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SUMMARY

Background: *Gender differences in schizophrenia have been recognized for a long time and it has been widely accepted that sex steroid hormones, especially estradiol, are strongly attributed to this fact. Two hypotheses regarding estradiol action in psychoses gained special research attention – the estrogen protection hypothesis and hypoestrogenism hypothesis. A growing number of studies have shown benefits in augmenting antipsychotic treatment with estrogens or selective estrogen receptor modulators (SERM).*

Methods: *This review is focused on the role of selective estrogen receptor modulators in the treatment of schizophrenic patients. In order to achieve this result PubMed was searched using the following terms: schizophrenia, raloxifene, humans. We reviewed only randomized, placebo-controlled studies.*

Results: *Raloxifene, a selective estrogen receptor modulator was identified as useful to improve negative, positive, and general psychopathological symptoms, and also cognitive functions. All reviewed studies indicated improvement in at least one studied domain. Augmentation with raloxifene was found to be a beneficial treatment strategy for chronic schizophrenia both in female and male patients, however potential side effects (a small increase in the risk of venous thromboembolism and endometrial cancer) should be carefully considered.*

Conclusions: *SERMs could be an effective augmentation strategy in the treatment of both men women with schizophrenia, although further research efforts are needed to study potential long-term side effects.*

Key words: *schizophrenia – raloxifene – SERM - selective estrogen receptor modulators – estradiol*

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INTRODUCTION

Gender differences in schizophrenia

Schizophrenia is a chronic mental disorder with variable phenotypic expression and multifactorial aetiology which involves a genetic contribution, environmental factors interacting with the genetic susceptibility and often early neurodevelopmental aberration with a lifetime prevalence of ~0.4% (Freedman 2003). Gender differences in schizophrenia have long been recognized. In particular, differences in the age of onset have been consistently reported across the studies (Feigenson et al. 2014). Typically, the illness onset in females is reported approximately 5 years later than in males, but the second peak of onset in women takes place in the perimenopause (Lindamer et al. 2003). Men are more likely to develop schizophrenia than women, with an incidence risk ratio of 1.4 (Slotema et al. 2012). Additionally, there are substantial gender differences in syndrome presentation, with women tending to present with more affective and paranoid psychotic symptoms, men tending to present with more negative symptoms, and women overall presenting with less severe clinical course and requiring fewer hospitalizations (Heringa et al. 2015).

Two hypotheses regarding estrogen action in schizophrenia

The more favorable course of disease in women is partially explained by one of the hypotheses regarding estrogen action in psychoses referred to as the estrogen protection hypothesis (Riecher-Rossler & Hafner 1993) which is based on several lines of evidence. Estrogen is regarded as an antipsychotic factor taking into account later onset, less severe course in women and loss of that protection in the perimenopause when estrogen production declines (Seeman & Lang 1990). The exact mechanism of antipsychotic action of estrogen is not yet fully understood. There is accumulating evidence that estrogens hold a variety of neuroprotective effects, including reducing free radicals, facilitating synaptic plasticity, and modulating NMDA signaling (Brann et al. 2007). Furthermore, there is evidence that estrogens exhibit anti-inflammatory effects in the CNS (Tenenbaum et al. 2007). Estrogen signaling has also been shown in animal models to decrease reactive microglial activity (Bruce-Keller et al. 2000). The second hypothesis regarding estrogen action in schizophrenia is the hypothesis of hypoestrogenism which relates to the observed estrogen deficiency in female patients leading to an elevated rate of menstrual dysfunctions, which have often been attributed to hyperprolactinemia-inducing antipsychotics (Huber et al. 2001). However, Bergemann et al. (2005) tested the "hypoestrogenism hypothesis" in 75 women with schizophrenia and recorded estradiol serum level below 30 pg/ml in the follicular phase and below 100 pg/ml in the periovulatory phase in about 60% of the patients. A possible effect of hyperprolactinemia was ruled out as low levels of estradiol were also found in patients treated with certain atypical antipsychotics known to induce only a mild increase in prolactin, or no increase at all. Huber et al. (2001) examined estradiol levels in 43 women admitted with a diagnosis of an

acute psychotic episode. Only 28% of the women exhibited estradiol and progesterone levels indicating a peri- or postovulatory phase and all of the estradiol levels on admission were either within the lower part of the cycle-dependent normal range or below normal; estradiol levels were significantly lower than in a control group of healthy volunteers and patients admitted with different psychiatric diagnoses. Importantly, periods of elevated estrogen levels over the course of a menstrual cycle and women's life cycle correlate with attenuated psychotic symptoms. Women significantly more often experience first onset or recurrence of a psychotic episode in low estrogen phases of the cycle. Childbirth is the reproductive event that is associated with the largest changes in female sex steroid production. During pregnancy, estradiol and progesterone serum concentrations gradually increase and reach values at term that are 100-200 times higher than in the early follicular phase of the menstrual cycle and immediately after the labor begin to decline to reach follicular phase levels within 2–3 days (Wieck 2011). It has been known for some time that childbirth can trigger psychotic illnesses, but two epidemiological studies covering the whole population of Denmark over three decades have quantified this effect for different diagnoses more precisely (Munk-Olsen et al. 2006, 2009). In these studies, inpatient admissions for first onsets and recurrences of schizophrenia were 2–5.7 times more common in the 2 months after childbirth than later in the first postnatal year. Also, there was a relationship between the puberty and onset of illness observed exclusively in women (Cohen 1998). In a group of 35 schizophrenic women, the earlier the age at menarche, the later the ages at both the first psychotic symptoms and the first hospitalization; there was no significant correlation between puberty and onset of symptoms in their male counterparts.

Estradiol as augmentation treatment

Taking into account aforementioned findings, not surprisingly there have been attempts to use estrogen as a treatment agent. A growing number of studies have shown some benefits in treating symptoms of schizophrenia and disease related cognitive impairments with estrogens or selective estrogen receptor modulators (SERM) (Kulkarni et al. 2008, Begemann et al. 2012, Heringa et al. 2015). However, there is substantial variability in the direction of effects, reflecting differences in dose, duration of treatment, experimental protocols and outcomes studied. A large, double-blind randomized trial of transdermal 17-b estradiol treatment (100 mg over 24 h) over 28 days as adjunct to antipsychotic medication was published by Kulkarni et al. (2008). Significant improvement was reported for the total PANSS (Possitive and Negative Symptoms Scale) score, the positive symptom subscale and the general psychopathology sub-scale, but not the negative symptom sub-scale. Those findings were later confirmed in a larger trial (Kulkarni et al. 2015). 183 females in child-bearing age with treatment-resistant schizophrenia received transdermal estradiol 200μg, transdermal estradiol 100 μg or an identical placebo patch. Both estradiol groups had greater decreases in PANSS positive, general and total symptoms compared with the placebo group, with a greater effect seen for the larger dose. A quantitative review of twenty-four double-blind, placebo-controlled, randomized studies confirmed that estrogens could be an effective augmentation strategy in the treatment of women with schizophrenia (Heringa et al. 2015). Superior efficacy was found for estrogen treatment in female patients on total symptom severity and on reducing positive and negative symptoms. Subgroup analyses yielded significant results for estrogens in premenopausal women for total, positive, and negative symptoms, results for cognition were inconsistent.

However, it is important to remember that estrogen treatment increases the risk of endometria hyperplasia cancer in women if not combined with progestogens (Beral et al. 2002), and exerts a feminizing effects in male patient. Raloxifene, a selective estrogen receptor modulator (SERM), does not carry these side effects, as it is selectively agonistic to estrogen receptors in the brain and bones, however, it has been associated with a small increase in the risk of venous thromboembolism and endometrial cancer (DeMichele et al. 2008).

METHODS

This review is focused on the role of selective estrogen receptor modulators in the treatment of schizophrenic patients of both genders. In order to achieve this result PubMed was searched (effective date 30.05.2016). During our search we used following terms: (schizophrenia (Title/Abstract) AND raloxifene (Title/Abstract)) (humans (MeSH Terms) AND English (lang) AND (1995/01/01(PDAT): 2016/05/30(PDAT)). We included only randomized, placebo-controlled studies.

RESULTS

Selective Estrogen Receptor Modulators as augmentation treatment

Treatment with raloxifene was piloted in a placebo-controlled trial by Kulkarni et al. (2010) in 35 postmenopausal women in the acute phase of schizophreniform or schizoaffective disorder. Patients were receiving either 60 or 120 mg of raloxifene or placebo as adjuncts to antipsychotic medication over 12 weeks. The authors reported a significant decrease in the total PANSS score and the general symptom score in the group treated with the larger dose after 12 weeks of treatment. Usall et al. (2011) performed a double-blind, randomized, placebo-controlled study to assess the utility of raloxifene in treating psychotic symptoms in

postmenopausal women with schizophrenia exhibiting prominent negative symptoms. Thirty-three women were randomized to either adjunctive raloxifene or adjunctive placebo for 12 weeks. The addition of raloxifene (60 mg/d) to regular antipsychotic treatment significantly reduced negative, positive and general psychopathological symptoms during the 12-week trial as compared with women receiving placebo. The group confirmed their results five years later on a larger sample (70 women) and during a longer observation period (24 weeks) (Usall et al. 2016). However, in an Iranian study (Kianimehr et al. 2014) on 46 postmenopausal women with chronic schizophrenia, raloxifene (120 mg/day) as an adjunctive treatment to risperidone (6 mg/day) was only found to be superior in improvement of positive symptoms and it was not effective in treating negative and general psychopathology symptoms (assessed with PANSS).

Treatment with SERMs was also found to be beneficial to male patients. In a randomized, double-blind, placebo-controlled study (Khodaie-Ardakani et al. 2015), forty-six male patients diagnosed with schizophrenia were randomized to either raloxifene (120 mg/day) or placebo in addition to risperidone (6 mg/day) for eight weeks. The group treated with raloxifene exhibited significant improvement on the negative subscale, the general psychopathology subscale and total PANSS score (but not on the positive subscale).

Additionally, raloxifene was found favourable not only to improve symptoms of schizophrenia but also cognitive functions. Huerta-Ramos et al. (2014) assessed the utility of raloxifene as an adjuvant treatment for cognitive symptoms in postmenopausal women with schizophrenia in a 12-week, double-blind, randomized, placebo-controlled study. The addition of raloxifene (60 mg) to regular antipsychotic improved verbal learning. No differences were observed in any of the variables of long-term memory or recognition. With respect to SERM treatment, an interesting finding was that a dosage of 120 mg raloxifene showed effects on symptom severity in all available studies whereas a dosage of 60 mg showed no effects. The first study to show that daily, oral adjunctive raloxifene treatment at 120 mg/day has beneficial effects on attention/processing speed and memory for both men and women with schizophrenia was performed by Weickert et al. in 2015. The group recruited ninety-eight young to middle-age men and women with a diagnosis of schizophrenia or schizoaffective disorder into a dual-site, thirteen-week, randomized, double-blind, placebo-controlled, crossover trial of adjunctive raloxifene treatment in addition to their usual antipsychotic medications. Symptom severity and cognition in the domains of working memory, attention/processing speed, language and verbal memory were assessed at baseline, 6 and 13 weeks. Analysis of the 13-week crossover data revealed significant improvement with raloxifene only in attention/processing speed.

CONCLUSIONS

The potential therapeutic utility of selective estrogen receptor modulators in schizophrenia is increasingly being recognized. Raloxifene, SERM which is selectively agonistic to estrogen receptors in the brain and bones was useful to improve not only negative, positive, and general psychopathological symptoms, but also cognitive functions, without having the side effects of neuroleptics. Nevertheless, treatment with SERMs is associated with small risk of endometrial cancer and venous thromboembolism. The article indicates raloxifene as a potential adjunctive treatment strategy for chronic schizophrenia both in female and male patients, however potential negative long-term implications of treatment should be considered.

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