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The role of estradiol in schizophrenia diagnosis and symptoms in postmenopausal women

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ABSTRACT

Schizophrenia is one of the most common mental illnesses in our society, affecting up to 1% of the population. There has been an increase in the number of people who are living longer with schizophrenia and people are being diagnosed later in life, with the majority of those later diagnoses being in women. In addition, there is a spike in diagnoses after women go through menopause, suggesting an important role for gonadal steroids in the disease. This paper examined aspects of aging and schizophrenia in the context of hormonal changes in women. With the rising prevalence rate of schizophrenia and the unique challenges that women face while aging with this disease, the idea of estrogen as a therapeutic agent to reduce symptom severity in postmenopausal women should be considered. In addition, we reviewed literature that suggests that estrogen interacts with the dopaminergic system to affect cognition and this should be studied further in older women with schizophrenia. Positive results in these studies have the potential to drastically improve the aging process for postmenopausal women with schizophrenia.

1. Introduction

Schizophrenia is a debilitating mental illness that affects up to 1% of the population. The prevalence rate has been rising over decades; in 2008, the number of people age 55 and older with a diagnosis of schizophrenia was projected to double over the next 20 years (Cohen et al., 2008). This likely represents a shift in the general demographics of the population in addition to better treatment and symptom management techniques allowing for improved disease outcomes. The general increase in longevity for patients living with schizophrenia poses numerous challenges for patients and their caregivers as they navigate the disease during aging.

As the diagnosis of schizophrenia increases in women after menopause, the challenges of the disease in aging are more prominent for women. The sex differences in schizophrenia have been described for over a century, with the first observation being that first time-hospitalization occurs at a younger age in men compared to women (i.e. (Hafner et al., 1991). Compared to men, women typically have a more favorable course of their illness in their early to mid-life before menopause. Furthermore, men experience only one peak in prevalence rate during their lifetime when they undergo puberty; this is compared to two peaks in prevalence rates in women: shortly after puberty and secondarily after the menopausal transition (Seeman, 2012). These events in a woman's lifetime are defined by fluctuating estrogen levels, specifically estradiol (E2), which is the primary female sex hormone.

Relevant to the current paper is that the neurobiological mechanisms by which estrogen affects brain functioning is by interacting with dopaminergic systems though a number of different mechanisms. Preclinical studies in animal models have examined mechanisms involved in the estrogen-dopamine interaction. Dluzen et al. (1996a, 1996b) showed that estrogen pretreatment prevented neurotoxic damage with MPTP and methamphetamine to the nigro-striatal pathway in a rodent model. Miller et al. (1998) found that effects of neurotoxic lesions were greater in male mice than female mice as evidenced by greater striatal dopamine depletion in males. Miller et al. (1998) also used ovariectomized mice with and without estrogen treatment and found that neurotoxic lesions produced less dopamine depletion in the estrogen-treated mice. These studies suggest a protective effect of estrogen on dopaminergic function and are likely to be neurobiological mechanisms by which estrogen is beneficial to women with schizophrenia.

In addition, estrogen's effects on the brain and peripheral tissues are also influenced by lifestyle factors such as physical exercise (i.e., (Erickson et al., 2007), smoking (i.e., (MacLennan et al., 2006)), and concomitant medications (Gonzalez-Rodriguez et al., 2016). While the interactions of these lifestyle factors and estrogen are complex and likely to influence brain functioning, it is important understand the risks and potential benefits of estrogen treatment that may occur for women with schizophrenia as they age past the menopause.

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Given the difference in age of onset between men and women, and the unique peak in schizophrenia prevalence for women after menopause (Seeman, 2012) this paper will explore how the changing hormones after menopause affect women with schizophrenia. Specifically, we will focus on how hormones relate to risk for schizophrenia diagnosis as well as how they impact symptoms of the disease including cognition particularly in postmenopausal women.

2. Premenopausal women and schizophrenia

During reproductive years, estradiol and progesterone fluctuate throughout the menstrual cycle. The menstrual cycle can be divided into two phases; a two-week time where there is a higher concentration of estradiol and lower concentration of progesterone in the body, which is called the follicular phase, and a two week period when there is a lower concentration of estradiol and higher concentration of progesterone, called the luteal phase.

It has been shown that women are more vulnerable to relapse during times of estrogen withdrawal, which occurs later in the luteal phase of the menstrual cycle, after childbirth, after cessation of hormone therapy, or after menopause (Begemann et al., 2012). Furthermore, symptom severity across the menstrual cycle has been shown to change as estrogen levels fluctuate, with more severe symptoms seen during periods of low estrogen (Hallonquist et al., 1993). An early study showed that first-time hospitalizations for women with schizophrenia most frequently occurred during the luteal phase of the menstrual cycle, when estrogen is lower (Dalton, 1959). Cohen et al. (1999) showed that there is an inverse relationship between age of menarche and onset of schizophrenia, suggesting a protective effect of estrogen on risk for schizophrenia. This has been called the estrogen hypothesis of schizophrenia (Seeman and Lang, 1990).

These studies indicate that women are at greater risk for diagnosis of schizophrenia during periods of low estrogen, and women with a diagnosis of schizophrenia experience more severe symptoms during these low estrogen times. Several studies have supported the estrogen hypothesis and have shown improvement in symptoms with supplemental estrogen in premenopausal women. Kulkarni et al. (1996) found that women receiving estrogen in addition to antipsychotic medication showed faster improvement in positive symptoms compared to women taking only antipsychotic medication. Kulkarni et al. (2015) completed a large scale randomized-controlled clinical trial of 100 μg and 200 μg of estrogen compared to placebo in premenopausal women with schizophrenia who suffered from ongoing psychosis despite use of antipsychotic medication. They found that both estradiol groups showed decreased positive, general, and total symptoms compared to placebo group, and that the 200 μg treatment group showed the most significant clinical improvement in positive symptoms.

The above studies support the estrogen hypothesis of schizophrenia in premenopausal women. However, while the effects of estradiol on symptoms of schizophrenia appear beneficial, there have not been more efforts to expand this research nor have these research findings made their way into clinical practice. Perhaps the general hesitation to recommend estrogen for treatment of psychiatric disorders is a result of the side effects observed in older healthy postmenopausal women from studies like the Women's Health Initiative (Shumaker et al., 2004; Shumaker et al., 2003). Additionally, there is far less literature related to disease course in postmenopausal women with schizophrenia. As menopause results in such a dramatic change in circulating hormone levels, it is important to examine how this age-related process affects schizophrenia risk and symptom development.

3. Postmenopausal women and schizophrenia

The estrogen hypothesis of schizophrenia has important implications for postmenopausal women. Estrogen is not approved for clinical use for management of neuropsychiatric symptoms due to prior literature that shows a greater risk for development of neurologic and physiologic disease profiles (Wassertheil-Smoller et al., 2014). Thus, few studies have been done with estrogen in postmenopausal women with schizophrenia. One study retrospectively compared postmenopausal women who had never used hormone therapy (HT) compared to women who had used HT for at least one year in the past (Lindamer et al., 2001). They found that those who had used HT showed few negative symptoms but had no change in overall psychopathology or positive symptoms.

To the best of our knowledge, this is the only study examining hormone exposure in relation to schizophrenia symptoms in postmenopausal women. There are however, several studies that have assessed the effects of selective estrogen receptor modulators (SERMs) on schizophrenia symptoms and cognition. SERMs work by binding to estrogen receptors in the brain and inducing a change in their three-dimensional conformation (Arevalo et al., 2011). They can have agonistic or antagonistic effects depending on the tissue that they bind to such as being antagonists in the breast and agonists in the bone. It has not been determined whether they act as agonists or antagonists at estrogen receptors in the brain. While the exact mechanisms are unclear, one SERM in particular, raloxifene, has been shown to prevent cognitive decline in postmenopausal women (Yaffe et al., 2001) and has been shown to improve verbal memory in late postmenopausal women (Jacobsen et al., 2010). Thus, the effects of raloxifene on the brain appear to be beneficial for cognition.

In postmenopausal women with schizophrenia, Huerta-Ramos et al. (2014) conducted a double-blind randomized controlled clinical trial using raloxifene versus placebo in addition to regular antipsychotic treatment. They found that typical treatment plus raloxifene had positive effects on verbal memory and executive functioning compared to placebo. In another randomized controlled clinical trial, the addition of raloxifene resulted in significant improvement in positive symptoms, but not negative symptoms (Kianimehr et al., 2014). More recently, Kulkarni et al. (2016) showed beneficial effects of raloxifene in a placebo control trial in middle aged women with schizophrenia who were refractory to treatment. Women in the raloxifene group showed improvements in positive and negative symptoms and had increased probability of a clinical response compared to the placebo treated women. While there are some inconsistencies across these studies in identifying the exact symptoms, positive or negative, that raloxifene affects in women with schizophrenia, the results overall showed beneficial effects of raloxifene for these women. This poses the question of whether or not raloxifene should be considered as an addition to standard therapy for postmenopausal women with schizophrenia and the accumulating evidence suggests a SERM like raloxifene is primarily beneficial for women with schizophrenia.

4. COMT, dopamine, and estrogen

It has been widely accepted that the neurobiology underlying schizophrenia is related to an alteration in dopamine (DA) signaling within the brain, specifically an excess in subcortical DA and a deficit in cortical DA (Davis et al., 1991). Decades of research have studied several genes related to DA synthesis, metabolism, and degradation in the brain (see review by (Weinstein et al., 2017)). The most widely studied gene is the catechol-*o*-methyltransferase (COMT) gene (Edwards et al., 2016) which codes for an enzyme that metabolizes DA when released into the synapse and is particularly important for regulating DA levels in the prefrontal cortex (PFC) (Lopez-Garcia et al., 2016). There are certain genetic polymorphisms on the COMT gene that have been considered to put individuals at an increased risk for developing schizophrenia. A specific polymorphism, $Val^{158}Met$, is known to alter the activity of the enzyme and thus change DA bioavailability; individuals with a Met allele have reduced COMT activity. Decreased COMT activity leads to greater DA availability.

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