EXPERT REVIEWS

Special biological issues in the management of women with schizophrenia

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Jayashri Kulkarni*, Emmy Gavrilidis, Emily Hayes, Victoria Heaton and Roisin Worsley

Monash Alfred Psychiatry Research Centre, Level One, Old Baker Building, The Alfred Hospital, Commercial Road, Melbourne 3004, Australia
**Author for correspondence:*
Tel.: +61 3 9076 6924
Fax: +61 3 9076 8545
j.kulkarni@alfred.org.au

Schizophrenia is a debilitating and pervasive mental illness with devastating effects on psychological, cognitive and social wellbeing, and for which current treatment options are far from ideal. Gender differences and the influence of the female reproductive life cycle on the onset, course and symptoms of schizophrenia and the discovery of estrogen's remarkable psychoprotective properties in animal models led to the proposal of the 'estrogen protection hypothesis' of schizophrenia. This has fueled the recent successful investigation of estradiol as a potential adjuvant therapeutic agent in the management of schizophrenia in women. This review explains the scientific rationale behind the estrogen hypothesis and how it can be clinically utilized to address concerns unique to the care of women with schizophrenia.

Keywords: estrogen • hormones • psychosis • schizophrenia • sex hormones

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), schizophrenia is a psychotic disorder characterized by a constellation of positive and negative symptoms, resulting in significant social and/or occupational dysfunction that is present for a period of at least 6 months [1].

The link between sex hormones and schizophrenia has been suspected for over a century [2]; however, it is only with more recent scientific advances that the profound effect hormones can have on mental health has become clear. Estrogen, in particular, has been the focus of much research attention, and evidence is rapidly emerging to support its protective role in the underlying etiology of schizophrenia and, importantly, in the management of this severe illness.

The hormonal etiological component of schizophrenia can have significant consequences for women with this disease, and medications that decrease estrogen may result in sequelae that can have serious repercussions for females in particular. These concerns are discussed in this paper, which also aims to clarify the clinical implications of the 'estrogen protection theory' and how they might be translated into gender sensitive practice that specifically addresses some of the issues encountered in the management of individuals with schizophrenia.

Gender differences in schizophrenia

Despite the early observation of Kraeplin that "the male sex appears in general to suffer somewhat more frequently from dementia praecox than the female" [3], for many years, this important fact was dismissed as merely a product of various confounding factors [4]. However, more recent epidemiological studies have demonstrated clear differences in the incidence and course of schizophrenia in men and women, indicating that it is in fact a sexually dimorphic disease.

Age at diagnosis

Although the lifetime prevalence of schizophrenia remains similar between the sexes [5,6], recent well-known meta-analyses and systematic reviews have concluded that the lifetime incidence of schizophrenia in men is approximately 1.5-times higher than that of women [7,8], even when potential biases, such as age range and diagnostic criteria, are taken into account [9]. The mean age of onset in females is also considerably higher than that for males: 30.6 years in women compared with 26.5 years in men [10]. It is hypothesized that women may be protected by the actions of estrogen on early stages of brain development, thus partially accounting for the lower incidence

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and delayed onset of schizophrenia in females [11] (although it is worth noting that a number of other aspects, such as culture, genetic factors and environmental factors, can also influence the age of onset of schizophrenia) [12]. Furthermore, there is a second, smaller peak of onset in women that does not occur in men, between the ages of 45 and 54 years, which coincides with the perimenopause, a time of fluctuant and, eventually, declining estradiol levels [2,10]. Thus, there is a male predominance in incidence before the age of 43 years, but a female predominance after this age [13].

Differences in symptoms & course of illness

Being diagnosed at a later age, women with schizophrenia often have obtained a higher level of social development than men [14]. Males with schizophrenia also tend to display higher levels of socially adverse illness behavior, as well as comorbid drug and alcohol abuse [15,16]. Such factors probably contribute to the favorable social course shown by premenopausal women with schizophrenia compared with their male counterparts, especially in the earlier stages of the disease [10].

Early studies suggested that women with schizophrenia, when compared with men, had more affective symptoms but less negative symptomatology [17,18]. More recently, large-scale studies have also found that premenopausal women tend to experience a more benign course of illness than men overall, displaying less severe levels of psychopathology and disability, and higher levels of insight, functioning, treatment adherence and response to antipsychotic medication [16,19]. Postmenopausal women, however, who have low levels of circulating estradiol, experience a more severe illness course and a decreased response to antipsychotic medication as compared with men in the same age group and women of reproductive age [20,21].

The course of schizophrenia in women has also been observed to vary during other times of the reproductive life cycle, presumably in conjunction with changes in estradiol levels. For example, women are at a 20-fold increased risk of a first episode or relapse of psychosis during the postpartum period, a time of precipitously decreasing estradiol levels [22], while chronic psychoses often remit during pregnancy when estradiol increases to well above nonpregnant physiological levels [23]. Similarly, it has been observed since the 1800s, when Kraft–Ebbing coined the term 'menstrual psychosis' [24], that mental state can vary over the course of the menstrual cycle. Convincing clinical research now clearly shows that, during the menstrual cycles of female schizophrenia patients, the high-estrogen midluteal phase is associated with significant improvements in psychopathology, functioning and treatment response compared with the low-estrogen early-follicular phase [25–29].

Psychoprotective properties of estrogens

Estrogens are a class of neurosteroids that interact with many neurotransmitters and brain circuits, in addition to exerting their primary endocrine and reproductive functions. In fact, their extensive neuroprotective and neuromodulatory properties have seen them dubbed 'nature's psychoprotectant' [30].

The three major isoforms of estrogen found in women are estrone (E1), estradiol (E2) and estriol (E3). While estriol is the most abundant form of estrogen in premenopausal women, estradiol has the highest affinity for estrogen receptors (ERs), and is therefore considered the most clinically important. Extensive animal work and neuroimaging studies have mapped ERs to many extrahypothalamic parts of the brain, including the limbic system, basal ganglia, cerebellum and many areas of the cerebral cortex [31,32]. While ER-α is found mostly in the hypothalamus, hypothalamic preoptic area and amygdala, ER-β is more widespread, as it is found in the pituitary, hippocampus, cerebral cortex, midbrain and brainstem [33]. Estrogen exerts both classical genomic and rapid nongenomic effects at ERs. Genomic responses are mediated by ligand-binding of the ER at the nuclear level, resulting in modulation of gene transcription occurring over several hours, whereas nongenomic responses are far quicker, occurring over seconds to minutes via the activation of second messenger cascades [34]. Through these diverse interactions with ERs, estrogen influences central signaling pathways and neurodegenerative processes, and may even permanently modify neural circuits through modulating the transcription of many enzymes, as well as the receptor proteins for multiple neurotransmitters and neuropeptides [35,36]. Thus, estrogenic systems have important roles in the regulation of mood and behavioral states [37].

Estrogens are neuroprotective

The pathogenesis of schizophrenia is widely considered to involve a progressive neurodegenerative component [38,39], with grey matter volume reductions, enlarged ventricles and medial temporal lobe, prefrontal cortex and cerebellar changes just some of the neuro-anatomical abnormalities described in the literature [39–41]. Grossly disturbed cytoarchitecture is also a common pathologic finding, including neuronal soma and neuropil volume reductions, irregular synaptic organization, ectopic neurons and decreased expression of neurotrophic factors [38,42].

Recent preclinical *in vivo* and *in vitro* research has demonstrated that estrogen has diverse neuroprotective properties that could contribute to its mediation of progressive neuropathology in schizophrenia. In particular, estrogen can protect neurons against injury from excitotoxicity, oxidative stress, inflammation, hypoglycemia, ischemia and apoptosis [43–47]. Estrogenic compounds also promote neurogenesis, angiogenesis, synaptic density, plasticity and connectivity, axonal sprouting and remyelination, and the expression of neurotrophic factors [48–51]. These trophic actions of estrogens have organizational effects on developing neurons and activational effects on mature neurons [52], and are thought to be mediated primarily through the actions of ER-α [53]. There is some recent research to suggest that the psychoprotective properties of estrogens might stem, in part from, their preservation and enhancement of neuronal mitochondrial function during cellular injury, as mitochondria are responsible for regulating the viability and death of neurons [54] and may be dysfunctional in the brains of individuals with schizophrenia [55].

From a neurodevelopmental perspective, estrogen and other gonadal steroids are known to have significant organizational effects on brain development during the perinatal period that are sexually dimorphic [56]. Another period of organization is thought

to occur during adolescence, in response to the pubertal surge in gonadal hormones at this time, and brain regions implicated in the pathophysiology of schizophrenia such as the cerebral cortex and limbic system may be particularly affected in a sex-specific manner [57]. Therefore, it is possible that the estrogen surge in females that occurs around the time of the menarche may have protective organizational effects on brain structures, neurotransmitter systems and behaviors of relevance to schizophrenia.

The effect of estradiol on neurotransmitter pathways

Traditionally, hyperactivity of dopaminergic neurotrans-mitter pathways was thought to be the primary pathophysiologic process at the core of schizophrenia, and thus the majority of antipsychotic medications share the property of dopamine (DA) D_2 receptor antagonism. While this hypothesis endures, it is now well established that dysfunction of additional neurotransmitter systems, such as serotonin and glutamate, is also most likely involved in the underlying pathogenesis of the condition [58]. Therefore second-generation antipsychotics are thought to be effective through their additional interactions with serotonin 5-HT_{1A} and 5-HT_{2A} receptors [59], although the exact nature of atypical antipsychotics' effects on the serotonin system is still the subject of considerable debate with some authors even denying such effects altogether [60]. Nonetheless, extensive preclinical research has demonstrated that estrogens have profound effects on the dopaminergic, serotonergic and glutamatergic systems, strongly suggesting neuroleptic-like properties similar to those of atypical antipsychotics.

The effects of estrogens on dopaminergic neurotransmission are thought to be particularly significant but exceedingly complex, with a recent review by Sánchez *et al.* highlighting considerable variations in the direction, extent and specificity of estrogen–DA interactions between studies [61]. Early observation of Di Paolo and Falardeau that estrogen decreases dopaminergic neurotransmission and induces a compensatory increase in DA binding-site density [62] has remained relatively consistent across time; however, an estrogen-related reduction in D_2 receptor sensitivity and an increase in D_2 receptor density in the striatum were also noted in many studies involving ovariectomized (OVX) rats [61] . Recently, it has been proposed that this increase in receptor density could be a compensatory response to an estrogen-induced decrease in DA levels [31], possibly via enhanced action of the DA transporter, as a recent study by Chavez *et al.* discovered that estradiol administration significantly increased the density of the DA transporter in the nucleus accumbens of OVX rats [63].

It has also been shown in animal studies that estradiol significantly modulates multiple components of the serotonergic neurotransmission system [64]. Specifically, estrogen has been found to increase both isoforms of tryptophan hydroxylase [65], decrease the activity of monoamine oxidase [66], influence the expression of the serotonin transporter [67], downregulate the expression of 5-HT_{1A} receptors [68] and upregulate the levels of 5-HT_{2A} receptors [69]. These actions have the overall effect of enhancing serotonergic neurotransmission, which could be important in attenuating affective and cognitive symptoms of schizophrenia.

Similarly, estrogen has also been found to enhance glutamatergic neurotransmission by upregulating NMDA receptors, manipulating their subunit configuration and increasing NMDA agonist binding [70]. These actions could theoretically help to reverse the hypoglutamatergic functioning that is believed to contribute to the pathogenesis of schizophrenia [71], and in particular, for the development of negative symptoms [72].

Pioneering work by Häfner, Gattaz and colleagues in the early 1990s demonstrated the potential of estradiol to attenuate DA agonist-induced psychomimetic behaviors and DA antagonist-induced motor disturbances in OVX rats, presumably through a downregulation of dopaminergic receptor function [73]. Importantly, more recent work examining the effects of estrogen in animal paradigms of psychosis confirms these early findings, and has yielded particularly promising results in support of the estrogen protection hypothesis, providing compelling evidence that the afore mentioned actions of estrogen on central neurotransmitter systems do translate into antipsychotic potential. For example, Gogos *et al.* demonstrated that estradiol treatment was able to effectively reverse psychomimetic states in female OVX rats induced by the administration of a D_2 receptor agonist, a 5-HT_{1A} agonist and a NMDA receptor antagonist respectively, strongly suggesting that estrogen does have an antipsychotic action via its neuromodulatory effects [74,75]. Arad and Weiner supplement these findings by reporting that estradiol ameliorated an amphetamine-induced psychosis in both OVX and intact female rats as effectively as clozapine or haloperidol; however, OVX rats required significantly higher doses of each compound to achieve this [76]. This provides preclinical support for the observation that postmenopausal women have a reduced response to antipsychotic medication compared with premenopausal women, as discussed earlier. Furthermore, ineffectual low doses of clozapine and haloperidol regained antipsychotic efficacy when combined with estradiol [76], justifying the clinical investigation and use of estradiol as an adjunctive treatment strategy for women with schizophrenia.

Clinical trials

Estrogen has been used successfully in a number of clinical trials to date, with results further supporting the neuroprotective potential of estrogen. In an important early study, Riecher-Rössler *et al.* objectively quantified a negative correlation between estradiol plasma levels and psychiatric symptomatology, behavior, paranoid tendencies and general wellbeing in 32 women with schizophrenia on an acute inpatient unit [29]. The researchers analyzed a panel of hormonal parameters and standardized psychopathology rating scales on a weekly basis for the duration of each patient's admission. They observed that women in their sample consistently displayed decreased circulating estradiol levels and blunting of the physiological fluctuation of hormones throughout the menstrual cycle compared with the general population. Furthermore, as serum–estradiol levels rose, psychopathology was observed to decrease significantly and *vice versa* ($p < 0.05$) [29].

Then, in a pioneering open-label study by Kulkarni *et al.*, 11 women of child-bearing age with schizophrenia were trialed

with 2 mg of oral estradiol valerate [77]. It was found that women receiving estradiol made a more rapid recovery from acute psychotic symptoms compared with a matched control group not receiving estradiol ($p < 0.05$).

These results, coupled with epidemiological and life-cycle observations as described earlier, allowed for more extensive and better-quality randomized clinical trials, such as the three-arm, double-blind, placebo-controlled dose-finding study of Kulkarni *et al.* [78]. In this study of 36 women with schizophrenia, 12 women received 50 µg transdermal estradiol plus standardized antipsychotic drug, 12 women received 100 µg transdermal estradiol plus standardized antipsychotic drug and 12 women received placebo plus standardized antipsychotic drug. The findings showed that the group that received 100 µg of adjunctive estradiol, in comparison to the other two groups, had the greatest improvement across the study using the well-validated Positive and Negative Syndrome Scale (PANSS) rating system ($p < 0.01$); the mean reduction in positive symptoms was even clinically significant at 21%. Continuing on from these promising pilot results was a double-blind randomized controlled trial of 102 women by Kulkarni *et al.*, with patients with DSM-IV-defined schizophrenia trialed on either 100 µg adjunctive estradiol skin patches ($n = 56$) or placebo ($n = 46$) [79]. Patients receiving the addition of 100 µg transdermal estradiol displayed significantly reduced positive ($p < 0.05$) and general psychopathological ($p < 0.05$) symptoms during the 28-day trial period compared with women receiving antipsychotic medication alone. Similarly, positive results were reported by Akhondzadeh *et al.*, who conducted a double-blind, placebo-controlled trial in 32 women of child-bearing age with schizophrenia, comparing the use of haloperidol 15 mg/day plus ethinyl estradiol 0.05 mg to haloperidol 15 mg/day plus placebo [80]. They observed statistically significant reductions in total, positive symptoms and general psychopathology PANSS scores for women in the ethinyl estradiol group compared with women who received placebo ($p < 0.001$). These reductions in PANSS scores were of substantial clinical significance in the estradiol group, with decreases of over 40% in all of total, positive symptom and general psychopathology PANSS scores. The results of this study are of particular significance, as the type and dose of standard antipsychotic medication were controlled for, eliminating a potential confounding variable.

Furthermore, in addition to its beneficial effects on psychotic symptomatolgy, estradiol has also been found to be effective in improving elements of neuropsychological and cognitive performance in women with schizophrenia compared with placebo [81,82]. For example, Bergemann *et al.* conducted an 8-month randomized, placebo-controlled, double-blinded, crossover study in 19 women with schizophrenia to investigate the effect of adjunctive estradiol treatment on neuropsychological performance [81]. They found that estradiol therapy was associated with significant improvements in the comprehension of metaphoric speech ($p = 0.01$). Another small, but good-quality, randomized, double-blind, placebo-controlled trial by Ko *et al.* in 28 premenopausal women with chronic schizophrenia also reported that 8 weeks of adjunctive hormone replacement therapy led to significant improvements on an extensive battery of cognitive assessment tasks [82].

Most recently, research has focused on the use of the selective ER modulator (SERM), raloxifene, in the treatment of post-menopausal women with psychosis. Usall *et al.* compared the addition of 60 mg raloxifene per day as an adjunct to regular antipsychotic treatment with placebo in a trial of 33 post-menopausal women with schizophrenia [83]. In this study, the treatment group of 16 women were found to have significantly reduced negative ($p = 0.04$), positive ($p = 0.03$) and general psychopathological ($p = 0.045$) symptoms compared with women receiving placebo. However, on further analysis, average decreases in symptoms from baseline in the treatment group were clinically modest at less than 15%. Aiming to establish an optimal dose of raloxifene to achieve clinical benefit, Kulkarni *et al.* undertook a randomized, double-blind, placebo-controlled trial comparing the efficacy of 60 and 120 mg/day of adjunctive oral raloxifene in the treatment of 35 women with acute postmenopausal schizophrenia [84]. The participants randomized to receive 120 mg/day raloxifene experienced a significantly more rapid recovery in total and general psychopathological symptoms compared with both 60 mg/day raloxifene hydrochloride and placebo ($p < 0.0005$). The results of these two trials are consistent with those of a small earlier study by Good *et al.*, who found that administering hormone replacement therapy to postmenopausal women with a psychotic disorder led to a significant improvement in negative symptoms over 6 months [85].

Despite the consistent positive results of these clinical trials of estradiol for schizophrenia in women, two recent reviews [86,87] concluded that estradiol does not seem to entail any benefit over placebo in the management of schizoprenia, as a number of the studies reviewed failed to produce significant results. For example, two high-quality, double-blind, randomized controlled trials by Bergemann *et al.* [88] and Louzã *et al.* [89], respectively, did not find estrogen to be an effective augmentation strategy in the treatment of women with schizophrenia: neither study reports any significant improvements in psychopathology or relapse rates for estrogen treatment compared with placebo. Similarly, no significant treatment effect of estrogen on psychopathological symptoms in women with schizophrenia was found in an earlier randomized controlled study by Glazer *et al.* [90]. However, it is important to interpret these results carefully. For one thing, the trial by Glazer *et al.* [90] included only ten participants in each group, making generalization of results problematic. In addition, despite the high-quality design and larger sample size ($n = 40$) in the investigation by Louzã *et al.*, women in the estrogen treatment group did not actually display an increase in serum–estradiol levels, which could explain why these women did not improve significantly over the placebo arm [89]. Furthermore, both Louzã *et al.* [89] and Glazer *et al.* [90] utilized conjugated estrogens in their studies, as opposed to 17β-estradiol, while Bergemann *et al.* [88] administered estradiol in combination with a synthetic progestin. These factors are noteworthy, given that conjugated estrogens do not have the same potency as 17β-estradiol in the brain, and the administration of a synthetic progestin in conjunction with estradiol is often found to attenuate any positive actions of estradiol on mental state [2,4]. Such differences in hormonal preparations between studies could

explain the positive results of some compared with the negative results of others. Nevertheless, it was emphasized in both reviews that adequately powered, well-designed randomized controlled trials are needed before any recommendations for broad clinical application can be made [86,87].

Novel hormone treatments

As the knowledge base on the complex CNS effects of estrogen has grown, the search has begun for other neuroactive steroids with potential neuromodulatory properties, with some likely contenders already identified [91]. Investigations have begun on the testosterone precursors dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S), but the results so far have been inconclusive. DHEA-S is psychoprotective in the rodent brain [92], while clinical studies have observed differences in DHEA-S blood levels between individuals with schizophrenia and healthy controls [93]. However, results from a small number of clinical trials piloting DHEA-S as an augmentation strategy have been contradictory, with some studies finding a limited treatment response, whereas others report no significant benefit compared with placebo [93].

Other compounds such as pregnenolone and oxytocin seem to be more promising. Pregnenolone and its metabolites, pregnenolone sulfate and allopgrenanolone, possess psychoprotective properties and exert positive effects in rodent models of cognition and psychosis [94]. Levels of serum pregnenolone have been observed to be significantly lower in psychotic patients than in healthy controls [93], and a recent review [94] of three small pilot studies investigating pregnenolone as an adjunctive intervention for patients with schizophrenia reports that pregnenolone was able to improve psychotic and cognitive symptoms in these patients. Promisingly, preliminary evidence also suggests that oxytocin may have a positive effect on psychological function. One recent study discovered that higher peripheral oxytocin levels were associated with decreased symptom severity in women with chronic schizophrenia [28], while a randomized, double-blind, crossover controlled trial by Feifel *et al.* reported that adjunctive treatment with intranasal oxytocin was significantly more effective than placebo in reducing PANSS scores in a sample of 15 schizophrenia patients [95]. With further research, novel hormonal compounds could be a source of hope for women in whom an augmentation strategy is needed, but for whom estrogen is not tolerated or is contraindicated.

Discussion

Given the extensive epidemiological, preclinical and clinical evidence in support of the estrogen protection hypothesis, it is hoped that this evidence can be translated into effective clinical use of estrogen in the area of women's mental health. In fact, the estrogen protection theory has numerous important clinical implications that could be considered and acted upon in the treatment of women with schizophrenia.

To begin with, a woman's hormonal status should be taken into consideration and integrated into the assessment and treatment of her psychotic illness, with particular attention being paid to periods of fluctuating estrogen levels, especially perimenstrually, postpartum and during the perimenopause. Prophylactic estrogen therapy could be a possibility for women who experience deteriorations in mental state during these times, a technique that has already proven successful for the treatment and prevention of severe postpartum depression [96]. The clinician should also be especially aware of the possibility of a relapse of psychosis around the time of menopause in women who do have a history of worsening psychopathology during the menstrual cycle or puerperium, as these women seem to be particularly vulnerable to fluctuations in the hormonal milieu. Given the additional proven physical and psychological benefits of hormone replacement therapy during the menopause (such as treatment of hot flushes, emotional liability, slowed cognition and genitourinary atrophy), it is this older age group who could potentially benefit substantially from estrogen augmentation therapy.

That is not to say that estrogen treatment has no place in younger women with schizophrenia; in fact, the opposite is true. It has been an enduring observation, since well before the beginning of the neuroleptic era [97], that women with schizophrenia are often hypoestrogenic compared with controls. For this reason, estrogen deficiency has actually been implicated in the pathogenesis of schizophrenia; the so-called 'hypothesis of hypoestrogenism' [4]. Abundant modern-day research demonstrates 'severely disturbed' gonadal function [29] and decreased bone mass density [98] (an indicator of chronic estrogen deficiency) in women admitted for first-episode psychosis, as well as hypoestrogenemia irrespective of prolactin level (that is, not just in those women with hyperprolactinemia) [99–101]. Hypoestrogenic women with schizophrenia are at increased risk of serious complications, such as premature ovarian failure and decreased bone mineral density, eventually leading to early-onset osteoporosis [98]. Furthermore, individuals with schizophrenia already have an increased incidence of cardiovascular disease compared with the general population [102], and an estrogen deficiency could further compound this risk, given that young women with premature ovarian failure or hypothalamic amenorrhea (both hypoestrogenic states) were found to be at increased risk of cardiovascular dysfunction and related mortality [103,104]. Estrogen therapy, with its ability to preserve bone mineral density [105] and its cardioprotective properties [106], could thus have the added benefit of helping to prevent such adverse health outcomes in younger female schizophrenia patients.

However, despite estradiol's impressive psychoprotective properties and a strong rationale for its use, its long-term safety is complicated by a range of significant adverse physical effects, including stimulation of breast and uterine tissues resulting in an increased risk of malignancy, as well as an increased risk of thromboembolic complications, such as deep vein thromboses, pulmonary embolisms and cerebrovascular accidents with oral estrogen therapy [107]. To protect the endometrium in women with an intact uterus, estradiol must be administered in conjunction with a synthetic progestin, which can have a range of physical and psychological side effects, including androgenic actions, disturbances in lipid and carbohydrate metabolism, and attenuation of any beneficial effects of estradiol on mental state [108,109]. Unfortunately, two well-known, large-scale

investigations, the Women's Health Initiative [110] and the Million Women Study [111], reported a significantly increased risk of breast cancer associated with the use of combination hormone replacement therapy. For these reasons, the recent research into SERMs, such as raloxifene, is particularly important, as they provide the potential to harness the positive effects of estrogens in the CNS, but without the dangerous stimulating effects on breast and uterine tissue. SERMs have been found to share the psychoprotective properties of estradiol in the brain through their actions on central ERs, but have tissue-specific effects on peripheral ERs [112–114]. Raloxifene, in particular, appears to act as an agonist in the brain, affecting the dopaminergic, serotonergic and glutamatergic systems in ways consistent with those of natural estradiol [115–117], while having antagonistic actions in breast and endometrial tissue [118]. Therefore, raloxifene could be expected to share the antipsychotic properties of estrogen, but without the risk of adverse physical side effects, and preliminary clinical evidence supporting its potential use as a safe and effective augmentation therapy in women with schizophrenia is already beginning to emerge [83,84].

It is of the utmost importance to establish safe and effective strategies to augment the use of antipsychotic medications in women in order to minimize their dosage, as women are particularly vulnerable to the side effects of these medications, which can have serious physical consequences and greatly reduce quality of life.

Antipsychotics, unfortunately, are notorious for having many adverse effects. Typical, or first-generation, antipsychotics tend to have a greater effect on the dopaminergic system, especially D_2 receptors, and thus primarily result in neurological extrapyramidal side effects (EPS). Interestingly, low estrogen levels have been associated with a greater risk of EPS [119], indicating that estrogen replacement could theoretically help reduce the risk of these debilitating motor disturbances in women being treated with typical antipsychotic medication, especially if they are hypoestrogenic. Newer neuroleptics, that is, atypical or second-generation antipsychotics, act on a myriad of other neurotransmitter systems and receptors in addition to DA, and because of this, they tend to have fewer EPS, but rather have been associated with adverse endocrine effects. There is particular concern regarding the side effect of hyperprolactinemia with antipsychotics such as risperidone, and other typical antipsychotics, in women. Women are twice as susceptible to antipsychotic-induced hyperprolactinemia as men [120], and it occurs at a lower daily dose of antipsychotics when compared with men [121]. Bergemann *et al.* found significantly elevated prolactin levels, with reduced estrogen levels, at three measurements during the menstrual cycle in 75 premenopausal women with schizophrenia [99]. Hyperprolactinemia induces hypogonadotrophic hypogonadism with low serum levels of estradiol and testosterone, thus compounding the effects of pre-existing hypoestrogenism as discussed earlier, and resulting in a multitude of adverse health outcomes for women, including decreased bone mineral density and osteoporosis [122], increased risk of breast cancer [123], menstrual irregularities, sexual dysfunction and even decreased fertility [124,125]. This is particularly noteworthy as separate research groups have found that women with schizophrenia do in fact have a slightly higher rate of breast cancer than the general population [126]. Therefore, considering that SERMs, such as raloxifene, actually preserve bone mineral density and have anticancer properties in breast tissue, they could be an ideal augmentation strategy for women who require maintenance on prolactin-elevating antipsychotics, such as risperidone or amisulpride.

Another important adverse effect of second-generation antipsychotic therapy, which has a gender bias, is the metabolic syndrome, in particular weight gain and obesity. Women with schizophrenia have a 2.5-fold increased prevalence of metabolic syndrome compared with the general population, whereas for men the prevalence is increased only 1.4-fold [127]. Antipsychotic-associated weight gain is also more frequent and pronounced in women than in men [128]. Weight gain in itself is an independent risk factor for the development of Type 2 diabetes mellitus, hypertension and coronary artery disease, with their serious sequelae of stroke, acute myocardial infarction and thus increased mortality. The decreased quality of life associated with obesity [129] should also be noted. Therefore, it is essential to attempt to minimize the dosage of antipsychotic medications so as to avoid these dangerous metabolic and circulatory side effects, and once again, raloxifene, which has been found to possess cardioprotective properties when used in premenopausal women [130], could be a valuable augmentation strategy.

Gender not only influences the propensity for women to experience certain adverse effects of antipsychotics, but also influences their pharmacokinetics. Women of reproductive age have been found to respond to lower doses of antipsychotics than men [131], and this is possibly due to women's slower gastric emptying and higher proportion of adipose tissue [124]. It could also be influenced by estrogen. Estrogen has an inhibitory effect on some hepatic enzymes [131], which may slow liver microsomal drug metabolism, and possibly lead to enhanced efficacy of antipsychotic treatment. Therefore, in addition to its additive neuroleptic effect, estrogen could also decrease the dosage requirement of standard antipsychotic treatments through its influence on the hepatic metabolism of such medications; however, this is a theory that is yet to be quantified and could be a topic for future research.

Finally, it is important not to overlook the fact that multiple studies demonstrate adjunctive estrogen treatment to significantly improve general psychopathologic symptoms, such as depression, anxiety, insight and cognition, in patients with schizophrenia. As schizophrenia is a complex disorder of mental state encompassing broad disturbances in not only reality testing but also affective and cognitive states, improvement in these additional domains regardless of changes in psychotic symptomatology can dramatically improve a patient's quality of life, engagement and compliance with treatment, response to stressors and overall psychosocial functioning [132].

Expert commentary

In summary, although there are strong scientific arguments for the estrogen hypothesis and many potential advantages for its clinical

translation, the evidence is still somewhat limited by small sample sizes and inadequate controls being employed. There is certainly a need for more investigations, with large sample sizes and sound study design, to be performed using adjunctive estrogen therapy in the form of estradiol or SERMs in women with schizophrenia. A particular focus should be placed on identifying optimal doses of adjunctive estrogen and investigating the benefits of different forms of delivery. Risks and benefits of hormone usage both in the short and long-term period should always be discussed with patients prior to starting any form of estrogen therapy.

Five-year view

The role of hormones in the pathophysiology and management of psychotic illness is a rapidly evolving field. Given the positive results of studies trialing the adjunctive use of estradiol in women with schizophrenia, it is possible that this hormone could also have merit as an adjunctive therapy in men. There is preliminary animal and clinical evidence in support of this potential development, with reports of estradiol displaying antipsychotic-like effects in male rats in rodent behavioral phenotypes of psychosis [133], and a recent randomized controlled trial demonstrating that psychotic men treated with adjunctive estradiol valerate made a faster recovery than those treated with placebo [134]. However, concern over feminizing side effects could limit the clinical uptake of estrogen as a treatment for men with schizophrenia. Therefore, SERMs, such as raloxifene, could be a preferable option, and investigation into their use in both sexes should be continued.

Investigation of novel hormonal compounds, such as testosterone precursors, pregnenolone and its metabolites, and oxytocin as therapeutic options, is a field still in its infancy, but could be a source of future hope. It can be expected that in the coming years, research into these promising compounds will continue apace, and the search for novel and safe therapeutic alternatives for the management of schizophrenia will intensify. It is hoped that these exciting developments in the field of psychoneuroendocrinology will continue to evolve and eventually be translated into successful clinical practice, to the benefit of patients suffering under the burden of psychotic illness.

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Key issues

- Epidemiological and life-cycle evidence suggest that schizophrenia is a sexually dimorphic condition and that estrogen is protective against psychotic illness. It delays the onset of schizophrenia in women by raising the vulnerability threshold for the condition, and fluctuations in circulating estradiol levels can correspond with changes in mental state.
- Extensive animal research has demonstrated the influence of estradiol on dopaminergic, serotonergic and glutamatergic neurotransmitter systems as the likely basis for its psychoprotective properties.
- Results of clinical intervention studies investigating the therapeutic use of estradiol in schizophrenia are promising; however, larger randomized trials are still needed before broader clinical applications can be made.
- Selective estrogen-receptor modulators, in particular raloxifene, which shares the psychoprotective properties of estradiol in the brain without posing a threat to breast and uterine tissue, could be a particularly valuable therapeutic possibility for women with schizophrenia.
- Factors such as hormonal status and issues surrounding medication side effects should be taken into account when managing women with psychotic illnesses. Augmentation therapy with selective estrogen-receptor modulators could be a potentially ideal way to combat some of the concerns unique to the management of women with schizophrenia.
- New research into other neuroactive steroids is beginning to provide the first evidence that hormones other than estrogen might also be implicated in the pathogenesis and treatment of schizophrenia.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

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