



Estrogens in schizophrenia: progress, current challenges and opportunities

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Purpose of review

Schizophrenia is a heterogeneous psychiatric disorder with a different, but not necessarily milder clinical presentation in women as compared to men. These sex differences have largely been attributed to the protective role of estrogens. This article reviews the current state of estrogen research in schizophrenia.

Recent findings

Estrogens regulate important pathophysiological pathways in schizophrenia, including dopamine activity, mitochondrial function, and the stress system. Estrogen deficiency is common in both sexes and is associated with increases in psychotic symptoms. Hyperprolactinemia causes secondary estrogen deficiency and can be a reaction to stress, or secondary to prolactin-raising antipsychotics. Therefore, prolactin-sparing antipsychotics should be preferred especially in premenopausal women, who are more prone to hyperprolactinemia. Premenopausal women furthermore require lower doses of antipsychotics than men, since estrogens raise the availability and efficacy of antipsychotics.

Summary

The past years have established the importance of estrogens in the pathophysiology of schizophrenia and have shown its relevance to clinical practice through its influence on antipsychotic drug efficacy. Future research should focus on the neurobiological and clinical effect of contraceptives in premenopausal women with schizophrenia. Furthermore, the potential of estrogen-like augmentation with raloxifene and phytoestrogens in schizophrenia should be established in the coming years.

Keywords

estrogen, psychosis, schizophrenia, sex differences, sex steroids

INTRODUCTION

Robust sex disparities are recognized in schizophrenia incidence, age of onset, risk factors, symptomatology, and disease course [1^{••}]. Men experience more severe negative and cognitive symptoms and perform worse on social functioning, whereas affective symptoms, self-harm, and suicide attempts are more frequent among women [1^{••},2,3]. This different presentation can cause diagnostic delay in women [1^{••}]. Despite earlier claims of a more benign clinical course, recent studies showed that women need just as many re-hospitalizations as men [1^{••}] and a meta-analysis found similar recovery rates for women (12.9%) and men (12.1%) [4]. Although women initially achieve better recovery, advantages on the long term are less evident [5]. Several factors may be associated with these sex disparities in schizophrenia, such as the faster brain development in women, different gender roles, differences in personality and different risk factors [1^{••},6,7]. For example, both childhood trauma and substance abuse are associated with the development of

schizophrenia, but the occurrence of these triggering factors differs largely between the sexes [1^{••},8].

The past years provided mounting evidence that the clinical differences between men and women with schizophrenia can partly be attributed to estrogens [9–12,13[•]]. Evidence for this estrogen hypothesis is at least twofold. On the one hand, women are

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KEY POINTS

- Recent clinical, preclinical and genetic research confirms that estrogens have neuroprotective effects that are associated with important pathophysiological pathways in schizophrenia, including dopamine, COMT, mitochondrial function, and the stress response system.
- Clinicians should focus on minimizing the risk of estrogen deficiency induced by hyperprolactinemia by prescribing prolactin-sparing antipsychotics, since estrogen deficiency is associated with more severe psychotic symptoms and relapses, as well as sexual dysfunction, infertility, and increased health risks.
- Premenopausal women require generally lower antipsychotic doses during high estrogenic phases of their cycle, since estrogens raise the availability and efficacy of antipsychotic drugs.
- Augmentation with estrogen-like drugs such as raloxifene is effective in reducing symptoms, improving cognition in postmenopausal women with schizophrenia, although further research is needed to expand these findings to men and younger women.
- Future (pre)clinical studies should establish the potential of phytoestrogens as potential SERM augmentation therapy in schizophrenia and should focus on the neurobiological and clinical effect of contraceptives in women with schizophrenia.

increasingly vulnerable to psychosis onset and experience more severe symptoms during low estrogenic phases (e.g. after menopause) [6,11,12]. On the other hand, estrogens have direct neuroprotective actions, for example by decreasing neuro-inflammation, promoting synaptic plasticity, and by influencing major neurotransmitter systems relevant for schizophrenia, such as dopamine signaling [12,14–16]. Through their influence on dopaminergic signaling, estrogens reduce impulsivity and risk for substance abuse in women [9–12,16]. In the current review, we summarize recent work regarding the role of estrogens in the pathology and treatment of schizophrenia. Specifically, we discuss new findings regarding the major neurobiological mechanisms underlying the estrogen hypothesis, as well as developments in the role of estrogens in treatment strategies. We further summarize recent implications of estrogens for clinical practice.

Neurobiological action of estrogens in schizophrenia

There are three types of estrogen, of which estradiol (estradiol-17 β) has the highest concentration in the brain [17]. Estrogens can exert direct neuroprotective

effects via genomic and nongenomic mechanisms (Fig. 1) [18]. Genomic actions involve activation of the estrogen receptor alpha (ER α) or beta (ER β). Upon binding, these receptors promote gene expression of antiapoptotic genes and neuroprotective growth factors, whereas the expression of pro-inflammatory molecules is repressed [17,19]. Previous studies have shown that genetic variants of the ER α coding gene (ESR1) are associated with schizophrenia development and symptomatology [10,20,21]. For example, the CC-homozygote of single nucleotide polymorphism (SNP) rs2234693 is more common in schizophrenia and has been associated with more severe general symptoms, whereas T-allele carriers have an earlier age of onset [10,20]. A genetic variant of the same gene, SNP rs2144025, is associated with specific symptoms, such as grandiose delusions and alogia [21]. Estrogens can engage in rapid nongenomic signaling events through activation of ER α/β , but specifically through binding to the G protein-coupled estrogen receptor (GPER) (Fig. 1) [22[■]]. GPERs are for example highly expressed in hippocampal neurons where they activate pathways involved in cognitive functioning [23].

Estrogens and dopamine

Although hyperactive dopamine signaling is known as a central mechanism affected in schizophrenia [24,25], its association with estrogens is less known. Dopaminergic function is regulated by estrogens in several ways (Fig. 2) [16,26–29]. Estrogens increase dopamine sensitivity of dopamine D2/D3 receptors in the ventral tegmental area (VTA) [30], which is part of the mesolimbic (associated with positive symptoms) and the mesocortical pathway (associated with negative and cognitive symptoms) [24,31]. By increasing dopamine sensitivity in the VTA, estrogens can thus reduce psychotic symptoms.

Estrogens also regulate dopamine activity through Catechol-O-methyltransferase (COMT), an enzyme that degrades dopamine (Fig. 3) [32,33]. Since estrogens inhibit COMT gene transcription [34[■],35], estrogen deficiency can lead to increased COMT activity and decreased dopaminergic functioning. Moreover, recent studies show that COMT inhibits estrogen activity [34[■],36,37].

Estrogens and the mitochondria

Mitochondrial deficits have been implicated as an important schizophrenia risk factor [38,39]. Mitochondria are the main providers of energy for cellular activities and mitochondrial deficits impair synaptic signaling, neurotransmission, and neurodevelopment [22[■],39]. Recent research revealed that

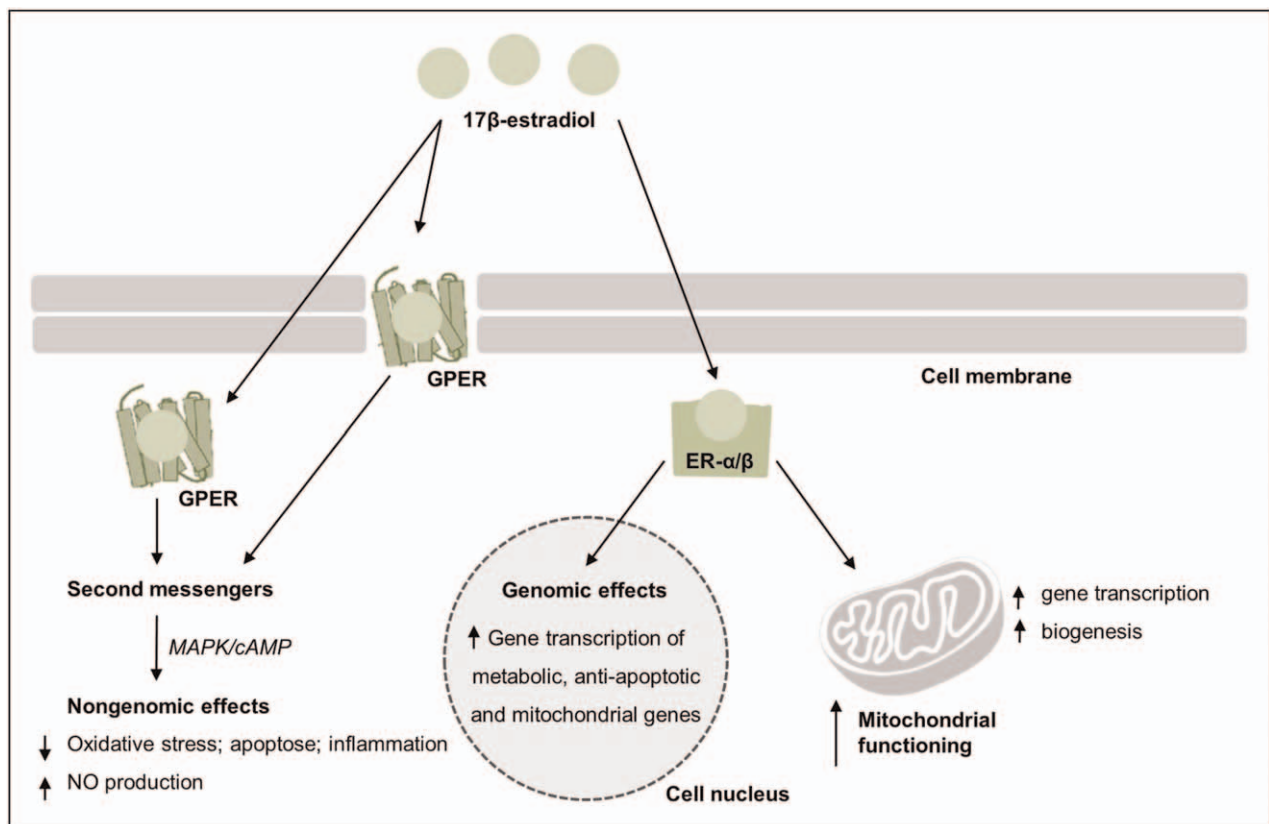


FIGURE 1. A simplified overview of the putative mechanisms involved in estrogens genomic and nongenomic actions. Genomic mechanisms involve activation of the estrogen receptors (ER α / β) by estrogen, which then translocate either to the cell nucleus or to the mitochondria resulting in transcription activation in the cell nucleus or in the mitochondria. Nongenomic mechanisms involve binding of estrogens to ERs or to a G protein coupled receptor (GPER), either at the plasma membrane or intracellularly to activate second messenger systems, such as those involving mitogen-activated protein kinase (MAPK) or cyclic adenosine 3',5'-monophosphate (cAMP) pathways. ER α / β activation can ameliorate mitochondrial activity directly by enhancing mitochondrial functioning through promoting gene transcription of mitochondrial DNA and indirectly, by promoting gene transcription of mitochondrial and metabolic genes in the cell nucleus. NO, nitric oxide.

estrogens ameliorate mitochondrial activity directly by promoting gene transcription of mitochondrial DNA and indirectly by promoting gene transcription of mitochondrial genes in the cell nucleus (Fig. 1) [22[■]]. Animal studies show that females have better mitochondrial function than males, reflected in increased mitochondrial biogenesis, oxidative capacity, and antioxidant defense as well as less release of mitochondrial apoptotic factors) [22[■],40]. Preclinical and clinical studies indicate that augmentation with plant-derived estrogens (i.e. phytoestrogens) improves mitochondrial functionality and decreases oxidative stress [22[■]]. However, additional research is required to extend these findings to schizophrenia patients.

Estrogens and response to stress

Estrogens influence the activity of the hypothalamic-pituitary-adrenal axis (HPA-axis) and thereby

contribute to the intrinsic differences in stress responses that are found between healthy men and women [41,42[■]]. Higher estrogen levels constitute a protective effect that modulates the stress response, whereas estrogen deficiency leads to increased activity (i.e. dysregulation) of the HPA-axis [43[■],44–46]. In schizophrenia, both sexes show a lower response to acute elevations in cortisol that may result from higher baseline cortisol levels [46]. This blunted stress response is more evident in male patients [47], whereas in female patients, low estrogen phases are associated with decreased stress resilience and increased HPA-axis dysregulation [48,49].

The role of estrogens in stress vulnerability is also reflected in the sex-dependent reaction to childhood trauma [50]. In schizophrenia, a history of childhood trauma results in sex-specific illness trajectories. Although both sexes have an earlier age of onset in case of trauma, female patients show more depressive symptoms, whereas male patients show

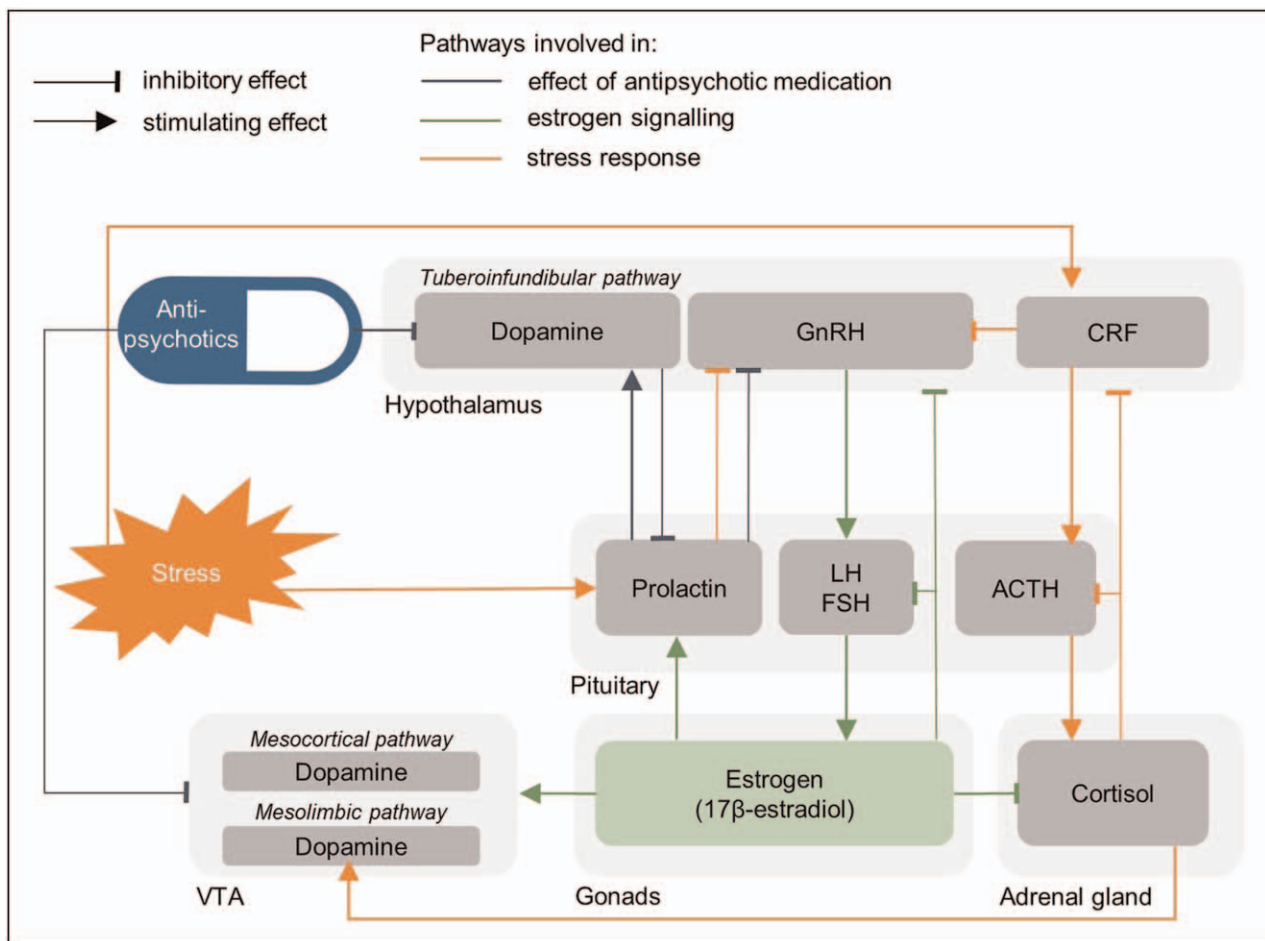


FIGURE 2. A simplified schematic overview of the interaction between estrogen signaling in orange, the stress response in red and antipsychotic effects in blue. ACTH, Adrenocorticotropic hormone; CRF, cortisol releasing factor; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

more negative symptoms [50]. Moreover, a more pronounced impact on longer-term outcome was observed in men. Childhood trauma thus seems to amplify the typical sex-specific expression of symptoms, possibly mediated by estrogens effects on the HPA-axis [45,50]. To make things more complicated, the type of trauma also differs between girls and boys, with girls more often experiencing traumatic situations involving caregivers, which constitutes trauma that is especially difficult to cope with [50].

Estrogen deficiency and hyperprolactinemia

Estrogen deficiency is common in both women and men with schizophrenia over the course of their disease; in prodromal and untreated phases of psychosis as well as in chronic schizophrenia [6,9,11,51–54]. On a clinical level, psychotic vulnerability is increased in women during low estrogenic periods (e.g. in the premenstrual cycle phase or after menopause) [55,56[†]]. Simultaneously with

the menopausal drop of estrogen levels, both prevalence and relapse rates of psychosis rise, whereas psychotic symptoms decrease when estrogen levels are high, for example during pregnancy [57–60]. A recent study furthermore showed that later menarche in women at clinical high risk (CHR) for psychosis (i.e. later rise of estrogen levels) was associated with abnormalities in hippocampal connectivity [61[†]]. Similarly, earlier studies indicate that later menarche is associated with an earlier onset of schizophrenia [62,63]. However, the larger literature reports contradicting evidence, including two cohort studies [64,65]. Although men naturally have lower estrogen levels than women, several studies found that men with schizophrenia have even lower levels of estrogens compared to healthy men [51,52]. In addition, male patients have lower levels of testosterone (which is converted to estrogens in the brain) [66,67].

Estrogen deficiency is often the result of hyperprolactinemia, which in itself can have different causes [63,64]. Antipsychotic medication can cause

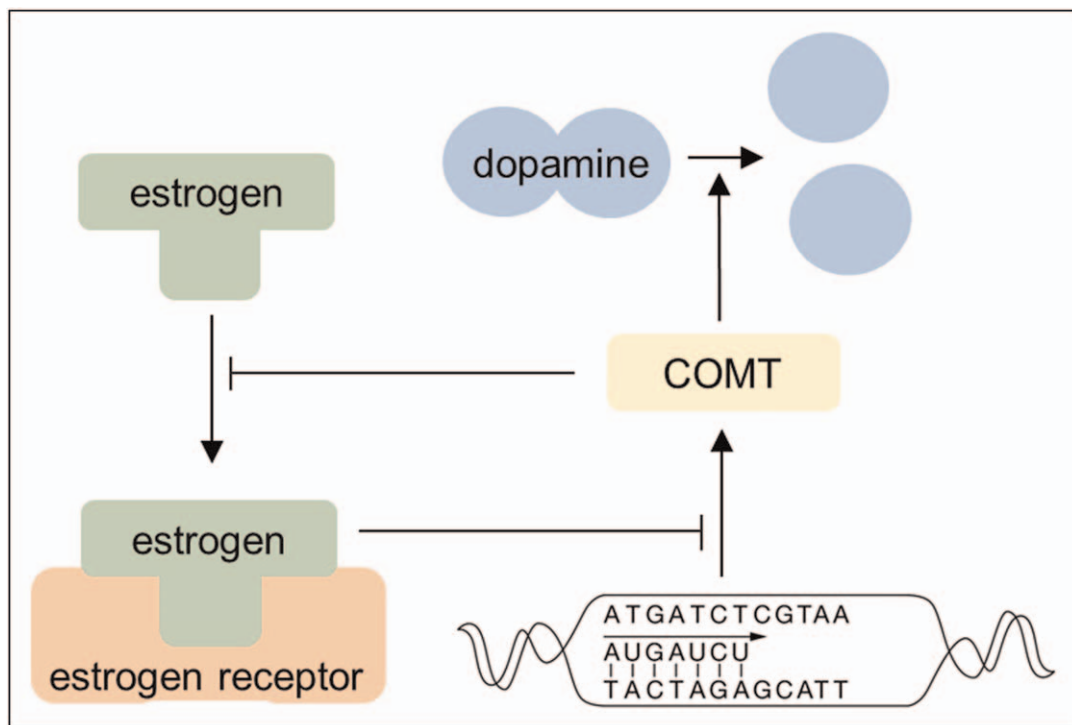


FIGURE 3. A simplified overview of the putative interaction between estrogens and Catechol-o-methyltransferase (COMT). Estrogens decrease COMT expression, inhibiting effect COMT gene transcription through activation of the estrogen receptor. COMT enzyme inhibits estrogen activity, through binding to estrogen.

hyperprolactinemia (see Table 1 for an overview based on Peuskens *et al.* [68] and Gonzalez-Rodriguez *et al.* [69[■]]), since dopamine inhibits prolactin production via the tuberoinfundibular pathway (Fig. 2) [69[■]]. However, hyperprolactinemia is also observed in antipsychotic-naïve patients of both sexes with (prodromal) psychosis [70–75, 76[■]]. It is hypothesized that this primary

Table 1. Estimated effects of antipsychotics on prolactin levels

Antipsychotic	Estimated prolactin elevation
Aripiprazole	0
Quetiapine	0/+
Asenapine	+
Clozapine	+
Sertindole	+
Ziprasidone	+
Lurasidone	+ / ++
Olanzapine	++
Amisulpride	+++
Haloperidol	+++
Paliperidone	+++
Risperidone	+++

0, minimal to no risk; +, low risk; ++, moderate risk; +++, high risk.

hyperprolactinemia is a result of the stress response system, since stress can induce the secretion of prolactin [9]. Prolactin in turn stimulates dopamine secretion, which can induce psychotic symptoms (Fig. 2) [63]. Within this framework, primary estrogen deficiency results from stress-induced increased prolactin secretion. This hypothesis is in line with recent studies showing that higher prolactin levels are associated with more severe psychotic [76[■]] and negative [73] symptoms in these treatment naïve patients. Other studies showed, conversely, that prolactin levels are inversely associated with treatment response [77–79]. Whether and how prolactin is involved as a pathophysiologic factor in schizophrenia thus remains not fully understood.

Although hyperprolactinemia is well known for its side-effects (e.g. Galactorrhea, cessation of normal cyclic ovarian function and hirsutism) its effect on estrogen levels is less well known, but at least as severe. The resulting secondary estrogen deficiency can lead to serious side-effects such as sexual dysfunction, decreased libido and infertility, but also to increased risk for osteoporosis and cardiovascular morbidity [80]. It has been suggested that antipsychotic-induced hyperprolactinemia is a potential explanation for the decreased biological fertility that is observed in women and men with schizophrenia [81]. In women, prolactin inhibits follicle

stimulating hormone (FSH) via inhibition of gonadotropin-releasing hormone (GnRH), thereby preventing ovulation. In men, prolactin inhibits the release of gonadotropins in a similar way, which has a direct effect on spermatogenesis [82,83]. Interestingly, a recent review showed that exposure to prolactin-raising medication during pregnancy was associated with increased risks of congenital malformations, whereas prolactin-sparing medication was not [84]. Yet, more research is needed to establish the effect of antipsychotic use during pregnancy.

Taken together, hyperprolactinemia should be minimized as much as possible. This is especially true for women with intrinsically higher estrogen levels that should be maintained (i.e. premenopausal women), especially since they are most vulnerable to hyperprolactinemia compared to other women and men [69[•]]. Prolactin-sparing medication should therefore be preferred over prolactin-raising medication (see Table 1). Interestingly, aripiprazole treatment even showed to have a reducing effect on prolactin levels [85,86].

Estrogens and antipsychotic treatment

Estrogens directly raise the plasma concentration of antipsychotic drugs by regulating enzymes that metabolize antipsychotics, which is most evident for clozapine and olanzapine [87[•]]. These antipsychotic drugs are both metabolized in the liver by the same isozyme (CYP1A2), of which the activity is inhibited by estrogens. In the CNS, estrogens increase the sensitivity of dopamine D2 receptors and thus they augment the efficacy of (D2-receptor binding) antipsychotics [88,89]. Eugene and Misiak [89] showed that women require only half of the olanzapine dosage as compared to men to achieve equal occupancy of the dopamine D2 receptor. The authors attribute much of this effect to the modulation of D2 receptors by estrogen. Moreover, a recent review even argued that estrogen may act as an antipsychotic agent itself, considering that it targets dopamine signaling in a similar way as antipsychotics do [90[•]].

Since estrogens raise the availability of antipsychotics, premenopausal women require lower antipsychotic dosages [91]. However, considering that psychotic symptoms increase during low estrogenic phases of the menstrual cycle [32,87[•],92], younger women can benefit from slight increases in antipsychotic doses during these phases, to prevent monthly exacerbations in their illness [56[•]]. For women who are sensitive to these monthly symptom increases, oral estrogenic contraceptives may be helpful. Similarly, higher doses of antipsychotics are

required after menopause, when symptoms increase and estrogen levels decline [32,86]. A recent meta-analysis showed that during pregnancy, when estrogen levels increase, decreased plasma levels are observed for quetiapine and aripiprazole, but not for olanzapine [93]. Pregnant women and their unborn child may therefore benefit from adjustments in the dosing of certain antipsychotics, to minimize the burden of side-effects of (overdosed) antipsychotics.

Despite some disagreement among clinical data, women are more vulnerable to side-effects of antipsychotics, including sexual dysfunction, cardiovascular effects and specific metabolic symptoms (i.e. weight gain and low HDL-cholesterol) as compared to men [94–97]. A large cross-sectional study [98] furthermore reported that women with schizophrenia are 134% more likely to develop metabolic syndrome, whereas male patients are 85% more likely to develop metabolic syndrome, when compared to healthy men and women, respectively. Importantly, antipsychotic-induced obesity adds to the risk of future metabolic dysfunction and cardiovascular problems. Another large trial [99] concluded that especially female patients taking olanzapine and clozapine represent a group at high risk for metabolic cardiovascular complications. This increased risk for adverse reactions may reflect the relative overdosage of antipsychotics female patients frequently experience [87[•],89]. In addition, side effects increase when antipsychotics are combined with other psychotropic drugs such as antidepressants, which is more common among women [1^{••},94]. Clinicians should therefore be wary of prescribing antipsychotics that induce weight gain to both pre and postmenopausal women.

Estrogenic treatment

Estrogenic contraceptives are commonly prescribed to premenopausal women, including women with schizophrenia, yet little is known about their clinical effects. Estrogenic contraceptives stabilize but also lower endogenous estrogen levels as they are counterbalanced with higher exogenous estrogen levels [100,101]. Instead, progestogen-only contraception, such as medroxyprogesterone acetate, can lower both endogenous and exogenous estrogen levels [101,102]. Although so far the effect of contraceptives in schizophrenia has not been studied, two epidemiological studies demonstrated that especially progestogen-only contraceptives increase the risk of depressive symptoms and suicide in the general population [103–105]. Given the prevalent affective symptoms in women with schizophrenia [1^{••}], estrogenic contraceptives (e.g. ethinylestradiol)

or combined contraceptives (e.g. ethinylestradiol/levonorgestrel) should be preferred over progestogen-only contraception until further research has been done regarding the potential risks and benefits of contraceptive use in schizophrenia [13[■]].

Double-blind, placebo-controlled, randomized trials provide evidence that estrogen augmentation is beneficial for women with schizophrenia [106–108], although not all clinical studies have reported significant effects (e.g. [109]). Estrogen treatment is less suitable for long-term treatment due to its considerable side effects on the sex organs of both sexes [13[■]]. Estrogen augmentation has been mostly investigated during and after menopause, a period in which estrogenic therapies can target both psychotic and menopausal complaints such as sleep disturbances and mood swings [106,108,110]; complaints which in themselves increase the risk of psychotic relapse [9].

Selective estrogen receptor modulators (SERMs), such as raloxifene, are an alternative for estrogens that seems more suitable for long term use [19] since SERMs have estrogenic effects on the brain and bone tissue, whereas having antiestrogenic effects on other tissues (such as breast and uterus) [111]. A recent meta-analysis [112] revealed that raloxifene improves symptom severity in schizophrenia, although the results on cognition are less consistent [113,114]. To date, studies have been predominantly performed in postmenopausal women, although some studies also included men and younger women and showed the latter two groups also to benefit from raloxifene augmentation [115,116]. Yet, further studies are needed to confirm its efficacy in men and premenopausal women.

Several preliminary studies have identified genetic and hormonal biomarkers that may aid to predict the response to raloxifene. For example, raloxifene is more effective in improving cognitive symptoms when endogenous estrogen levels are low [117[■]]. Additionally, Kindler *et al.* [118] showed that raloxifene increases activity in the prefrontal cortex during emotional response inhibition in both genders. Increased activity was greater in AA-homozygotes for rs9340799 of the ESR1 gene, relative to G carriers. These results were however not reflected by Labad *et al.*, who performed a pharmacogenetic study on the effects of raloxifene in postmenopausal women [119]. Yet, the latter study did show that CC-homozygotes of the rs1042597 of the UGT1A8 gene showed more improvements in negative symptoms in response to raloxifene, when compared to G carriers. ESR1 rs2234693 genotype was furthermore associated with a distinct response in general psychopathology [119]. In addition, protein levels of specificity protein 4 that interacts with ER α are

indicated as potential biomarker for raloxifene efficacy [120[■]]. Although these initial results require replication, they suggest potential for future personalized pharmacotherapy.

Preclinical and translational studies indicate that phytoestrogens can also be a natural alternative to SERMs [43[■],121–123]. For example, the larvae of the mealworm *Tenebrio Molitor* contain high concentrations of phytoestrogens and have high antioxidant and anti-inflammatory effects [124]. Administration of these larvae in female ovariectomized mice restored estrogen deficiency in a similar way as artificial SERMs [43[■]]. Moreover, HPA-axis deregulation was restored after treatment. Phytoestrogens, present in certain food products like tofu, can have both estrogenic and antiestrogenic effects. Therefore, they can have a more beneficial side-effect profile when compared to conventional estrogen augmentation. However, the transformation of phytoestrogens by intestinal microbiota is essential for reaping their beneficial effects, since the metabolites of phytoestrogens (e.g. equol) have more estrogenic/antiestrogenic and antioxidant activity than their precursors [125]. In this way, the health effects of phytoestrogens are strongly determined by the gut bacteria of each individual. More studies on the bioavailability and bioactivity of different types of phytoestrogens are essential to establish their function in schizophrenia, either as SERM augmentation therapy or as dietary product.

CONCLUSION

In summary, recent findings support the decisive role of estrogens in schizophrenia. Estrogens regulate clinical symptoms through their influence on with dopamine pathways, as well as by regulating mitochondrial functioning and the stress response system. Estrogen deficiency is common in schizophrenia and is often related to hyperprolactinemia in both medication-naïve and chronic patients. In order to minimize the risk of estrogen deficiency, prolactin-sparing antipsychotics (e.g. aripiprazole) should be preferred, especially in premenopausal women as they are more susceptible to estrogen deficiency following hyperprolactinemia. Since estrogens raise the availability of antipsychotic drugs, which needs to be taken into account for the establishment of optimal starting doses in women. Furthermore, premenopausal women generally require lower drug dosages than men and postmenopausal women whereas women may require slight increases of their dose to prevent relapse of symptoms during low estrogenic phases. Furthermore, progestogen-only contraceptives are known to constitute permanent low estrogen levels

in premenopausal women, which causes depressive symptoms in the general population. In order to preserve and protect natural estrogen levels, estrogenic contraceptives should be preferred over progestogen-only contraceptives. Although the past decade has firmly established the efficacy and safety of estrogen-like augmentation with raloxifene in postmenopausal women, forthcoming clinical trials should assess whether these findings extend to men and premenopausal women. With this approach, we expect that the protective role of estrogen will become increasingly important for schizophrenia treatment in the coming years.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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