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Hypothalamic-pituitary-gonadal axis dysfunction: An innate pathophysiology of schizophrenia?

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ABSTRACT

The female hormone 17β-estradiol is postulated to be protective against schizophrenia onset and severity. Hypoestrogenism is a common phenomenon in women with schizophrenia that has serious effects that adds to the burden of an already very onerous disease. The cause of hypoestrogenism is largely attributed to antipsychotic-induced hyperprolactinemia. Evidence suggest however that a significant portion of female schizophrenia patients develop hypoestrogenism either before antipsychotic treatment or without regard to the level of prolactin, suggesting that for a sizeable segment of female patients, gonadal abnormality may be an innate and early aspect of the disease. This review aims to summarise the available literature that examines gonadal dysfunction in schizophrenia through this prism as well as to outline some recent developments in treatment strategies that may provide feasible ways to successfully tackle hypoestrogenism in schizophrenia.

1. Modulation of schizophrenia by estrogen

Schizophrenia is a crippling psychiatric disorder affecting around 0.3–0.7% of the general population (Saha et al., 2005). Despite its relatively low prevalence, schizophrenia was ranked among the top 25 leading causes of disability worldwide in 2013 due to its high morbidity rates (Global Burden of Disease Study, 2015). Schizophrenia is characterised by three symptom domains – positive symptoms (e.g. hallucinations and delusions), negative symptoms (e.g. apathy, lack of motivation) and cognitive symptoms (e.g. memory impairment, executive function impairment). Unsurprisingly, besides the obvious health problems, schizophrenia imposes a heavy economic burden, with the cost of treatment and care for diagnosed patients accounting between 1.5 and 3% of total national health expense in most developed countries (Knapp et al., 2004). This financial cost is most likely a vast underestimate as schizophrenia imposes a high level of indirect costs of approximately 50% of total costs associated with the disease (Gustavsson et al., 2011; Marcellusi et al., 2018). Furthermore, the trajectory of the prevalence of schizophrenia is growing across the world (Charlson et al., 2018). The cornerstone of treatment for schizophrenia is antipsychotics, which suppress the positive symptoms. However, antipsychotic medications are limited by their inability to treat other symptom domains, the heterogeneity in patient responses, which leads to a trial-and-error strategy in prescription, as well as variances in efficacy in addition to a wide array of side effects including extrapyramidal symptoms and cardiometabolic dysfunctions (Blair and Dauner, 1992; Lally and MacCabe, 2015). Hence there is a great need for novel treatments to fill these gaps.

The onset of schizophrenia typically peaks during early adulthood. However, clear sex differences in age of onset have been found by epidemiological studies. Females tend to have a delayed mean peak onset age compared to males, by about 3–4 years (Hafner, 2003; Hafner et al., 1992). Indeed, earlier age of menarche in females is associated with later onset of schizophrenia, whereas there is no correlation between age of puberty and disease onset in males (Cohen et al., 1999; Kilicaslan et al., 2014), suggesting longer exposure to the female sex hormone estrogens, especially the most potent estrogen, 17β-estradiol (E2), is protective against schizophrenia during the peak onset period of the disease. Females also show less incidence rates compared to males overall and typically present with milder symptoms, lower levels of disability and require lower doses of antipsychotics (Canuso and Pandina, 2007; Hafner, 2003; Melkersson et al., 2001; Morgan et al., 2008), although females tend to suffer more from affective symptoms than males (Cotton et al., 2009). Noticeably, females experience a second peak of onset around the age of menopause, when circulating E2 levels drop significantly (Riecher-Rossler and Hafner, 1993). These epidemiological findings suggest that the female sex hormone, E2, is protective against the onset of schizophrenia.

Evidence also suggests that E2 can modulate the severity of schizophrenia symptoms in patients. Studies have shown that the severity of symptoms from all three symptom domains vary in female patients according to the menstrual cycle, worsening during low E2 phases and vice versa, with the possible exception of depressive symptoms (Bergemann et al., 2007; Grigoriadis and Seeman, 2002; Gurvich et al.,

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2018; Riecher-Rossler et al., 1994a; Riecher-Rossler et al., 1994b; Rubin et al., 2010). For this reason, there is an over-representation of women admitted to the hospital for exacerbation of schizophrenia symptoms during low E2 phases (Bergemann et al., 2002; Herceg et al., 2018). A later age of menarche in female patients has been found to be correlated with greater functional impairment (GAF) and higher negative symptom scores (PANSS) (Hochman and Lewine, 2004). Time since menopause was also found to be negatively correlated with overall antipsychotic response, accounting for 41% of the variance (Gonzalez-Rodriguez et al., 2016). Collectively, the above evidence gave rise to the 'estrogen hypothesis of schizophrenia', which proposes that estrogen, in particular E2, offers relative protection against schizophrenia in women, and that hypoestrogenism in women exacerbates the risk and course of schizophrenia (Riecher-Rossler, 2002). This insight offers potentially exciting opportunities for treatment options, given current antipsychotic drugs chiefly only target the positive symptoms but leave, for example, cognitive symptoms, which are both prevalent and highly predictive of functional outcomes (Green et al., 2004), unmedicated.

2. Mechanisms of estrogen in schizophrenia

E2 can modulate neurotransmitter networks known to be disrupted in schizophrenia-related pathology, namely the dopaminergic and glutamatergic networks (Barth et al., 2015; Cyr et al., 2002; Rao and Kolsch, 2003). For example, E2 can modulate the expressions of dopamine receptors and dopamine transporter (Di Paolo, 1994) as well as dopamine synthesis (Pasqualini et al., 1995). E2 can also regulate hippocampal dendritic spine density through NMDA receptor-dependent mechanism (Woolley and McEwen, 1994; Woolley et al., 1997) and is protective against NMDA-induced neurotoxicity (Kurata et al., 2004; Lan et al., 2014). Furthermore, estrogen receptors may influence metabotropic glutamate receptor signalling (Tonn Eisinger et al., 2018). Additionally, the major inhibitory network, the GABAergic network, which regulates both the dopaminergic (Enomoto et al., 2011) and glutamatergic networks (Coyle, 2004; Johns et al., 2002), is disrupted in schizophrenia (Blum and Mann, 2002). The work in our laboratory has shown that E2 modulates the adolescent development of parvalbumin-expressing GABAergic interneurons in the hippocampus (Wu et al., 2014) and prefrontal cortex (Du et al., 2018) of mice. We have also demonstrated that E2 modifies gamma band oscillations, which is coordinated by PV interneurons during decision making in a cognitive task (Schroeder et al., 2017). Furthermore, E2 can also promote synaptic plasticity (Bi et al., 2001; Liu et al., 2008) and possesses anti-inflammatory properties (Pozzi et al., 2006; Vegeto et al., 2003), potentially able to combat the synaptopathy (Calabrese et al., 2016; Osimo et al., 2018) and increased inflammation in schizophrenia (Boerrigter et al., 2017; Marques et al., 2018). Some of these effects may be through E2's ability to regulate the expression of neurotrophins, in particular, brain-derived neurotrophic factor (BDNF), which is a vital neurotrophin with many neuroprotective effects (Begliuomini et al., 2007; Engler-Chiurazzi et al., 2011; Gibbs, 1999; Hill, 2012; Pan et al., 1999; Scharfman and MacLusky, 2006; Wu et al., 2013).

3. Hypoestrogenism in schizophrenia

Given the palpable positive effects of E2 in schizophrenia, it is not surprising that hypoestrogenism is often detected in female schizophrenia patients. In PubMed, using the search term 'Schizophrenia' in combination with 'hypoestrogenism' or 'estradiol' or 'HPG-axis' or 'menstrual cycle' yielded 5 relevant original studies that looked at E2 level and menstrual cycling in female patients of reproductive age. For example, Riecher-Rossler and colleagues examined 32 acutely admitted female schizophrenia patients who were all cycling regularly, across at least one menstrual cycle with serum samples taken at least once every 7 days for hormone measurement via immunoassay. This group of women had markedly reduced circulating E2 levels compared to a sample of 350 healthy controls, with the natural fluctuations of E2 throughout the cycle also being dampened in comparison to healthy controls (Riecher-Rossler et al., 1994b). Ko and colleagues recruited 35 chronic schizophrenia inpatients who had at least two consecutive regular menstrual cycles before participation. The patients performed psychopathology and cognition testing as well as blood sampling during the follicular phase. The authors reported that 62% of their 35 patients examined exhibited hypoestrogenism (< 18.9 pg/ml) according to reference values of E2 for healthy women during the follicular phase, which correlated with poorer cognitive performance (Ko et al., 2006). Bergemann and colleague found in a cohort of 75 patients that 57.3% were hypoestrogenic, according to the established range of E2 in healthy women during the follicular (< 30 pg/ml) and periovulatory phases (< 100 pg/ml) (Bergemann et al., 2005). More recently, Gleeson and colleagues found that 41% of 139 chronic female patients examined displayed irregular menses (defined as not occurring once every 3–5 weeks), which correlated with reduced circulating E2 levels compared to those with regular menses (Gleeson et al., 2015). Another study from the same group found that 41.2% of 204 premenstrual female schizophrenia patients exhibited irregular cycling, and that menstrual cycling irregularity predicted significantly poorer performance in multiple cognitive tasks including verbal fluency and verbal memory (Gurvich et al., 2018).

Besides the classic schizophrenia symptoms, other manifestations of reduced estrogen such as lower bone mineral density and increases in the risk of osteoporosis (Kishimoto et al., 2012; Tseng et al., 2015), increased rates of urinary tract infection (Carson et al., 2017; Graham et al., 2014) and sexual dysfunction (Kockott and Pfeiffer, 1996) are all over represented in the schizophrenia population. These undoubtedly contribute to the high morbidity of the disease.

The prevailing view of the cause of hypoestrogenism in schizophrenia has traditionally been attributed to the use of antipsychotic medications (Buchanan et al., 2010). Blockage of the dopamine D2 receptor is a major mechanism of action of antipsychotic drugs. As prolactin secretion is inhibited by dopamine from the arcuate nucleus of the hypothalamus acting on dopamine D2 receptors in the pituitary gland, hyperprolactinemia is a common side effect of antipsychotic medication, especially in females (Kinon et al., 2003). One consequence of abnormally increased prolactin levels is hypoestrogenism, as prolactin suppresses the hypothalamic-pituitary-gonadal (HPG) axis (Smith et al., 2002). This is especially seen with "tight binding" drugs that block the dopamine D2 receptor most robustly, such as risperidone, which can cause hyperprolactinemia in a majority of users (Kinon et al., 2003). On the other hand, other atypical antipsychotics, which dissociate faster from dopamine D2 receptors, tend not to increase prolactin to the same extent as typical antipsychotics (Kapur et al., 2001).

Examining clinical trials by searching for key words 'schizophrenia' with 'estrogen treatment' or 'estradiol treatment' yielded 5 original studies in premenopausal women who have had chronic schizophrenia. These clinical studies have shown that adjunct E2 treatment may be beneficial for schizophrenia, aiding improvement of PANSS positive, negative, general and total symptoms and comprehension of metaphoric speech (Bergemann et al., 2008; Ghafari et al., 2013; Kulkarni et al., 1996; Kulkarni et al., 2015; Kulkarni et al., 2001). However, given the limitations of using E2 as treatment, due to its feminizing quality in men and its propensity to induce breast and endometrial cancers as well as increasing the risk of embolism and stroke (Manson et al., 2013; Rossouw et al., 2002), a better understanding of the cause of hypoestrogenism may help unveil novel treatment strategies. Some evidence may suggest that hypoestrogenism does not in fact exclusively occur as a result of antipsychotic drug-induced hyperprolactinemia. In a significant proportion of female schizophrenia patients, there is evidence that hypoestrogenism may arise as an innate and early pathophysiology of schizophrenia, which will be discussed below. If so, hypoestrogenism may exacerbate the manifestation of schizophrenia during the dynamic adolescent and early adulthood phase.

4. Hypoestrogenism independent of antipsychotic-induced hyperprolactinemia

Few studies particularly examined the contribution of antipsychotic-induced hyperprolactinemia towards gonadal abnormalities. Searching PubMed with the key words ‘schizophrenia’, ‘hyperprolactinaemia’ and ‘estradiol’; ‘schizophrenia’, ‘hyperprolactinaemia’, ‘amenorrhea’ and ‘antipsychotics’ found 3 relevant original studies. One study (Canuso et al., 2002) looked at a small sample of 16 female patients, eight of whom were treated with known prolactin-raising antipsychotics (typical antipsychotics and risperidone) and eight with prolactin-sparing antipsychotics (clozapine, olanzapine, and quetiapine). While prolactin levels in the former group were significantly greater than the latter, there were no differences in rates of menstrual dysfunction between the groups. The mean E2 levels of the two groups were similar, and 15/16 subjects examined, irrespective of prolactin levels, had peak E2 levels that fell below the normal reference median for E2 in the periovulatory phase of the menstrual cycle (200 pg/ml). Indeed 11 subjects had E2 levels beneath the lower limit of normal E2 level expected for this phase (100 pg/ml), as measured by radioimmunoassay level. The authors conclude that antipsychotic mediated increase in prolactin level alone do not fully explain the high rates of ovarian dysfunction observed in women with schizophrenia.

Bergemann and colleagues, in their 2005 study (Bergemann et al., 2005) of 75 women with schizophrenia found that just under 60% of the subjects displayed hypoestrogenism (E2 values of < 100 pg/ml during the periovulatory phase and < 30 pg/ml during the follicular phase), according to measures by electrochemiluminescence immunoassay. These subjects did not include any women with pre-existent amenorrhea or irregular menses. Similar to the study by Canuso and colleagues, the authors separated their subjects into those taking typical antipsychotics and atypical antipsychotics known to induce only mild elevations in prolactin (clozapine and olanzapine). While the prolactin levels of these two groups reflected the nature of the antipsychotics, with those patients on atypical antipsychotics having significantly lower prolactin level across the different phases of the menstrual cycle than those on typical antipsychotics, the serum E2 levels of both groups were low nonetheless. Indeed, only 19% of patients receiving conventional antipsychotics and 27% of patients receiving clozapine had E2 level over 100 pg/ml during the periovulatory phase, where the expected range is 150–300 pg/ml in healthy women. These findings led the authors to conclude that hypoestrogenism may occur regardless of antipsychotic-induced hyperprolactinemia.

Another study (Chen et al., 2013) set out to examine how antipsychotic medication contributes towards amenorrhea in first-episode female patients. The authors examined 62 drug-naïve patients from their admission till 12 weeks post treatment with risperidone, the most widely used antipsychotic in China, where the study was carried out. The study found that while prolactin levels increased 4-fold in patients given risperidone, the pre and post-treatment prolactin levels did not predict whether a patient developed amenorrhea. However, lower pretreatment E2 levels were significantly associated with the development of amenorrhea upon risperidone treatment. This suggests that dysfunction of the gonadal axis already exists in some patients prior to antipsychotic treatment and that antipsychotics might exacerbate this dysfunction.

Few studies have looked at drug-naïve patients in this regard. Using key terms ‘schizophrenia’, ‘drug-naïve’ or ‘drug free’ and ‘hyperprolactinaemia’; ‘schizophrenia’, ‘first episode’ and ‘hyperprolactinaemia’ yielded 5 relevant original studies. These available evidence agree with the proposition that dysfunction of the gonadal axis may precede antipsychotic treatment in a proportion of patients. Aston and colleagues reported hyperprolactinaemia in 10 out of 43 At-Risk Mental State individuals (ARMS) as well as 6 out of 26 first-episode psychosis patients who were all drug-naïve (Aston et al., 2010). In a follow up study in a larger cohort of drug-naïve subjects, the group reported 37 out of 116 ARMS individuals and 17 out of 49 first-episode psychosis patients presented with hyperprolactinaemia (Ittig et al., 2017). In this study, females of both groups are more likely to display hyperprolactinaemia (41% women vs 28% men of ARMS; 53% women vs 26% men of first-episode psychosis). A study examining 74 drug-naïve, first-episode patients from the European First Episode Schizophrenia Trial saw 11 out of 22 women and 18 out of 52 men exhibiting hyperprolactinemia (Riecher-Rossler et al., 2013). A recent study examining 40 drug-naïve, newly diagnosed schizophrenia patients found elevated serum prolactin level compared to healthy controls (Petrikis et al., 2016). In a Chinese study, which examined 81 first-episode schizophrenia patients consisting of 39 male and 42 females, the authors reported a significant elevation in serum prolactin levels in schizophrenia patients of both sexes compared to healthy controls. In addition, male patients exhibited reductions in testosterone while female patients displayed reductions in E2. In patients of both sexes, E2 levels were correlated with cognitive performance. In male patients, E2 levels were negatively correlated with negative symptoms while in females E2 was negatively correlated with positive symptoms and total PANSS score (Yuan et al., 2016). Corroborating this finding, a recent systematic review of studies that examined prolactin levels in antipsychotic-naïve patients with schizophrenia and related disorders reported that prolactin levels are significantly elevated in both male and female patients and that the elevation was not correlated with confounding factors such as cortisol level or BMI (Gonzalez-Blanco et al., 2016).

While more large scale studies are required to confirm the extent and nature of gonadal axis dysfunction in early schizophrenia (see Table 1 for summary of existent data), the literature so far suggest that a sizeable proportion of patients may display abnormalities at the time of their first episode, and before antipsychotic treatment initiation.

5. Potential treatment strategy

The evidence of early HPG-axis dysfunction in particularly female schizophrenia patients may have important ramifications towards the guidance of antipsychotic choice. For example, in first-episode patients who already present with reduced E2 it may be best avoid prolactin-raising antipsychotics. Recently there has been accumulating evidence from small-scale clinical studies that indicate adjunct treatment using the selective estrogen receptor modulator (SERM) raloxifene is

Table 1
Studies examining E2 level in female schizophrenia patients.

Study	Subjects	Normal blood E2 reference range	Schizophrenia patient level
Riecher-Rossler et al., 1994b	32 female patients	550–1,660 pmol/L (preovulatory peak)	28/32 subjects showed peak E2 < 550 pmol/L (below lower limit of normal) across 3–8 weeks
Ko et al., 2006	35 female patients	18.9–246.7 pg/mL (follicular phase)	22/35 subjects showed E2 < 18.9 pg/mL (mean 21.05 ± 21.32 pg/mL)
Bergemann et al, 2005	75 female patients	150–350 pg/mL (periovulatory phase)	70/75 subjects showed peak E2 < 150 pg/mL (lower limit of normal range)
Canuso et al., 2002	16 female patients	100–280 pg/mL (periovulatory phase)	11/16 subjects showed peak E2 < 100 pg/mL (lower limit of normal)
Yuan et al., 2016	42 first episode female patients	63 ± 66 pg/mL (40 healthy female controls)	51 ± 40 pg/mL

beneficial for schizophrenia patients across all classic symptom domains and with apparently minimal deleterious side effects (de Boer et al., 2018; Kulkarni et al., 2016; Kulkarni et al., 2010; Weickert et al., 2015; Zhu et al., 2018). Raloxifene is a FDA approved drug for the treatment of postmenopausal osteoporosis and prevention of breast cancer. While acting through the estrogen pathway, raloxifene avoids many of the problems facing E2 by having tissue-specific actions, acting as an antagonist in the breast (Cummings et al., 2002) and uterus (Mitlak and Cohen, 1999) but as an agonist in bone (Muchmore, 2000). While a lack of knowledge of SERM actions in the brain has impeded furtherance of larger-scale and longer-term clinical trials, SERMs may prove to be a valuable adjunct treatment especially for patients exhibiting HPG-axis dysfunction upon onset. Interestingly, a recent case study revealed that a 12-week adjunct raloxifene trial in a 44 year old woman with schizophrenia who has had amenorrhea for four years was able to reinstate menses and improve various symptoms without lowering prolactin. Amenorrhea returned after the cessation of the raloxifene trial (Grigg et al., 2017). This case study is the first to show recovery of menses in a schizophrenia patient with amenorrhea using raloxifene and suggests that the function of the HPG-axis, even in patients with prolonged amenorrhea, can be recovered.

Further and deeper studies in this area are needed to continue to uncover the underlying pathophysiology in subsets of schizophrenia patients that display early HPG-axis dysfunction. For example, it is conceivable that abnormal gonadal development and function throughout adolescence may be a risk factor that plays a contributing role in the development of schizophrenia for some patients. The function of raloxifene and other SERMs such as the 3rd generation bazedoxifene require closer scrutiny with regards to their actions in the brain to fully exploit their beneficial properties. The better understanding of this phenomenon can help to generate informed application of the most appropriate treatments as well as aid in the evolution of new treatments to ameliorate the high burden of schizophrenia.

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Conflicts of interest

The authors declare no conflicts of interest.

References

Aston, J., Rechsteiner, E., Bull, N., Borgwardt, S., Gschwandtner, U., Riecher-Rossler, A., 2010. Hyperprolactinaemia in early psychosis-not only due to antipsychotics. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 34 (7), 1342–1344. https://doi.org/10.1016/j.pnpbp.2010.02.019.

Barth, C., Villringer, A., Sacher, J., 2015. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Front. Neurosci. 9, 37. https://doi.org/10.3389/fnins.2015.00037.

Begliuomini, S., Casarosa, E., Pluchino, N., Lenzi, E., Centofanti, M., Freschi, L., Genazzani, A.R., 2007. Influence of endogenous and exogenous sex hormones on plasma brain-derived neurotrophic factor. Hum. Reprod. 22 (4), 995–1002. https://doi.org/10.1093/humrep/del479.

Bergemann, N., Mundt, C., Parzer, P., Jannakos, I., Nagl, I., Salbach, B., Resch, F., 2005. Plasma concentrations of estradiol in women suffering from schizophrenia treated with conventional versus atypical antipsychotics. Schizophr. Res. 73 (2–3), 357–366. https://doi.org/10.1016/j.schres.2004.06.013.

Bergemann, N., Parzer, P., Jaggy, S., Auler, B., Mundt, C., Maier-Braunleder, S., 2008. Estrogen and comprehension of metaphoric speech in women suffering from schizophrenia: results of a double-blind, placebo-controlled trial. Schizophr. Bull. 34 (6), 1172–1181. https://doi.org/10.1093/schbul/sbm138.

Bergemann, N., Parzer, P., Nagl, I., Salbach, B., Runnebaum, B., Mundt, C., Resch, F., 2002. Acute psychiatric admission and menstrual cycle phase in women with schizophrenia. Arch. Womens Ment. Health 5 (3), 119–126. https://doi.org/10.1007/s00737-002-0004-2.

Bergemann, N., Parzer, P., Runnebaum, B., Resch, F., Mundt, C., 2007. Estrogen, menstrual cycle phases, and psychopathology in women suffering from schizophrenia. Psychol. Med. 37 (10), 1427–1436. https://doi.org/10.1017/S0033291707000578.

Bi, R., Foy, M.R., Vouimba, R.M., Thompson, R.F., Baudry, M., 2001. Cyclic changes in estradiol regulate synaptic plasticity through the MAP kinase pathway. Proc. Natl. Acad. Sci. U.S.A. 98 (23), 13391–13395. https://doi.org/10.1073/pnas.241507698.

Blair, D.T., Dauner, A., 1992. Extrapyramidal symptoms are serious side-effects of antipsychotic and other drugs. Nurse Pract. 17 (11).

Blum, B.P., Mann, J.J., 2002. The GABAergic system in schizophrenia. Int. J. Neuropsychopharmacol. 5 (2), 159–179. https://doi.org/10.1017/S1461145702002894.

Boerrigter, D., Weickert, T.W., Lenroot, R., O'Donnell, M., Galletly, C., Liu, D., Weickert, C.S., 2017. Using blood cytokine measures to define high inflammatory biotype of schizophrenia and schizoaffective disorder. J. Neuroinflam. 14 (1), 188. https://doi.org/10.1186/s12974-017-0962-y.

Buchanan, R.W., Kreyenbuhl, J., Kelly, D.L., Noel, J.M., Boggs, D.L., Fischer, B.A., Schizophrenia Patient Outcomes Research, T., 2010. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr. Bull. 36 (1), 71–93. https://doi.org/10.1093/schbul/sbp116.

Calabrese, F., Riva, M.A., Molteni, R., 2016. Synaptic alterations associated with depression and schizophrenia: potential as a therapeutic target. Expert Opin. Ther. Targets 20 (10), 1195–1207. https://doi.org/10.1080/14728222.2016.1188080.

Canuso, C.M., Goldstein, J.M., Wojcik, J., Dawson, R., Brandman, D., Klibanski, A., Green, A.I., 2002. Antipsychotic medication, prolactin elevation, and ovarian function in women with schizophrenia and schizoaffective disorder. Psychiatry Res. 111 (1), 11–20.

Canuso, C.M., Pandina, G., 2007. Gender and schizophrenia. Psychopharmacol. Bull. 40 (4), 178–190.

Carson, C.M., Phillip, N., Miller, B.J., 2017. Urinary tract infections in children and adolescents with acute psychosis. Schizophr. Res. 183, 36–40. https://doi.org/10.1016/j.schres.2016.11.004.

Charlson, F.J., Ferrari, A.J., Santomauro, D.F., Diminic, S., Stockings, E., Scott, J.G., Whiteford, H.A., 2018. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. Schizophr. Bull. https://doi.org/10.1093/schbul/sby058.

Chen, H., Qian, M., Shen, X., Yang, S., Yang, J., Song, J., Shen, Z., 2013. Risk factors for medication-induced amenorrhea in first-episode female Chinese patients with schizophrenia treated with risperidone. Shanghai Arch. Psychiatry 25 (1), 40–47. https://doi.org/10.3969/j.issn.1002-0829.2013.01.008.

Cohen, R.Z., Seeman, M.V., Gotowiec, A., Kopala, L., 1999. Earlier puberty as a predictor of later onset of schizophrenia in women. Am. J. Psychiatry 156 (7), 1059–1064.

Cotton, S.M., Lambert, M., Schimmelmann, B.G., Foley, D.L., Morley, K.I., McGorry, P.D., Conus, P., 2009. Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis. Schizophr. Res. 114 (1–3), 17–24. https://doi.org/10.1016/j.schres.2009.07.002.

Coyle, J.T., 2004. The GABA-glutamate connection in schizophrenia: which is the proximate cause? Biochem. Pharmacol. 68 (8), 1507–1514. https://doi.org/10.1016/j.bcp.2004.07.034.

Cummings, S.R., Duong, T., Kenyon, E., Cauley, J.A., Whitehead, M., Krueger, K.A., Multiple Outcomes of Raloxifene Evaluation, T., 2002. Serum estradiol level and risk of breast cancer during treatment with raloxifene. JAMA 287 (2), 216–220.

Cyr, M., Calon, F., Morissette, M., Di Paolo, T., 2002. Estrogenic modulation of brain activity: implications for schizophrenia and Parkinson's disease. J. Psychiatry Neurosci. 27 (1), 12–27.

de Boer, J., Prikken, M., Lei, W.U., Begemann, M., Sommer, I., 2018. The effect of raloxifene augmentation in men and women with a schizophrenia spectrum disorder: a systematic review and meta-analysis. NPJ Schizophr. 4 (1), 1. https://doi.org/10.1038/s41537-017-0043-3.

Di Paolo, T., 1994. Modulation of brain dopamine transmission by sex steroids. Rev. Neurosci. 5 (1), 27–41.

Du, X., Serena, K., Hwang, W., Grech, A.M., Wu, Y.W.C., Schroeder, A., Hill, R.A., 2018. Prefrontal cortical parvalbumin and somatostatin expression and cell density increase during adolescence and are modified by BDNF and sex. Mol. Cell. Neurosci. 88, 177–188. https://doi.org/10.1016/j.mcn.2018.02.001.

Engler-Chiurazzi, E., Tsang, C., Nonnenmacher, S., Liang, W.S., Corneveaux, J.J., Prokai, L., Bimonte-Nelson, H.A., 2011. Tonic Premarin dose-dependently enhances memory, affects neurotrophin protein levels and alters gene expression in middle-aged rats. Neurobiol. Aging 32 (4), 680–697. https://doi.org/10.1016/j.neurobiolaging.2009.09.005.

Enomoto, T., Tse, M.T., Floresco, S.B., 2011. Reducing prefrontal gamma-aminobutyric acid activity induces cognitive, behavioral, and dopaminergic abnormalities that resemble schizophrenia. Biol. Psychiatry 69 (5), 432–441. https://doi.org/10.1016/j.biopsych.2010.09.038.

Ghafari, E., Fararouie, M., Shirazi, H.G., Farhangfar, A., Ghaderi, F., Mohammadi, A., 2013. Combination of estrogen and antipsychotics in the treatment of women with chronic schizophrenia: a double-blind, randomized, placebo-controlled clinical trial. Clin. Schizophr. Relat. Psychoses 6 (4), 172–176. https://doi.org/10.3371/CSRP.GHFA.01062013.

Gibbs, R.B., 1999. Treatment with estrogen and progesterone affects relative levels of brain-derived neurotrophic factor mRNA and protein in different regions of the adult rat brain. Brain Res. 844 (1–2), 20–27.

Gleeson, P.C., Worsley, R., Gavrilidis, E., Nathoo, S., Ng, E., Lee, S., Kulkarni, J., 2015. Menstrual cycle characteristics in women with persistent schizophrenia. Aust. N. Z. J. Psychiatry. https://doi.org/10.1177/0004867415590459.

Global Burden of Disease Study, C, 2015. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of

Disease Study 2013. Lancet 386 (9995), 743–800. https://doi.org/10.1016/S0140-6736(15)60692-4.

Gonzalez-Blanco, L., Greenhalgh, A.M.D., Garcia-Rizo, C., Fernandez-Egea, E., Miller, B.J., Kirkpatrick, B., 2016. Prolactin concentrations in antipsychotic-naive patients with schizophrenia and related disorders: a meta-analysis. Schizophr. Res. 174 (1–3), 156–160. https://doi.org/10.1016/j.schres.2016.03.018.

Gonzalez-Rodriguez, A., Catalan, R., Penades, R., Ruiz Cortes, V., Torra, M., Seeman, M.V., Bernardo, M., 2016. Antipsychotic response worsens with postmenopausal duration in women with schizophrenia. J. Clin. Psychopharmacol. 36 (6), 580–587. https://doi.org/10.1097/JCP.0000000000000571.

Graham, K.L., Carson, C.M., Ezeoke, A., Buckley, P.F., Miller, B.J., 2014. Urinary tract infections in acute psychosis. J. Clin. Psychiatry 75 (4), 379–385. https://doi.org/10.4088/JCP.13m08469.

Green, M.F., Kern, R.S., Heaton, R.K., 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr. Res. 72 (1), 41–51. https://doi.org/10.1016/j.schres.2004.09.009.

Grigg, J., Worsley, R., Kulkarni, J., 2017. Raloxifene for schizophrenia and symptoms of hyperprolactinaemia? Aust. N. Z. J. Psychiatry 51 (3), 294. https://doi.org/10.1177/0004867416670014.

Grigoriadis, S., Seeman, M.V., 2002. The role of estrogen in schizophrenia: implications for schizophrenia practice guidelines for women. Can. J. Psychiatry 47 (5), 437–442. https://doi.org/10.1177/070674370204700504.

Gurvich, C., Gavrilidis, E., Worsley, R., Hudaib, A., Thomas, N., Kulkarni, J., 2018. Menstrual cycle irregularity and menopause status influence cognition in women with schizophrenia. Psychoneuroendocrinology 96, 173–178. https://doi.org/10.1016/j.psyneuen.2018.06.022.

Gustavsson, A., Svensson, M., Jacobi, F., Allgulander, C., Alonso, J., Beghi, E., Group, C.D., 2011. Cost of disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol. 21 (10), 718–779. https://doi.org/10.1016/j.euroneuro.2011.08.008.

Hafner, H., 2003. Gender differences in schizophrenia. Psychoneuroendocrinology 28 (Suppl 2), 17–54.

Hafner, H., Riecher-Rossler, A., Maurer, K., Fatkenheuer, B., Loffler, W., 1992. First onset and early symptomatology of schizophrenia. A chapter of epidemiological and neurobiological research into age and sex differences. Eur. Arch. Psychiatry Clin. Neurosci. 242 (2–3), 109–118.

Herceg, M., Puljic, K., Sisek-Sprem, M., Herceg, D., 2018. Influence of hormonal status and menstrual cycle phase on psychopatology in acute admitted patients with schizophrenia. Psychiatr. Danub. 30 (Suppl 4), 175–179.

Hill, R.A., 2012. Interaction of sex steroid hormones and brain-derived neurotrophic factor-tyrosine kinase B signalling: relevance to schizophrenia and depression. J. Neuroendocrinol. 24 (12), 1553–1561. https://doi.org/10.1111/j.1365-2826.2012.02365.x.

Hochman, K.M., Lewine, R.R., 2004. Age of menarche and schizophrenia onset in women. Schizophr. Res. 69 (2–3), 183–188.

Ittig, S., Studerus, E., Heitz, U., Menghini-Muller, S., Beck, K., Egloff, L., Riecher-Rossler, A., 2017. Sex differences in prolactin levels in emerging psychosis: indication for enhanced stress reactivity in women. Schizophr. Res. 189, 111–116. https://doi.org/10.1016/j.schres.2017.02.010.

Johns, L., Sinclair, A.J., Davies, J.A., 2002. Effects of bilobalide on hypoxia/hypoglycemia-stimulated glutamate efflux from rat cortical brain slices. Neurochem. Res. 27 (5), 369–371.

Kapur, S., Roy, P., Daskalakis, J., Remington, G., Zipursky, R., 2001. Increased dopamine d(2) receptor occupancy and elevated prolactin level associated with addition of haloperidol to clozapine. Am. J. Psychiatry 158 (2), 311–314. https://doi.org/10.1176/appi.ajp.158.2.311.

Kilicaslan, E.E., Erol, A., Zengin, B., Cetinay Aydin, P., Mete, L., 2014. Association between age at onset of schizophrenia and age at menarche. Noro Psikiyatr Ars 51 (3), 211–215. https://doi.org/10.4274/npa.y6675.

Kinon, B.J., Gilmore, J.A., Liu, H., Halbreich, U.M., 2003. Prevalence of hyperprolactinemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone. Psychoneuroendocrinology 28 (Suppl 2), 55–68.

Kishimoto, T., De Hert, M., Carlson, H.E., Manu, P., Correll, C.U., 2012. Osteoporosis and fracture risk in people with schizophrenia. Curr. Opin. Psychiatry 25 (5), 415–429. https://doi.org/10.1097/YCO.0b013e328355e1ac.

Knapp, M., Mangalore, R., Simon, J., 2004. The global costs of schizophrenia. Schizophr. Bull. 30 (2), 279–293.

Ko, Y.H., Joe, S.H., Cho, W., Park, J.H., Lee, J.J., Jung, I.K., Kim, S.H., 2006. Estrogen, cognitive function and negative symptoms in female schizophrenia. Neuropsychobiology 53 (4), 169–175. https://doi.org/10.1159/000093780.

Kockott, G., Pfeiffer, W., 1996. Sexual disorders in nonacute psychiatric outpatients. Compr. Psychiatry 37 (1), 56–61.

Kulkarni, J., de Castella, A., Smith, D., Taffe, J., Keks, N., Copolov, D., 1996. A clinical trial of the effects of estrogen in acutely psychotic women. Schizophr. Res. 20 (3), 247–252.

Kulkarni, J., Gavrilidis, E., Gwini, S.M., Worsley, R., Grigg, J., Warren, A., Davis, S.R., 2016. Effect of adjunctive raloxifene therapy on severity of refractory schizophrenia in women: a randomized clinical trial. JAMA Psychiatry 73 (9), 947–954. https://doi.org/10.1001/jamapsychiatry.2016.1383.

Kulkarni, J., Gavrilidis, E., Wang, W., Worsley, R., Fitzgerald, P.B., Gurvich, C., Burger, H., 2015. Estradiol for treatment-resistant schizophrenia: a large-scale randomized-controlled trial in women of child-bearing age. Mol. Psychiatry 20 (6), 695–702. https://doi.org/10.1038/mp.2014.33.

Kulkarni, J., Gurvich, C., Lee, S.J., Gilbert, H., Gavrilidis, E., de Castella, A., Davis, S.R., 2010. Piloting the effective therapeutic dose of adjunctive selective estrogen receptor modulator treatment in postmenopausal women with schizophrenia. Psychoneuroendocrinology 35 (8), 1142–1147. https://doi.org/10.1016/j.psyneuen.2010.01.014.

Kulkarni, J., Riedel, A., de Castella, A.R., Fitzgerald, P.B., Rolfe, T.J., Taffe, J., Burger, H., 2001. Estrogen – a potential treatment for schizophrenia. Schizophr. Res. 48 (1), 137–144.

Kurata, K., Takebayashi, M., Morinobu, S., Yamawaki, S., 2004. beta-estradiol, dehydroepiandrosterone, and dehydroepiandrosterone sulfate protect against N-methyl-D-aspartate-induced neurotoxicity in rat hippocampal neurons by different mechanisms. J. Pharmacol. Exp. Ther. 311 (1), 237–245. https://doi.org/10.1124/jpet.104.067629.

Lally, J., MacCabe, J.H., 2015. Antipsychotic medication in schizophrenia: a review. Br. Med. Bull. 114 (1), 169–179. https://doi.org/10.1093/bmb/ldv017.

Lan, Y.L., Zhao, J., Li, S., 2014. Estrogen receptors' neuroprotective effect against glutamate-induced neurotoxicity. Neurol. Sci. 35 (11), 1657–1662. https://doi.org/10.1007/s10072-014-1937-8.

Liu, F., Day, M., Muniz, L.C., Bitran, D., Arias, R., Revilla-Sanchez, R., Brandon, N.J., 2008. Activation of estrogen receptor-beta regulates hippocampal synaptic plasticity and improves memory. Nat. Neurosci. 11 (3), 334–343. https://doi.org/10.1038/nn2057.

Manson, J.E., Chlebowski, R.T., Stefanick, M.L., Aragaki, A.K., Rossouw, J.E., Prentice, R.L., Wallace, R.B., 2013. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 310 (13), 1353–1368. https://doi.org/10.1001/jama.2013.278040.

Marcellusi, A., Fabiano, G., Viti, R., Francesa Morel, P.C., Nicolo, G., Siracusano, A., Mennini, F.S., 2018. Economic burden of schizophrenia in Italy: a probabilistic cost of illness analysis. BMJ Open 8 (2), e018359. https://doi.org/10.1136/bmjopen-2017-018359.

Marques, T.R., Ashok, A.H., Pillinger, T., Veronese, M., Turkheimer, F.E., Dazzan, P., Howes, O.D., 2018. Neuroinflammation in schizophrenia: meta-analysis of in vivo microglial imaging studies. Psychol. Med. 1–11. https://doi.org/10.1017/S0033291718003057.

Melkersson, K.I., Hulting, A.L., Rane, A.J., 2001. Dose requirement and prolactin elevation of antipsychotics in male and female patients with schizophrenia or related psychoses. Br. J. Clin. Pharmacol. 51 (4), 317–324.

Mitlak, B.H., Cohen, F.J., 1999. Selective estrogen receptor modulators: a look ahead. Drugs 57 (5), 653–663.

Morgan, V.A., Castle, D.J., Jablensky, A.V., 2008. Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders. Aust. N. Z. J. Psychiatry 42 (1), 74–82. https://doi.org/10.1080/00048670701732699.

Muchmore, D.B., 2000. Raloxifene: a selective estrogen receptor modulator (SERM) with multiple target system effects. Oncologist 5 (5), 388–392.

Osimo, E.F., Beck, K., Reis Marques, T., Howes, O.D., 2018. Synaptic loss in schizophrenia: a meta-analysis and systematic review of synaptic protein and mRNA measures. Mol. Psychiatry. https://doi.org/10.1038/s41380-018-0041-5.

Pan, Y., Anthony, M., Clarkson, T.B., 1999. Evidence for up-regulation of brain-derived neurotrophic factor mRNA by soy phytoestrogens in the frontal cortex of retired breeder female rats. Neurosci. Lett. 261 (1–2), 17–20.

Pasqualini, C., Olivier, V., Guibert, B., Frain, O., Leviel, V., 1995. Acute stimulatory effect of estradiol on striatal dopamine synthesis. J. Neurochem. 65 (4), 1651–1657.

Petrikis, P., Tigas, S., Tzallas, A.T., Archimandriti, D.T., Skapinakis, P., Mavreas, V., 2016. Prolactin levels in drug-naive patients with schizophrenia and other psychotic disorders. Int. J. Psychiatry Clin. Pract. 20 (3), 165–169. https://doi.org/10.1080/13651501.2016.1197274.

Pozzi, S., Benedusi, V., Maggi, A., Vegeto, E., 2006. Estrogen action in neuroprotection and brain inflammation. Ann. N. Y. Acad. Sci. 1089, 302–323. https://doi.org/10.1196/annals.1386.035.

Rao, M.L., Kolsch, H., 2003. Effects of estrogen on brain development and neuroprotection–implications for negative symptoms in schizophrenia. Psychoneuroendocrinology 28 (Suppl 2), 83–96.

Riecher-Rossler, A., 2002. Oestrogen effects in schizophrenia and their potential therapeutic implications–review. Arch. Womens Ment. Health 5 (3), 111–118. https://doi.org/10.1007/s00737-002-0003-3.

Riecher-Rossler, A., Hafner, H., 1993. Schizophrenia and oestrogens–is there an association? Eur. Arch. Psychiatry Clin. Neurosci. 242 (6), 323–328.

Riecher-Rossler, A., Hafner, H., Dutsch-Strobel, A., Oster, M., Stumbaum, M., van Gulick-Bailer, M., Loffler, W., 1994a. Further evidence for a specific role of estradiol in schizophrenia? Biol. Psychiatry 36 (7), 492–494.

Riecher-Rossler, A., Hafner, H., Stumbaum, M., Maurer, K., Schmidt, R., 1994b. Can estradiol modulate schizophrenic symptomatology? Schizophr. Bull. 20 (1), 203–214.

Riecher-Rossler, A., Rybakowski, J.K., Pflueger, M.O., Beyrau, R., Kahn, R.S., Malik, P., Group, E.S., 2013. Hyperprolactinemia in antipsychotic-naive patients with first-episode psychosis. Psychol. Med. 43 (12), 2571–2582. https://doi.org/10.1017/S0033291713000226.

Rossouw, J.E., Anderson, G.L., Prentice, R.L., LaCroix, A.Z., Kooperberg, C., Stefanick, M.L., Writing Group for the Women's Health Initiative, I., 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 288 (3), 321–333.

Rubin, L.H., Carter, C.S., Drogos, L., Pournajafi-Nazarloo, H., Sweeney, J.A., Maki, P.M., 2010. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. Schizophr. Res. 124 (1–3), 13–21. https://doi.org/10.1016/j.schres.2010.09.014.

Saha, S., Chant, D., Welham, J., McGrath, J., 2005. A systematic review of the prevalence of schizophrenia. PLoS Med. 2 (5), e141. https://doi.org/10.1371/journal.pmed.0020141.

Scharfman, H.E., MacLusky, N.J., 2006. Estrogen and brain-derived neurotrophic factor (BDNF) in hippocampus: complexity of steroid hormone-growth factor interactions in the adult CNS. Front. Neuroendocrinol. 27 (4), 415–435. https://doi.org/10.1016/j.yfrne.2006.09.004.

Schroeder, A., Hudson, M., Du, X., Wu, Y.W.C., Nakamura, J., van den Buuse, M., Hill, R.A., 2017. Estradiol and raloxifene modulate hippocampal gamma oscillations during a spatial memory task. Psychoneuroendocrinology 78, 85–92. https://doi.org/10.1016/j.psyneuen.2017.01.022.

Smith, S., Wheeler, M.J., Murray, R., O'Keane, V., 2002. The effects of antipsychotic-induced hyperprolactinaemia on the hypothalamic-pituitary-gonadal axis. J. Clin. Psychopharmacol. 22 (2), 109–114.

Tonn Eisinger, K.R., Gross, K.S., Head, B.P., Mermelstein, P.G., 2018. Interactions between estrogen receptors and metabotropic glutamate receptors and their impact on drug addiction in females. Horm. Behav. https://doi.org/10.1016/j.yhbeh.2018.03.001.

Tseng, P.T., Chen, Y.W., Yeh, P.Y., Tu, K.Y., Cheng, Y.S., Wu, C.K., 2015. Bone mineral density in schizophrenia: an update of current meta-analysis and literature review under guideline of PRISMA. Medicine (Baltimore) 94 (47), e1967. https://doi.org/10.1097/MD.0000000000001967.

Vegeto, E., Belcredito, S., Etteri, S., Ghisletti, S., Brusadelli, A., Meda, C., Maggi, A., 2003. Estrogen receptor-alpha mediates the brain antiinflammatory activity of estradiol. Proc. Natl. Acad. Sci. U.S.A. 100 (16), 9614–9619. https://doi.org/10.1073/pnas.1531957100.

Weickert, T.W., Weinberg, D., Lenroot, R., Catts, S.V., Wells, R., Vercammen, A., Weickert, C.S., 2015. Adjunctive raloxifene treatment improves attention and memory in men and women with schizophrenia. Mol. Psychiatry 20 (6), 685–694. https://doi.org/10.1038/mp.2015.11.

Woolley, C.S., McEwen, B.S., 1994. Estradiol regulates hippocampal dendritic spine density via an N-methyl-D-aspartate receptor-dependent mechanism. J. Neurosci. 14 (12), 7680–7687.

Woolley, C.S., Weiland, N.G., McEwen, B.S., Schwartzkroin, P.A., 1997. Estradiol increases the sensitivity of hippocampal CA1 pyramidal cells to NMDA receptor-mediated synaptic input: correlation with dendritic spine density. J. Neurosci. 17 (5), 1848–1859.

Wu, Y.C., Du, X., van den Buuse, M., Hill, R.A., 2014. Sex differences in the adolescent developmental trajectory of parvalbumin interneurons in the hippocampus: a role for estradiol. Psychoneuroendocrinology 45, 167–178. https://doi.org/10.1016/j.psyneuen.2014.03.016.

Wu, Y.C., Hill, R.A., Gogos, A., van den Buuse, M., 2013. Sex differences and the role of estrogen in animal models of schizophrenia: interaction with BDNF. Neuroscience 239, 67–83. https://doi.org/10.1016/j.neuroscience.2012.10.024.

Yuan, X.X., Zhu, Q.Y., Liang, H.B., Hei, G.R., Li, X., Pang, L.J., Song, X.Q., 2016. Correlations between hormone levels and psychiatric symptoms as well as cognitive function in drug-free first-episode schizophrenics. Zhonghua Yi Xue Za Zhi 96 (27), 2155–2160. https://doi.org/10.3760/cma.j.issn.0376-2491.2016.27.009.

Zhu, X.M., Zheng, W., Li, X.H., Cai, D.B., Yang, X.H., Ungvari, G.S., Xiang, Y.T., 2018. Adjunctive raloxifene for postmenopausal women with schizophrenia: a meta-analysis of randomized, double-blind, placebo-controlled trials. Schizophr. Res. https://doi.org/10.1016/j.schres.2018.01.017.