Women's mental health 1

Oestrogens, prolactin, hypothalamic-pituitary-gonadal axis, and schizophrenic psychoses

Anita Riecher-Rössler

Interest is growing in the potential effect of gonadal hormones, prolactin, and the hypothalamic–pituitary–gonadal axis in schizophrenic psychoses. Many studies from clinical, epidemiological, and fundamental research have confirmed that oestradiol, the main component of oestrogens, can have protective effects in schizophrenic psychoses. Furthermore, many patients with schizophrenic psychoses—even in the untreated prodromal stages—have hyperprolactinaemia and gonadal dysfunction, with oestrogen deficiency in women and testosterone deficiency in men. The understanding of the pathogenetic mechanisms underlying these findings could contribute to a better understanding of the aetiopathogenesis of schizophrenic psychoses and improve therapeutic approaches. In this Series paper, we aim to review methodologically sound studies in this area, propose a theory to explain these findings in the context of psychosis, and suggest therapeutic strategies and implications for further research.

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This is the first of a Series of four papers on Women's mental health

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Introduction

Schizophrenic psychoses still pose many challenges to psychiatry. We do not yet fully understand the aetiopathogenetic mechanisms of these disorders, nor can we sufficiently treat them, especially with regards to cognitive and negative symptoms. The cognitive symptoms are often the main obstacles to a full recovery. Outcomes of research on oestrogens, prolactin, and the hypothalamic–pituitary–gonadal axis might give us some important insights and offer therapeutic possibilities.

On the one hand, numerous clinical, epidemiological, and fundamental research studies have shown that oestradiol, the main component of oestrogens, has protective effects in schizophrenic psychoses.[1–4] On the other hand, gonadal dysfunction, hyperprolactinaemia, and states of oestrogen deficiency in women with schizophrenia have been reported.[1–4] These observations led us to formulate the hypotheses of (1) oestrogen protection and (2) hypo-oestrogenism and gonadal dysfunction in schizophrenic psychoses.[1,2]

Growing evidence for hyperprolactinaemia has also emerged in many patients with psychosis who are antipsychotic-naive and even in individuals with an at-risk mental state.[5–9] Since prolactin suppresses the production of gonadal hormones such as oestrogens and testosterone, this hyperprolactinaemia could explain these hormonal deficiencies. Furthermore, hyperprolactinaemia could contribute to explaining how stress can trigger the outbreak of psychosis in vulnerable individuals, as formulated in the stress–prolactin–dopamine hypothesis.[5]

This Series paper will give an update on studies investigating three hypotheses (oestrogen protection, hypo-oestrogenism and hypothalamic–pituitary–gonadal dysfunction, and stress–prolactin–dopamine) with a focus on clinical studies. Implications for the clinic and for research will be described.

The oestrogen protection hypothesis

Epidemiological and clinical studies

The hypothesis of oestrogens being protective against psychosis, first mentioned in the middle of the past century,[1,2] has since gained support from many epidemiological and clinical studies.

Oestrogen withdrawal can cause psychosis in formerly healthy individuals, known as premenstrual psychosis, post-abortion psychosis, and psychoses associated with the removal of a hydatidiform mole, discontinuation of oral contraceptives, administration of clomifene or tamoxifen (both oestrogen receptor antagonists), or a gonadorelin agonist (which blocks pituitary stimulation of endogenous oestrogen secretion). These psychotic episodes are typically acute, short, and show an extensive range of psychotic and affective symptoms. Patients sometimes have a history of post-partum psychosis (ie, women seem to be sensitive to withdrawal of oestrogens) and usually remit with oestrogen substitution.[10]

With regards to schizophrenic psychoses, clear sex differences might partly be attributed to the influence of sex hormones. Thus, women seem to have a slightly lower incidence of schizophrenic psychoses than men.[11] The incidence is particularly low in women younger than 40 years, corresponding to a delayed age of onset, but higher thereafter.[11–13] Furthermore, the course of the disease is more favourable in younger women than in those older than 40 years.[12,13] The ABC study[14,15] was an epidemiological study on a representative sample of 392 first-time admitted patients with schizophrenia. We found that women had a later peak of illness onset than did men. Women also exhibited an additional, smaller peak of illness onset after age 45 years (figure 1). After we excluded psychosocial factors as explanations, we suggested that the production of physiologically high oestradiol in young and fertile women delays the onset and improves the course of schizophrenia in women up until menopause. Then, before and around menopause

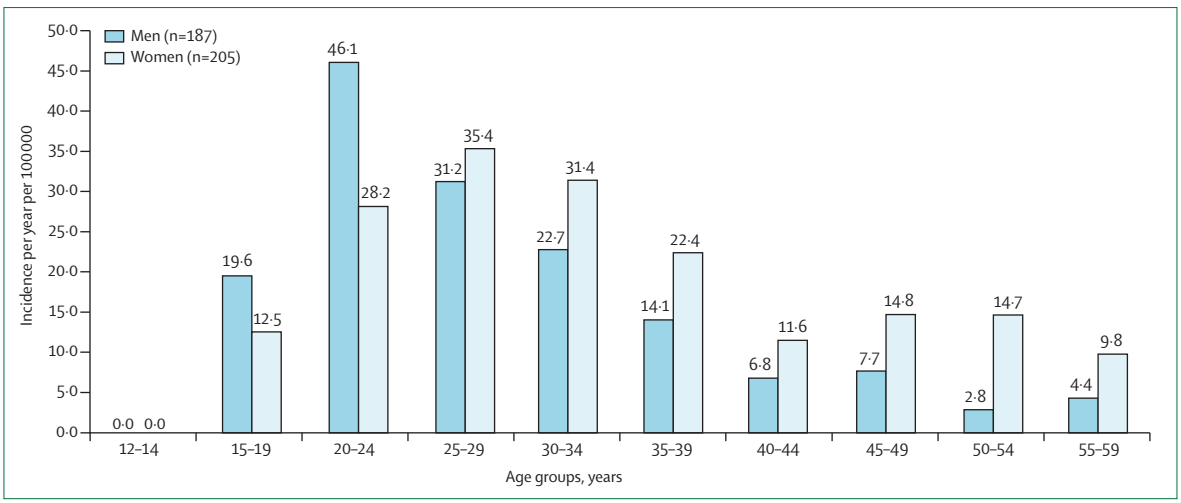

Figure 1: **Sex-specific distribution at first admission for schizophrenia—broad definition, ICD-9: 295, 297, 298.3, 298.4**
Data are all admissions in a defined catchment area in and around Mannheim, Germany, in 1987 and 1988. Data compiled from Häfner and colleagues.[14]

the drop of oestrogens leads to the second peak of onsets in women and to the poorer course of the disease in elderly women.[12,13,15]

Studies of late-onset schizophrenia are consistent with these fingings.[12,13,16] We have shown that there are twice as many women as men with onset of schizophrenic psychoses beyond age 40 years—8·9 per 100 000 women per year, but only 4·2 per 100 000 men per year in the age group 40–59 years.[12] Furthermore, symptomatology and disease course are unexpectedly severe in women with this late onset.[12,13,16] Similarly, results from our long-term studies on earlier onset schizophrenia (before age 40 years) showed that in women the course of illness tends to deteriorate rapidly after menopause.[1,17]

There might be different subgroups of schizophrenic psychoses, not all of which are affected by oestrogens. Hence, the sex difference in the age of onset seems smaller in the subgroup of patients with a genetic risk or perinatal complications than in patients without these risk factors.[18]

Studies on the age at menarche also suggest a protective effect of oestrogens. Thus, later menarche—ie, later rise of oestrogen levels—seems to be associated with an earlier onset of the disorder.[19,20] In line with this, we found a significantly later age of menarche in women with schizophrenic psychoses than in healthy controls.[21]

Clinically, psychotic symptomatology in women often correlates with the oestrogenic state.[1–3] Thus, chronic psychoses appear to improve during pregnancy, when oestrogen concentrations are increased by about 100 times to 200 times, whereas after delivery, which is accompanied by a sudden drop of oestrogens, there is marked excess of psychoses.[22]

In patients with schizophrenia, psychotic symptoms often deteriorate premenstrually or perimenstrually (ie, in the low-oestrogen phase of the cycle).[3,4,21] We showed not only a significant excess of patient admissions during the perimenstrual low-oestrogen phase of the cycle, but also an inverse correlation of oestradiol concentrations in the blood with psychopathology.[23,24] When oestradiol concentrations in the blood increased naturally during the cycle, there appeared to be an improvement in psychotic and total symptomatology, and vice versa.

Many other investigators have also reported a significant association between the menstrual cycle phase and 17-β-oestradiol concentrations on cognition and on positive and negative symptoms.[3,4]

However, effects of oestrogens might not be specific for psychosis. For example, an increased number of patient admissions during the perimenstrual period has been found independent of diagnosis for other disorders.[3] In patients with schizophrenia, an exacerbation of many psychiatric symptoms, not only psychotic symptoms, has been observed during the perimenstrual period.[3] This lack of specificity is expected because of the multiple effects of oestrogens on mental functioning.

Oestrogen effects in the brain

The aetiopathogenesis of schizophrenic psychoses is widely considered to involve mainly neurodevelopmental abnormalities, but also neurodegenerative changes in the brain, as well as neurotransmitter dysfunctions. Oestrogens seem to be able to influence all these domains.

In animals, oestrogens and testosterone strongly affect brain development during late gestation, in the early postnatal period, and around puberty. Along with others, they affect sexual dimorphism—ie, structural differences between normal male and female brains.[25,26] This dimorphism might be disrupted in schizophrenic psychoses.[27,28]

Additionally, oestrogens have many neuroprotective effects. The most active natural oestrogen in the brain, 17-β-oestradiol, promotes neuronal sprouting and

myelination, enhances synaptic density and plasticity, facilitates neuronal connectivity, acts as an anti-inflammatory and as an antioxidant, inhibits neuronal cell death, and improves cerebral blood flow and glucose metabolism.[17,25,26,29–31] Furthermore, oestrogens might mediate BDNF expression and activity.[32]

Circulating oestrogens also modulate the dopaminergic and other neurotransmitter systems relevant to schizophrenic psychoses, such as the serotonergic, glutamatergic, noradrenergic, and cholinergic systems,[2,33,34] and can modulate the sensitivity and number of dopamine receptors.[2,33] Some authors have even suggested that 17-β-oestradiol in the brain should be regarded as a neurotransmitter itself.[35]

In different animal models, oestrogens show similar effects on animal behaviour to those of antipsychotics.[1,2] They also positively influence many pathologies associated with schizophrenia, such as disturbances of latent inhibition, prepulse inhibition, auditory processing or mismatch negativity, and selective attention.[4,36–38]

Oestrogens not only act via the classic genomic pathway, but also show non-genomic, rapid interactions.[29,39] At least two subtypes of oestrogen receptors are known, namely oestrogen receptor-α and oestrogen receptor-β.[40] These receptors are expressed in several areas of the human brain that are associated with neuroendocrine function and with emotion, memory, and cognition.[29] Variations in the oestrogen receptor-α (ESR1) have been associated with schizophrenia.[41,42] Some authors suggested that the brain response to oestrogens in patients with schizophrenia might be inadequate.[4,31] More details on recent molecular and preclinical findings are given in a comprehensive review by Gogos and colleagues.[34]

Intervention studies with oestrogens

Several intervention studies with oestrogens, especially with oestradiol, have shown positive results in women with schizophrenic psychoses.[1,3,43–45]

Kulkarni and colleagues[3,46–49] were the first to conduct systematic trials. In different studies, they found that women with schizophrenia who received oestradiol as an adjunct to antipsychotics showed a more rapid and greater symptom improvement than did women taking antipsychotics alone. Patients receiving an oestradiol transdermal adjunct significantly improved in their total positive, negative, and general symptoms,[46,47,49] and also in cognition in one study.[48] Cognitive improvement would be in line with studies suggesting a positive effect of 17-β-oestradiol on cognitive function in healthy ageing women,[30,50] but could not be confirmed in their last study.[49]

Women with schizophrenia in the study by Akhondzadeh and colleagues[51] achieved positive effects also with ethinyl-oestradiol as an adjunct to haloperidol. Furthermore, these patients needed significantly less anticholinergic medication than did patients who received haloperidol alone, which is in line with other studies, suggesting that oestrogen treatment can ameliorate extrapyramidal side-effects.[3] Louza and colleagues[52] did not report a positive response to oestrogen treatment in their study, which might be because of their use of conjugated oestrogens rather than 17-β-oestradiol (the most active oestrogen in the brain).

In 2005, on the basis of the results of a Cochrane review[53] it was concluded that the effects of oestrogens were still unclear and that further, larger clinical trials were needed. However, the studies reviewed that had negative results did not use 17-β-oestradiol, but used conjugated oestrogens. Furthermore, to prevent endometrial hyperplasia, the oestrogens were usually combined with different progestogens, which unfortunately can counteract the positive effects of oestradiol in the brain.[4] Since the Cochrane review, two quantitative reviews on oestrogen augmentation, which included new randomised trials and applied stricter inclusion criteria, reported superior efficacy when antipsychotics were augmented with oestrogens as compared with antipsychotics alone. These effects were even larger when oestradiol was used in addition to antipsychotics.[43,44] Additionally, in a systematic review of 26 randomised trials on the efficacy of anti-inflammatory drugs to improve symptoms in patients with schizophrenia, Sommer and colleagues[45] found oestrogens to be one of three promising drugs, acknowledging that oestrogens not only have anti-inflammatory, but also have other properties.

Table 1 shows an overview on the randomised, double-blind, placebo-controlled trials on oestrogen augmentation in schizophrenic psychoses.[46–49,51,52,54]

Overall, the oestrogen protection hypothesis is supported by these studies. In particular, the addition of transdermally delivered 17-β-oestradiol to standard antipsychotics seems to be associated with a significant reduction of psychotic and other, particularly depressive, symptoms and potentially also with cognitive improvements in women with schizophrenic psychoses.

The greatest effect of oestrogen treatment would be expected to happen in postmenopausal women, who have oestrogen deficiency. However, most studies of oestrogen treatment have been done in young women. One exception is a small study by Good and colleagues[55] who examined postmenopausal women with schizophrenia. After receiving hormone replacement therapy (HRT) for 6 months, these women showed a significant improvement of verbal memory compared with women who did not receive HRT. Similarly, the results of a community study of postmenopausal women with schizophrenia who received HRT for gynaecological reasons showed less severe negative symptoms and these patients needed lower doses of antipsychotics than women with the same diagnosis but who did not receive HRT.[56]

In women with post-partum psychosis and sustained oestrogen deficiency, the substitution of 17-β-oestradiol produced a substantial antipsychotic effect within 1 week, without antipsychotics.[57]

	Population	Type of oestrogen	Number of patients given oestrogen	Number of patients given placebo	Weeks of treatment	Daily augmentation dose	Outcome measures	Results
Kulkarni et al (2001)[46]*	DSM-IV schizophrenia, schizophreniform, or schizoaffective disorder, active phase of illness	Two groups receiving oestradiol	24 (12 in 50 µg group and 12 in 100 µg group)	12	4	50 µg and 100 µg (both transdermal)	PANSS	Significant improvement of positive psychotic and general symptoms in both groups; in the 100 µg group also significant improvement of negative symptoms
Kulkarni et al (2008)[47] and Kulkarni (2009)[48]	DSM-IV schizophrenia, schizoaffective, or schizophreniform disorder, acute or chronic phase	Oestradiol	56	46	4	100 µg (transdermal)	PANSS	Significant improvement of positive psychotic and general psychopathological symptoms; significant improvement of cognition
Kulkarni et al (2015)[49]*	DSM-IV TR schizophrenia, schizoaffective or schizophreniform disorder, treatment resistant	Two groups receiving oestradiol	56 for 100 µg group and 62 for 200 µg group	62	8	100 µg and 200 µg (both transdermal)	PANSS, cognitive tests	Improvement of positive in particular, but also of general and total symptoms (stronger effect with 200 µg); no effect on cognition
Akhondzadeh et al (2003)[51]	DSM-IV chronic schizophrenia, active phase of illness	Ethinyl oestradiol	16	16	8	50 µg (oral)	PANSS	Significant improvement of positive, negative, and general symptoms
Louza et al (2004)[52]	DSM-IV schizophrenia, active phase of illness	Conjugated oestrogens	21	19	4	625 µg (oral)	Brief Psychiatric Rating Scale, Negative Symptom Rating Scale	No response
Ghafari et al (2013)[54]	DSM-IV chronic schizophrenia	Conjugated oestrogens	16	16	4	625 µg (oral)	PANSS	Significant decrease in positive, negative, general, and total PANSS scores

PANSS=Positive and Negative Syndrome Scale. *Administered two different doses in different subsamples.

Table 1: **Randomised, double-blind, placebo-controlled trials on oestrogen augmentation in premenopausal women with schizophrenic psychoses**

By contrast with studies of women with schizophrenic psychoses, there are only a few small studies of male patients. In men, adjunctive oestradiol showed a significant reduction of psychotic symptoms compared with placebo.[3] However, long-term application is not possible because of the risk of feminisation. Testosterone augmentation improved negative, but not positive, symptoms in one study.[58]

The hypothesis of hypo-oestrogenism and hypothalamic–pituitary–gonadal dysfunction

Outcomes of many studies have in the meantime confirmed earlier findings of oestrogen deficiency and disturbed gonadal function in women with schizophrenia.[1,3–5,25,59] These studies reported menstrual irregularities and reduced concentrations of oestradiol, progesterone, and gonadotropins (follicle-stimulating hormone, luteinising hormone) in the blood throughout the menstrual cycle, as well as anovulation in many women with schizophrenic psychoses.

Furthermore, in men with (emerging) psychosis, blood levels of oestradiol[44,59–61] and testosterone[44,59–63] seem to be decreased. Fertility seems to be reduced in both sexes.[64]

One of the main reasons for gonadal dysfunction and hypo-oestrogenism is probably hyperprolactinaemia; increased prolactin blood levels have been found in many patients with schizophrenia[5] and it is well known that hyperprolactinaemia can suppress gonadal function.[4,65] Traditionally, hyperprolactinaemia in patients with psychosis has been interpreted as a side-effect of antipsychotics. However, increased prolactin concentrations or hyperprolactinaemia have been shown in patients who are antipsychotic-naive with first-episode psychosis or who have an at-risk mental state for psychosis, especially in female patients.[5–9]

Furthermore, hypo-oestrogenism was observed in people with psychosis long before the introduction of antipsychotics,[1,2] and oestradiol concentrations below normal were found irrespective of medication type or prolactin status in women[61,66] and men[61] with schizophrenia. Additionally, in patients with schizophrenia who were antipsychotic-free, low concentrations of oestrogens and testosterone have been shown;[60] low concentrations of testosterone were even present in adolescent boys with prodromal symptoms.[62] Women with first-episode psychosis, who were retrospectively interviewed regarding clinical signs of gonadal dysfunction before the onset of the disease, have reported such signs as mid-cycle bleedings, loss of hair, hirsutism, and infertility more often than a control group of age-matched healthy women.[21]

In accordance with this, reduced bone mineral density, one of the long-term consequences of gonadal suppression,[4] was found in women with first-episode psychosis, although they had only minimal previous exposure to antipsychotics.[67]

Of utmost interest in the context of hyperprolactinaemia is the finding of enlarged pituitary volumes in patients who were antipsychotic-free with first-episode psychosis or who were in an at-risk mental state, especially in those with a later transition to psychosis.[68] This finding might be

a further indication of an increased prolactin production during (emerging) psychosis, since an increase of prolactin production can enlarge the pituitary gland.[69]

All in all, there are many indications of a dysfunction of the hypothalamic–pituitary–gonadal axis with hyperprolactinaemia and deficient sex hormone production in—at least a subgroup of—patients with schizophrenic psychoses.

Implications for the clinic

Assessment and therapy of hyperprolactinaemia and gonadal dysfunction

In the future, oestrogens, prolactin, and the gonadal axis should be taken more seriously in the assessment and treatment of patients with schizophrenic psychoses.

Psychiatric history assessment should always include questions on galactorrhoea, sexual problems, and infertility in both sexes, and menstrual irregularities and amenorrhoea in women. If any of these symptoms or other clinical signs (panel 1)[17,61] are present (premature) gonadal insufficiency should be suspected. Gonadal insufficiency is due to hyperprolactinaemia in many cases, which might be a side-effect of certain antipsychotics but can occur independently of medication. Prolactin serum concentrations should therefore be tested in patients with these symptoms. Routine testing of prolactin has even been suggested in all patients with psychosis by some authors, preferably before being given antipsychotics[70] because gonadal dysfunction can often be found even in women who are menstruating[24,70] and hyperprolactinaemia might be underdiagnosed.[65]

In patients with schizophrenia, these concomitant risks of hyperprolactinaemia and gonadal dysfunction are often further increased by additional risk factors such as poor diet, smoking, and not enough regular exercise.[40,65,70]

In the case of hyperprolactinaemia, prolactin-sparing antipsychotics (eg, clozapine, quetiapine, aripiprazole, or olanzapine) should be the preferred pharmacological treatment option.[65] Before switching to prolactin-sparing antipsychotics, contraception counselling is mandatory since gonadal function often normalises in women with pre-existing gonadal suppression and fertility is regained, with a high risk of unplanned pregnancy.[17] If switching is not possible and if the patient has oestrogen deficiency, the hormone should be substituted in cooperation with a specialist.[71] The same might be true for testosterone, although much less research has been done on this. Furthermore, there might be cases with premature gonadal insufficiency without hyperprolactinaemia.

Oestradiol as a therapeutic drug?

Evidence that oestradiol could be used as an adjunct to antipsychotic medication even without an oestrogen deficiency state is increasing. Further replications of these findings in large controlled studies by different groups are urgently awaited.

In women with frequent perimenstrual relapses, continuous use of oral contraceptives without hormone-free intervals might be an option.[21]

In women with declining oestrogen production during perimenopause and postmenopause, hormonal replacement seems promising. It might augment the effect of the antipsychotics and thus minimise their dosage, and simultaneously reduce perimenopausal complaints such as hot flushes, night sweats with sleep disturbances, and general irritability (panel 2),[16,30,71–77] thereby contributing to general wellbeing and possibly to prevention of psychotic relapses. Furthermore, other positive effects of oestrogens, such as a positive influence on cognitive function[30,50] and on bone mineral density,[67,78] could be especially helpful in patients with psychosis of this age group. Despite these potentially helpful aspects, women with schizophrenia have so far been less likely to use HRT than mentally healthy women.[79]

Oestrogen replacement in perimenopause and postmenopause has been challenged by several studies,[80,81] especially by the Women's Mental Health Initiative (WHI) study,[80] because of suspected side-effects. However, the WHI study[80] was criticised by many experts[82–84] for method flaws, particularly the high age of the women studied (mean age 63 years) and their high prevalence of cardiovascular risk factors. Thus, many of the complications reported were probably associated with pre-existing risk factors. A reanalysis[74] of the WHI data could not confirm the complications, but rather showed a cardiovascular benefit when oestrogen replacement was started early after menopause. There seems to be a window of opportunity for starting hormone replacement.[72,74] Furthermore, the WHI study[80] had used continuous conjugated equine oestrogen rather than physiological oestradiol, although the latter is known to have less side-effects. The patients were given the drug orally rather than transdermally as recommended. It was also combined with the progestogen medroxyprogesterone acetate, which is probably responsible for the slightly increased risk of breast cancer if given for more than 7 years.[72] A protective effect on memory has been shown when treatment starts

***Panel 1*: Potential consequences of hyperprolactinaemia with gonadal suppression[17,61]**

- Galactorrhoea, mammary engorgement, possibly breast cancer
- Gonadal suppression with decline of oestrogen production in women and decline of testosterone production in men
  - Early consequences: loss of libido, orgasmic dysfunction (erectile dysfunction, disturbance of ejaculation, reduced spermatogenesis in men); reduced fertility; hot flushes, urogenital symptoms, dyspareunia in women; possibly depression; emotional lability and risk of relapse
  - Late consequences: osteopenia, osteoporosis, fragility fractures; cardiovascular risk, skin ageing, possibly cognitive disturbance

***Panel 2*: Important effects of oestrogen replacement in the menopause and suggested guidelines**[16,30,71–77]

Positive

Perimenopausal complaints reduced

- Physical: hot flushes, genital discomfort, ageing of collagen (skin, joints, intervertebral discs) reduced
- Mental: depression, irritability, emotional lability, psychotic symptoms reduced

Risk of osteoporosis and fragility fracture reduced

Possible delay of cognitive decline and Alzheimer's disease

Possible cardiovascular protection (only if started immediately after menopause)

Negative

Increase in endometrial carcinoma if unopposed oestrogens are administered

- In women without hysterectomy combine with progesterone

Possible risk of breast cancer increased (probably due to combination with progestogen)

- Do not give to patients with a familial or own risk, and usually not for longer than 7 years

Risk of thrombosis, cerebral insult, and coronary heart disease increased

- No prescription for patients at risk
- Rather use 17-β-oestradiol and transdermal application
- Start only within the first 10 years after menopause and do not apply in patients aged >60 years

early and 17-β-oestradiol is given.[50,83] A meta-analysis[84] on 43 RCTs found that menopausal hormone therapy did not increase mortality, neither all cause nor cardiac deaths, or those from stroke or cancer.

A very important argument in the controversy about the advantages and disadvantages of oestrogen substitution is that we have to distinguish a preventive application from a therapeutic use. In women with psychosis, oestradiol would be used therapeutically. Potential side-effects would have to be outweighed by the benefits and have to be compared with the side-effects of antipsychotics and other adjunct medications. Pros and cons have to be carefully assessed in each woman individually, and the final decision has to be made by the well informed woman herself. Oestrogens should only be substituted in women without risk factors, in close cooperation with a gynaecologist, and with close monitoring.

Psychiatrists should have the knowledge to be the advisers of their patients and the cooperation partners of the gynaecologists. To this end, they should know the best method of hormone replacement.[3] The natural 17-β-oestradiol not only seems to be the oestrogen with the best benefit-risk profile, but also the most active in the brain.[26] Transdermal application (patches or gel) has fewer side-effects than oral application.[75] Progestogens have to be added to oestrogens for endometrial protection. In this case, the natural, body identical, micronised progesterone seems to be the one with the least side-effects.[75]

Promising alternatives to oestrogens are being studied, especially so-called selective oestrogen receptor modulators. Raloxifene, for example, mainly acts on the bone, but might also act on different brain receptors.[85] However, according to several studies,[44,86,87] raloxifene does not improve psychotic symptoms but only negative and total symptoms in postmenopausal women with schizophrenia. Furthermore, a positive effect might be possible on cognition in patients with schizophrenia, although not confirmed.[31,87,88] Although the use of raloxifene is relatively safe, there seems to be a low risk of blood clots.[31]

A novel compound, 17-α-oestradiol, has been shown to be as equally protective as conventional 17-β-oestradiol with regards to cognitive deficits, depression-like symptoms, and problems with motor coordination in rats and, most importantly, without increasing oestradiol concentrations or markers of feminising action.[89]

Implications for research

Clinical research

There are many open research questions regarding the best clinical regimens for the different patient groups mentioned in this Series paper.

What kind of hormone replacement is best for patients with psychosis who have premature gonadal insufficiency or menopausal symptoms? For women, transdermal 17-β-oestradiol seems to be a good option. However, we do not know whether the recommended ultra-low doses for hormone replacement in otherwise healthy women who are perimenopausal or postmenopausal would still benefit the mental state of patients with psychosis. Furthermore, we know very little about the mental effects of the progestogen progesterone, which is recommended to be added to protect the endometrium.[75]

Similar questions have to be posed with regards to adjunct oestrogen therapy in younger women. So far, the doses applied in acutely ill patients seem too high for long-term use. What could an adequate long-term regimen be? Possibly the dose should be adjusted according to the physiological oestrogen concentrations still produced by the women themselves, in the context of individualised therapy. However, no studies have been done on this subject.

Most importantly, hardly any studies have been done on men. How many have low testosterone concentrations and how should those concerned be treated?

Further studies are urgently needed on compounds that have more specific and potent oestrogenic activity in the brain than in other tissues. Such compounds should both minimise the side-effects of hormonal therapy and permit new therapeutic strategies in men.

Research into pathogenetic mechanisms and the stress–prolactin–dopamine hypothesis

The findings on hyperprolactinaemia and gonadal insufficiency might give important insights into the pathogenetic mechanisms of emerging psychosis. Thus, we have speculated that hyperprolactinaemia in prodromal and first-episode psychosis is caused by psychological stress associated with the (emerging)

illness.[5] This stress-induced hyperprolactinaemia could contribute to triggering the onset of acute psychotic symptoms since hyperprolactinaemia in a feedback loop induces the production of the prolactin-inhibiting factor (PIF),[5] and PIF is mainly dopamine,[90,91] a neurotransmitter well known to provoke psychotic symptoms.[92]

The onset of psychosis has been linked to stress on the one hand,[93–96] and to an increase of dopaminergic neurotransmission on the other.[92,93] Furthermore, stress can lead to an increased dopamine release.[93,96,97] However, how stress can enhance dopaminergic neurotransmission has not yet been really understood.[92,93] Explanations have so far discussed a role for the concomitantly enhanced stress hormone cortisol and inflammation markers,[94,98] or a hyper-reactivity of dopamine neurons to stress.[95,97] But these theories neither integrate the findings of hyperprolactinaemia, nor those of low levels of gonadal hormones.

Therefore, we have suggested the stress–prolactin–dopamine hypothesis.[5] According to this hypothesis, the well known increase of prolactin due to stress[90,94,99] enhances dopamine release (ie, PIF) in a feedback mechanism (figure 2).[90,91,100] This increase of dopamine can then provoke psychotic symptoms in people with a susceptibility for psychosis. This hypothesis would mean that the tuberoinfundibular dopamine pathway might be involved in the pathogenesis of schizophrenic psychoses, and not just the mesolimbic and mesocortical pathways, as hypothesised prominently in the literature.

The stress–prolactin–dopamine hypothesis would explain the well known fact that stress can trigger the onset of psychosis. At the same time, stress-induced hyperprolactinaemia would explain the oestrogen deficiency in (a subgroup of) women with psychosis, since enhanced prolactin suppresses ovarian oestrogen production. Together with the oestrogen protection hypothesis, this stress–prolactin–dopamine hypothesis might also help to explain why schizophrenic psychoses often occur or relapse during periods with strong fluctuations of sex hormones and prolactin, such as in adolescence, post partum, or perimenopause.

Further support for this hypothesis came from Labad and colleagues.[94] They found increased prolactin (not cortisol) to be a predictor of the transition to psychosis.

Hyperprolactinaemia and increased pituitary volumes have predominantly been found in women with psychosis. This occurrence might be explained by oestrogens sensitising the pituitary to release prolactin.[90,100] In line with this would be functional MRI findings showing that women react differently to stress than men do, especially in their high oestrogen phases of the menstrual cycle.[101]

Unfortunately, very little research has been done in this area in men with psychosis, apart from studies showing that there is a subgroup with hyperprolactinaemia[5,6] and that some men with (emerging) psychosis have low testosterone or oestrogen concentrations. More research in men is needed in this area.

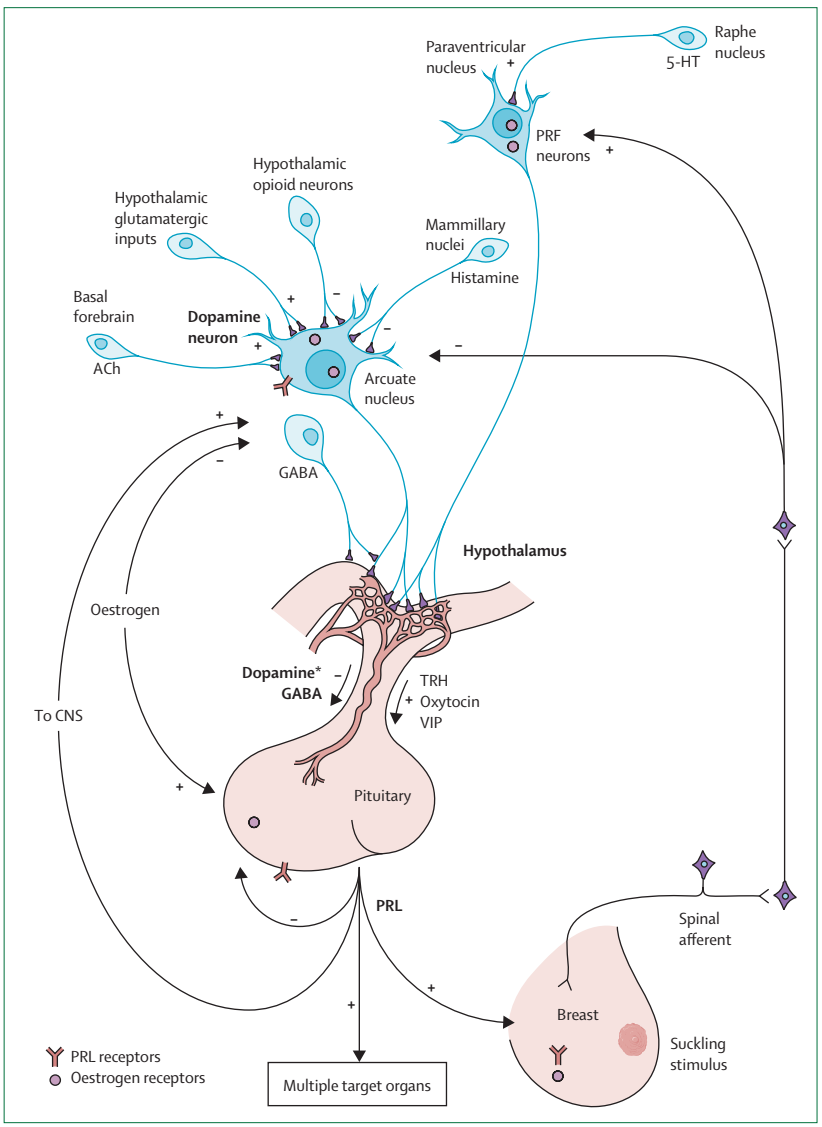

***Figure 2*: Control of prolactin production and secretion**
*Dopamine is prolactin-inhibiting factor. PRL=prolactin. PRF=prolactin-releasing factor. TRH=thyrotropin-releasing hormone. VIP=vasoactive intestinal polypeptide. GABA=γ-aminobutyric acid. ACh=acetylcholine. 5-HT=5-hydroxytryptamine. This figure has been adapted from the figure published in *Williams Textbook of Endocrinology*, Low, Neuroendocrinology, 126–127, Copyright Elsevier (2008).[90]

As to the specificity of the results for psychoses, other psychiatric disorders also seem to show some disturbances of the gonadal axis, although not to the same degree, and secondary amenorrhoea is a well known phenomenon in periods of stress.[102]

Conclusions

Clinically, evidence that 17-β-oestradiol could be a useful adjunctive therapy is emerging. It could complement and improve the drug therapies that are traditionally used for women with schizophrenic psychoses. In particular, it might be used as an adjunct in therapy-resistant women. Further studies on its potential for enhancing cognition

Search strategy and selection criteria

I searched MEDLINE, PubMed, and Google Scholar for articles published in the past 5 years with the MeSH major topics "schizophrenia", "estrogens", "estradiol", "prolactin", "pituitary" [Other Term], "testosterone", and "selective estrogen receptor modulators". The date of my last search was Aug 16, 2016. I applied no language restrictions. I searched the reference lists of these articles for important earlier papers. These publications were supplemented with earlier landmark papers and reviews. Because of space restrictions, I mainly cited review articles regarding older publications.

would be very important since we still do not have potent drugs here, as the results of a review[103] on cognition-enhancing drugs in schizophrenia showed. Furthermore, raloxifene might be an option if cognition is the target. Also, this treatment option needs further studies.

In perimenopause and postmenopause, oestrogen replacement for women has been recommended for many reasons (panel 2). Schizophrenic psychoses could potentially be an additional indication.

Of course the decision to apply oestradiol must always be made on the basis of an individual risk–benefit assessment[72] and in close collaboration with a gynaecologist. The challenge here is that after the first alarming results of the WHI study,[80] not all professionals and patients have kept updated with newer, contrasting results and now "overestimate the risks and contraindications, and underestimate the impact of menopausal symptoms on a woman's quality of life".[71] As particularly in women with psychosis the benefits might often outweigh the risks, more research is urgently needed.

Other strategies should already be part of standard clinical care, such as assessments of symptoms of gonadal insufficiency, with differential diagnosis and therapeutic actions if indicated.

More research is also needed regarding the poorly understood disturbances of the hypothalamic–pituitary–gonadal axis, hyperprolactinaemia, and sex hormone deficiency in patients with schizophrenic psychoses. Our understanding of the pathogenesis of these disorders, at least in a subgroup of patients, might benefit substantially from further research in this area.

Declaration of interests

I declare no competing interests.

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References

1 Riecher-Rössler A, Häfner H. Schizophrenia and oestrogens—is there an association? *Eur Arch Psychiatry Clin Neurosci* 1993; **242:** 323–28.

2 Riecher-Rössler A. Estrogens and schizophrenia. In: Bergemann N, Riecher-Rössler A, eds. Estrogen effects in psychiatric disorders. Vienna: Springer, 2005: 31–52.

3 Riecher-Rössler A, Kulkarni J. Estrogens and gonadal function in schizophrenia and related psychoses. *Curr Top Behav Neurosci* 2011; **8:** 155–71.

4 Markham JA. Sex steroids and schizophrenia. *Rev Endocr Metab Disord* 2012; **13:** 187–207.

5 Riecher-Rössler A, Rybakowski JK, Pflueger MO, et al. Hyperprolactinemia in antipsychotic-naive patients with first-episode psychosis. *Psychol Med* 2013; **43:** 2571–82.

6 Aston J, Rechsteiner E, Bull N, Borgwardt S, Gschwandtner U, Riecher-Rössler A. Hyperprolactinaemia in early psychosis—not only due to antipsychotics. *Prog Neuropsychopharmacol Biol Psychiatry* 2010; **34:** 1342–44.

7 González-Blanco L, Greenhalgh AMD, Garcia-Rizo C, Egea EF, Miller BJ, Kirkpatrick B. Prolactin concentrations in antipsychotic-naïve patients with schizophrenia and related disorders: a meta-analysis. *Schizophr Res* 2016; **174:** 156–60.

8 Ittig S, Studerus E, Riecher-Rössler A. M58. A possible role for prolactin in emerging psychosis. Abstracts from the 5th Biennial SIRS Conference—poster abstracts. Florence; http://www.nature.com/public/article-assets/npg/npjschz/abstracts/npjschz20168.pdf (accessed Oct 7, 2016).

9 Petrikis P, Tigas S, Tzallas AT, Archimandriti DT, Skapinakis P, Mavreas V. Prolactin levels in drug-naive patients with schizophrenia and other psychotic disorders. *Int J Psychiatry Clin Pract* 2016; **20:** 165–69.

10 Mahe V, Dumaine A. Oestrogen withdrawal associated psychoses. *Acta Psychiatr Scand* 2001; **104:** 323–31.

11 van der Werf M, Hanssen M, Kohler S, et al. Systematic review and collaborative recalculation of 133,693 incident cases of schizophrenia. *Psychol Med* 2014; **44:** 9–16.

12 Riecher-Rössler A. Die Spätschizophrenie—eine valide Entität? Eine empirische Studie zu Risikofaktoren, Krankheitsbild und Verlauf. Habilitationsschrift. Mannheim: Fakultät für klinische Medizin Mannheim, Universität Heidelberg, 1994.

13 Riecher-Rössler A, Löffler W, Munk-Jorgensen P. What do we really know about late-onset schizophrenia? *Eur Arch Psychiatry Clin Neurosci* 1997; **247:** 195–208.

14 Häfner H, Riecher-Rössler A, Hambrecht M, et al. [Sex differences in schizophrenic diseases]. *Fortschr Neurol Psychiatr* 1991; **59:** 343–60 (in German).

15 Häfner H, Riecher-Rössler A, An Der Heiden W, Maurer K, Fatkenheuer B, Löffler W. Generating and testing a causal explanation of the gender difference in age at first onset of schizophrenia. *Psychol Med* 1993; **23:** 925–40.

16 Riecher-Rössler A. Psychotic disorders and menopause: the untold story. In: Soares C, Warren M, eds. The menopausal transition—interface between gynecology and psychiatry. Basel: Karger, 2009: 115–26.

17 Riecher-Rössler A. Oestrogens and schizophrenia. *Curr Opin Psychiatry* 2003; **16:** 187–92.

18 Könnecke R, Häfner H, Maurer K, Löffler W, an der Heiden W. Main risk factors for schizophrenia: increased familial loading and pre- and peri-natal complications antagonize the protective effect of oestrogen in women. *Schizophr Res* 2000; **44:** 81–93.

19 Cohen RZ, Seeman MV, Gotowiec A, Kopala L. Earlier puberty as a predictor of later onset of schizophrenia in women. *Am J Psychiatry* 1999; **156:** 1059–64.

20 Hayeems R, Seeman MV. Puberty and schizophrenia onset. In: Bergemann N, Riecher-Rössler A, eds. Estrogen efects in psychiatric disorders. Vienna, New York, NY: Springer, 2005: 95.

21 Riecher-Rössler A. Oestrogen effects in schizophrenia and their potential therapeutic implications–review. *Arch Womens Ment Health* 2002; **5:** 111–18.

22 Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses. *Br J Psychiatry* 1987; **150:** 662–73.

23 Riecher-Rössler A, Häfner H, Dutsch-Strobel A, et al. Further evidence for a specific role of estradiol in schizophrenia? *Biol Psychiatry* 1994; **36:** 492–94.

24 Riecher-Rössler A, Häfner H, Stumbaum M, Maurer K, Schmidt R. Can estradiol modulate schizophrenic symptomatology? *Schizophr Bull* 1994; **20:** 203–14.

25 Melcangi RC, Panzica G, Garcia-Segura LM. Neuroactive steroids: focus on human brain. *Neuroscience* 2011; **191:** 1–5.

26 McCarthy MM. Estradiol and the developing brain. *Physiol Rev* 2008; **88:** 91–124.

27 Jimenez JA, Mancini-Marie A, Lakis N, Rinaldi M, Mendrek A. Disturbed sexual dimorphism of brain activation during mental rotation in schizophrenia. *Schizophr Res* 2010; **122:** 53–62.

28 Mendrek A. Reversal of normal cerebral sexual dimorphism in schizophrenia: evidence and speculations. *Med Hypotheses* 2007; **69:** 896–902.

29 DonCarlos LL, Azcoitia I, Garcia-Segura LM. Neuroprotective actions of selective estrogen receptor modulators. *Psychoneuroendocrinology* 2009; **34** (suppl 1)**:** S113–22.

30 Pompili A, Arnone B, Gasbarri A. Estrogens and memory in physiological and neuropathological conditions. *Psychoneuroendocrinology* 2012; **37:** 1379–96.

31 Weickert TW, Weinberg D, Lenroot R, et al. Adjunctive raloxifene treatment improves attention and memory in men and women with schizophrenia. *Mol Psychiatry* 2015; **20:** 685–94.

32 Wu YC, Hill RA, Gogos A, van den Buuse M. Sex differences and the role of estrogen in animal models of schizophrenia: interaction with BDNF. *Neuroscience* 2013; **239:** 67–83.

33 Garcia-Segura L, Azcoitia I, Doncarlos L. Neuroprotection by estradiol. *Prog Neurobiol* 2001; **63**: 29–60.

34 Gogos A, Sbisa AM, Sun J, Gibbons A, Udawela M, Dean B. A role for estrogen in schizophrenia: clinical and preclinical findings. *Int J Endocrinol* 2015; **2015:** 16.

35 Balthazart J, Ball GF. Is brain estradiol a hormone or a neurotransmitter? *Trends Neurosci* 2006; **29:** 241–49.

36 Arad M, Weiner I. Contrasting effects of increased and decreased dopamine transmission on latent inhibition in ovariectomized rats and their modulation by 17beta-estradiol: an animal model of menopausal psychosis? *Neuropsychopharmacology* 2010; **35:** 1570–82.

37 Arad M, Weiner I. Abnormally rapid reversal learning and reduced response to antipsychotic drugs following ovariectomy in female rats. *Psychoneuroendocrinology* 2012; **37:** 200–12.

38 Gogos A, Kwek P, van den Buuse M. The role of estrogen and testosterone in female rats in behavioral models of relevance to schizophrenia. *Psychopharmacology (Berl)* 2012; **219:** 213–24.

39 Vasudevan N, Pfaff DW. Non-genomic actions of estrogens and their interaction with genomic actions in the brain. *Front Neuroendocrinol* 2008; **29:** 238–57.

40 Oesterlund M. The role of estrogens in neuropsychiatric disorders. *Curr Opin Psychiatry* 2002; **15:** 307–12.

41 Weickert CS, Miranda-Angulo AL, Wong J, et al. Variants in the estrogen receptor alpha gene and its mRNA contribute to risk for schizophrenia. *Hum Mol Genet* 2008; **17:** 2293–309.

42 Min JA, Kim JJ, Pae CU, et al. Association of estrogen receptor genes and schizophrenia: A preliminary study. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; **36:** 1–4.

43 Begemann MJ, Dekker CF, van Lunenburg M, Sommer IE. Estrogen augmentation in schizophrenia: a quantitative review of current evidence. *Schizophr Res* 2012; **141:** 179–84.

44 Heringa SM, Begemann MJ, Goverde AJ, Sommer IE. Sex hormones and oxytocin augmentation strategies in schizophrenia: A quantitative review. *Schizophr Res* 2015; **168:** 603–13.

45 Sommer IE, van Westrhenen R, Begemann MJ, de Witte LD, Leucht S, Kahn RS. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. *Schizophr Bull* 2014; **40:** 181–91.

46 Kulkarni J, Riedel A, de Castella AR, et al. Estrogen–a potential treatment for schizophrenia. *Schizophr Res* 2001; **48:** 137–44.

47 Kulkarni J, de Castella A, Fitzgerald PB, et al. Estrogen in severe mental illness: a potential new treatment approach. *Arch Gen Psychiatry* 2008; **65:** 955–60.

48 Kulkarni J: Oestrogen—a new treatment approach for schizophrenia? *Med J Aust* 2009; **190:** S37–38.

49 Kulkarni J, Gavrilidis E, Wang W, et al. Estradiol for treatment-resistant schizophrenia: a large-scale randomized-controlled trial in women of child-bearing age. *Mol Psychiatry* 2015; **20:** 695–702.

50 Sherwin BB. Estrogen and memory in women: how can we reconcile the findings? *Horm Behav* 2005; **47:** 371–75.

51 Akhondzadeh S, Nejatisafa AA, Amini H, et al. Adjunctive estrogen treatment in women with chronic schizophrenia: a double-blind, randomized, and placebo-controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; **27:** 1007–12.

52 Louza MR, Marques AP, Elkis H, Bassitt D, Diegoli M, Gattaz WF. Conjugated estrogens as adjuvant therapy in the treatment of acute schizophrenia: a double-blind study. *Schizophr Res* 2004; **66:** 97–100.

53 Chua WL, Izquierdo de Santiago A, Kulkarni J, Mortimer A. Estrogen for schizophrenia. *Cochrane Database Syst Rev* 2005; **4:** CD004719.

54 Ghafari E, Fararouie M, Shirazi HG, Farhangfar A, Ghaderi F, Mohammadi A. 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* 2013; **6:** 172–76.

55 Good KP, Kopala LC, Martzke JS, et al. Hormone replacement therapy in postmenopausal women with schizophrenia: preliminary findings. *Schizophr Res* 1999; **12:** 131.

56 Lindamer LA, Buse DC, Lohr JB, Jeste DV. Hormone replacement therapy in postmenopausal women with schizophrenia: positive effect on negative symptoms? *Biol Psychiatry* 2001; **49:** 47–51.

57 Ahokas A, Aito M, Rimon R. Positive treatment effect of estradiol in postpartum psychosis: a pilot study. *J Clin Psychiatry* 2000; **61:** 166–69.

58 Ko YH, Jung SW, Joe SH, et al. Association between serum testosterone levels and the severity of negative symptoms in male patients with chronic schizophrenia. *Psychoneuroendocrinology* 2007; **32:** 385–91.

59 da Silva TL, Ravindran AV. Contribution of sex hormones to gender differences in schizophrenia: a review. *Asian J Psychiatry* 2015; **18:** 2–14.

60 Taherianfard M, Shariaty M. Evaluation of serum steroid hormones in schizophrenic patients. *Indian J Med Sci* 2004; **58:** 3–9.

61 Huber TJ, Tettenborn C, Leifke E, Emrich HM. Sex hormones in psychotic men. *Psychoneuroendocrinology* 2005; **30:** 111–14.

62 van Rijn S, Aleman A, de Sonneville L, et al. Neuroendocrine markers of high risk for psychosis: salivary testosterone in adolescent boys with prodromal symptoms. *Psychol Med* 2011; **41:** 1815–22.

63 Akhondzadeh S, Rezaei F, Larijani B, Nejatisafa AA, Kashani L, Abbasi SH. Correlation between testosterone, gonadotropins and prolactin and severity of negative symptoms in male patients with chronic schizophrenia. *Schizophr Res* 2006; **84:** 405–10.

64 Bundy H, Stahl D, MacCabe JH. A systematic review and meta-analysis of the fertility of patients with schizophrenia and their unaffected relatives. *Acta Psychiatr Scand* 2011; **123:** 98–106.

65 Maguire GA. Prolactin elevation with antipsychotic medications: mechanisms of action and clinical consequences. *J Clin Psychiatry* 2002; **63** (suppl 4)**:** 56–62.

66 Canuso CM, Goldstein JM, Wojcik J, et al. Antipsychotic medication, prolactin elevation, and ovarian function in women with schizophrenia and schizoaffective disorder. *Psychiatry Res* 2002; **111:** 11–20.

67 Maric N, Popovic V, Jasovic-Gasic M, Pilipovic N, van Os J. Cumulative exposure to estrogen and psychosis: a peak bone mass, case-control study in first-episode psychosis. *Schizophr Res* 2005; **73:** 351–55.

68 Nordholm D, Krogh J, Mondelli V, Dazzan P, Pariante C, Nordentoft M. Pituitary gland volume in patients with schizophrenia, subjects at ultra high-risk of developing psychosis and healthy controls: a systematic review and meta-analysis. *Psychoneuroendocrinology* 2013; **38:** 2394–404.

69 MacMaster FP, El-Sheikh R, Upadhyaya AR, Nutche J, Rosenberg DR, Keshavan M. Effect of antipsychotics on pituitary gland volume in treatment-naive first-episode schizophrenia: a pilot study. *Schizophr Res* 2007; **92:** 207–10.

70 Smith S, Wheeler MJ, Murray R, O'Keane V. The effects of antipsychotic-induced hyperprolactinaemia on the hypothalamic-pituitary-gonadal axis. *J Clin Psychopharmacol* 2002; **22:** 109–14.

71 National Institute for Health and Care Excellence. Menopause: diagnosis and management. NICE guidelines 23. London: NICE, 2015. https://www.nice.org.uk/guidance/NG23 (accessed Jan 16, 2016).

72 Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2010; **95** (suppl 1)**:** s1–66.

73 Gurney EP, Nachtigall MJ, Nachtigall LE, Naftolin F. The Women's Health Initiative trial and related studies: 10 years later: a clinician's view. *J Steroid Biochem Mol Biol* 2014; **142:** 4–11.

74 Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; **297:** 1465–77.

75 L'Hermite M. HRT optimization, using transdermal estradiol plus micronized progesterone, a safer HRT. *Climacteric* 2013; **16** (suppl 1): 44–53.

76 de Villiers TJ, Gass MLS, Haines CJ, et al. Global consensus statement on menopausal hormone therapy. *Maturitas* 2013; **74:** 391–92.

77 Rozenberg S, Vandromme J, Antoine C. Postmenopausal hormone therapy: risks and benefits. *Nat Rev Endocrinol* 2013; **9:** 216–27.

78 van der Leeuw C, Peeters S, Domen P, et al. Bone mineral density as a marker of cumulative estrogen exposure in psychotic disorder: a 3 year follow-up study. *PLoS One* 2015; **10:** e0136320.

79 Lindamer LA, Buse DC, Auslander L, Unutzer J, Bartels SJ, Jeste DV. A comparison of gynecological variables and service use among older women with and without schizophrenia. *Psychiatr Serv* 2003; **54:** 902–04.

80 Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA* 2002; **288:** 321–33.

81 Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. *JAMA* 2002; **287:** 591–97.

82 Birkhäuser MH, Panay N, Archer DF, et al. Updated practical recommendations for hormone replacement therapy in the peri- and postmenopause. *Climacteric* 2008; **11:** 108–23.

83 Azcoitia I, Arevalo MA, De Nicola AF, Garcia-Segura LM. Neuroprotective actions of estradiol revisited. *Trends Endocrinol Metab* 2011; **22:** 467–73.

84 Benkhadra K, Mohammed K, Al Nofal A, et al. Menopausal hormone therapy and mortality: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2015; **100:** 4021–28.

85 Landry M, Levesque D, Di Paolo T. Estrogenic properties of raloxifene, but not tamoxifen, on D2 and D3 dopamine receptors in the rat forebrain. *Neuroendocrinology* 2002; **76:** 214–22.

86 Usall J, Huerta-Ramos E, Labad J, et al. Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a 24-week double-blind, randomized, parallel, placebo-controlled trial. *Schizophr Bull* 2016; **42:** 309–17.

87 Kulkarni J, Gavrilidis E, Gwini SM, et al. Effect of adjunctive raloxifene therapy on severity of refractory schizophrenia in women: a randomized clinical trial. *JAMA Psychiatry* 2016; **73:** 947–54.

88 Huerta-Ramos E, Iniesta R, Ochoa S, et al. Effects of raloxifene on cognition in postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. *Eur Neuropsychopharmacol* 2014; **24:** 223–31.

89 Kaur SP, Bansal S, Chopra K. 17α-Estradiol: a candidate neuroserm and non-feminizing estrogen for postmenopausal neuronal complications. *Steroids* 2015; **96:** 7–15.

90 Low MJ. Neuroendocrinology. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds. Williams textbook of endocrinology, 11th edn. Philadelphia, PA: Saunders Elsevier Co, 2008: 85–154.

91 Egli M, Leeners B, Kruger THC. Prolactin secretion patterns: basic mechanisms and clinical implications for reproduction. *Reproduction* 2010; **140:** 643–54.

92 Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III–the final common pathway. *Schizophr Bull* 2009; **35:** 549–62.

93 van Winkel R, Stefanis NC, Myin-Germeys I. Psychosocial stress and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. *Schizophr Bull* 2008; **34:** 1095–105.

94 Labad J, Stojanovic-Perez A, Montalvo I, et al. Stress biomarkers as predictors of transition to psychosis in at-risk mental states: roles for cortisol, prolactin and albumin. *J Psychiatr Res* 2015; **60:** 163–69.

95 Myin-Germeys I, van Os J. Stress-reactivity in psychosis: evidence for an affective pathway to psychosis. *Clin Psychol Rev* 2007; **27:** 409–24.

96 Aiello G, Horowitz M, Hepgul N, Pariante CM, Mondelli V. Stress abnormalities in individuals at risk for psychosis: a review of studies in subjects with familial risk or with "at risk" mental state. *Psychoneuroendocrinology* 2012; **37:** 1600–13.

97 Mizrahi R, Addington J, Rusjan PM, et al. Increased stress-induced dopamine release in psychosis. *Biol Psychiatry* 2012; **71:** 561–67.

98 Mondelli V. From stress to psychosis: whom, how, when and why? *Epidemiol Psychiatr Sci* 2014; **23:** 215–18.

99 Prabhakar VK, Davis JR. Hyperprolactinaemia. *Best Pract Res Clin Obstet Gynaecol* 2008; **22:** 341–53.

100 Fitzgerald P, Dinan TG. Prolactin and dopamine: what is the connection? A review article. *J Psychopharmacol* 2008; **22** (suppl 2): 12–19.

101 Goldstein JM, Jerram M, Abbs B, Whitfield-Gabrieli S, Makris N. Sex differences in stress response circuitry activation dependent on female hormonal cycle. *J Neurosci* 2010; **30:** 431–38.

102 Huber TJ, Rollnik J, Wilhelms J, von zur Muhlen A, Emrich HM, Schneider U. Estradiol levels in psychotic disorders. *Psychoneuroendocrinology* 2001; **26:** 27–35.

103 Keefe RSE, Buchanan RW, Marder SR, et al. Clinical trials of potential cognitive-enhancing drugs in schizophrenia: what have we learned so far? *Schizophr Bull* 2013; **39:** 417–35.