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Estrogens and SERMS as adjunctive treatments for schizophrenia

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ABSTRACT

More than thirty years have passed since sex and gender differences were noted in the age of onset, course and outcomes for schizophrenia. The 'estrogen hypothesis" was coined in the 1990's to describe neuroprotective effects of estrogen.

Intervention studies in schizophrenia patients with estradiol and selective estrogen receptor modulators (SERMs) are promising but psychiatrists and other health practitioners do not generally take up this useful adjunctive treatment for their female patients with schizophrenia. The reasons for this are manifold, but overall a cultural shift in the practice of psychiatry is needed to recognise the specific needs of women with schizophrenia and tailor treatments, such as hormone adjuncts to improve the outcomes for this significant population.

The two main aims of this article are to review the evidence and theory of estrogen treatments in schizophrenia and to recommend translation of adjunctive estrogen treatment into clinical practice for women with schizophrenia.

The estrogen hypothesis of gender differences in schizophrenia

For over three decades, there has been a growing acceptance that gonadal steroids, especially estrogens, might be responsible in part for sex differences in the age of onset of schizophrenia, clinical symptoms and treatment outcomes. Estrogens have been shown to influence brain development and brain functioning (McEwen and Milner, 2017). Numerous studies have shown that estradiol, a major class of estrogen, exerts protective effects in psychosis (Markham, 2012; Riecher-Rössler, 2017). It has been shown that when CNS estrogen levels fluctuate and decrease, across the menstrual or life cycles, that the neuroprotective effect is diminished. This is the case in the premenstrual low estrogen phase of the menstrual cycle and during the perimenopause (menopausal transition) period, when psychotic symptoms may worsen (Seeman and Lang, 1990, Riecher-Rössler and Häfner, 1993). Furthermore, there is mounting evidence that many women with psychosis have subnormal estrogen levels, even in the prodromal and untreated phases of the disease (Riecher-Rössler and Häfner, 1993; Riecher-Rössler et al., 1998; Melcangi et al., 2011; Riecher-Rössler and Kulkarni, 2011; Markham, 2012; da Silva and Ravindran, 2015; Riecher-Rössler, 2017).

These observations led Riecher-Rössler and colleagues to propose two, strongly interconnected hypotheses (Riecher-Rössler and Häfner, 1993):

- Hypothesis one: that estrogens provide protection against psychosis (the 'estrogen protection' hypothesis);
- Hypothesis two: that psychosis is associated with hypoestrogenism and dysfunction of the hypothalamic-pituitary-gonadal axis

In this context, it has been suggested that women who are 'vulnerable' to the development of schizophrenia may have a generally lower level of endogenous estrogens than healthy women (Riecher-Rössler and Häfner, 1993, Riecher-Rössler et al., 1998). Should that be the case, they would be less likely to experience the neuroprotective effects of endogenous estrogens, and this potentially contributes to the onset of schizophrenia (Taylor et al., 2009).

An impressive body of work has been done by Seeman and Lang (1990), who independently formulated a version of the 'estrogen hypothesis' that detailed the organizational, activational, and cyclical role of estrogens as major determinants of the gender differences described in schizophrenia. Seeman (2012) also advised that post menopause, the woman's general health may also deteriorate and antipsychotic treatment may need to be modified as well as instituting more cardiac and metabolic health monitoring.

More than three decades ago, the 'estrogen hypothesis' which is a

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compelling hypothesis to explain sex and gender differences in the onset and outcomes for people with schizophrenia was expounded. The hypothesis is supported by robust animal studies as well as clinical observations. The hypothesis that estrogens have a neuroprotective effect in schizophrenia underpins the development of new clinical treatments with estrogen compounds.

1. Estrogen as a treatment in schizophrenia

Men and women with schizophrenia often 'plateau' in their treatment responses to antipsychotic medications. Unfortunately, there are a significant number of people who do not respond well to antipsychotic treatment at all (Kane, 2012). In such patients, novel adjunctive treatments such as estradiol augmentation may be an important consideration. The term *neurosteroid* was coined by Baulieu and refers to steroids synthesized in the brain. The term, *neuroactive steroid* coined by Paul and Purdy, refers to steroids that can be synthesized in the brain or in an endocrine gland, that then reach the brain through the bloodstream and have effects on brain function.

Estradiol is a neuroactive steroid that interacts with many neurotransmitters and brain circuitry, as well as having major endocrine and reproductive functions. In fact, estrogens' extensive neuroprotective and neuromodulatory properties have led to them being dubbed "nature's psychoprotectant" (Fink et al., 1996).

1.1. The effect of estradiol on neurotransmitter pathways - animal study evidence

Traditionally, hyperactivity of dopaminergic neurotransmitter pathways was thought to be the primary pathophysiologic process at the core of schizophrenia, and thus most antipsychotic medications share the property of dopamine (DA) D_2 receptor antagonism. While this hypothesis endures, it is now well established that dysfunction of additional neurotransmitter systems, such as serotonin and glutamate, are likely to be involved in the underlying pathogenesis of schizophrenia (Gonzalez-Maeso et al., 2008).

Therefore, the second generation or 'atypical' antipsychotics are thought to be effective because of their additional interactions with serotonin 5-HT_{1A} and 5-HT_{2A} receptors (Horacek et al., 2006). The exact nature of atypical antipsychotics' effects on the serotonin system is still the subject of considerable debate with some authors denying such effects altogether (Kuroki et al., 2008).

Nonetheless, extensive preclinical research has demonstrated that estrogens have profound effects on the dopaminergic, serotonergic and glutamatergic systems, strongly suggesting neuroleptic-like properties, similar to those of atypical antipsychotics.

The effect of estrogens on dopaminergic neurotransmission is often described as particularly significant but exceedingly complex. A recent review by Sánchez et al. highlights considerable variations in studies conducted on the direction, extent and specificity of estrogen-DA interactions (Sanchez et al., 2010). Early animal study observations by Di Paolo and Falardeau (1985) were that estrogens decrease dopaminergic neurotransmission and induce a compensatory increase in DA binding-site density. Pioneering work by Häfner, Gattaz and colleagues in the early 1990s demonstrated the potential of estradiol to attenuate DA agonist-induced psychomimetic behaviors and DA antagonist-induced motor disturbances in OVX rats, presumably through a down regulation of dopaminergic receptor function (Häfner et al., 1991).

An estrogen-related reduction in D_2 receptor sensitivity and an increase in D_2 receptor density in the striatum has been noted more recently in many studies involving ovariectomized (OVX) rats (Sanchez et al., 2010). It has been proposed that this increase in receptor density could be a compensatory response to an estrogen-induced decrease in DA levels, possibly via enhanced action of the DA transporter. A recent study by Chavez et al. (2010) showed that estradiol administration significantly increased the density of the DA transporter in the nucleus accumbens of OVX rats.

It has also been shown in animal studies that estradiol significantly modulates multiple components of the serotonergic neurotransmission system (Lokuge et al., 2010). Specifically, estrogens have been found to increase both isoforms of tryptophan hydroxylase (Bethea et al., 2000), decrease the activity of monoamine oxidase (Gundlah et al., 2002), influence the expression of the serotonin transporter (Smith et al., 2004), down regulate the expression of 5-HT_{1A}receptors, and up regulate the levels of 5-HT_{2A} receptors (Moses et al., 2000). These actions have the overall effect of enhancing serotonergic neurotransmission, which could be important in attenuating affective and cognitive symptoms of schizophrenia.

Similarly, estrogens have also been found to enhance glutamatergic neurotransmission by up regulating NMDA receptors, manipulating their subunit configuration and increasing NMDA agonist binding (Adams et al., 2004). These actions could theoretically help to reverse the hypoglutamatergic functioning that is believed to contribute to the pathogenesis of schizophrenia (Bubenikova-Valesova et al., 2008) and the development of negative symptoms (Goff and Coyle, 2001).

Recent work (Gogos et al., 2010; Gogos et al., 2012) examining the effects of estrogens in animal paradigms of psychosis confirms the estrogen protection hypothesis, providing compelling evidence that the actions of estrogens on central neurotransmitter systems translate into antipsychotic potential. Gogos et al. demonstrated that estradiol treatment could effectively reverse psychomimetic states in female OVX rats induced by the separate administration of a D_2 receptor agonist, a 5-HT_{1A} agonist and an NMDA receptor antagonist, strongly suggesting that estrogens have an antipsychotic action via its neuromodulatory effects (Gogos et al., 2010; Gogos et al., 2012).

Arad and Weiner supplement these findings by reporting that estradiol ameliorated an amphetamine-induced psychosis in both OVX and intact female rats as effectively as clozapine or haloperidol. However, the OVX rats required significantly higher doses than intact female rats of each compound to achieve psychosis amelioration (Arad and Weiner, 2010).

1.2. Human clinical trials in schizophrenia with estrogens

Animal studies provide preclinical support for Seeman's observation that postmenopausal women have a reduced response to antipsychotic medication compared with premenopausal women, as discussed earlier. Adding to this, in a clinical trial, Kulkarni et al. (2008) observed that ineffectual low doses of clozapine and haloperidol regained antipsychotic efficacy when combined with estradiol, justifying the use of estradiol as an adjunctive treatment strategy for women with schizophrenia.

Estrogens have been successfully tested in many clinical intervention trials to date, with results further supporting the treatment potential of this class of hormone.

In a pioneering open-label study by Kulkarni et al. (1996), 18 women of childbearing age with schizophrenia treated with 2 mg of oral estradiol valerate, in addition to antipsychotic medication, made a more rapid recovery from acute psychotic symptoms compared with a matched control group. These results, coupled with epidemiological and life-cycle observations as described earlier, led to more extensive and better-quality randomized clinical trials, such as the three-arm, double-blind, placebo-controlled dose-finding study of adjunctive transdermal estradiol in women with schizophrenia (Kulkarni et al., 2001). This dose – finding study showed that the group of women who received 100 μg of adjunctive estradiol, in comparison to 50 μg of adjunctive estradiol or adjunctive placebo, had the greatest improvement in symptoms. Replicating these promising results, Kulkarni and colleagues published a double-blind randomized controlled trial of 102 reproductive age women (Kulkarni et al., 2008), again showing that women receiving the addition of 100 μg transdermal estradiol displayed significantly reduced positive and general psychopathological

symptoms during the 28-day trial period compared with women receiving antipsychotic medication alone. Negative symptoms of schizophrenia were not improved by the addition of estradiol in any of the adjunctive estradiol studies. A limitation of the Kulkarni et al. study (2008) was the inclusion of different antipsychotics as the primary treatment. Estradiol adjunct impact may vary depending on the antipsychotic, but the study was not powered to compare this effect between medications.

Similar overall positive results were also reported by Akhondzadeh et al. (2003) who trialed the effect of adding 0.05 mg ethinyl estradiol to standard haloperidol treatment in a study of 32 women of reproductive age. They observed statistically significant reductions in total, positive symptoms and general psychopathology PANSS scores for women in the ethinyl estradiol group compared with women who received placebo.

Furthermore, in addition to its beneficial effects on psychotic symptomatology, estradiol has been found to be effective in improving elements of cognitive performance in women with schizophrenia compared with adjunctive placebo (Ko et al., 2006; Bergemann et al., 2008).

A detailed meta-analysis of estrogen use in clinical trials in people with schizophrenia was done by Begemann et al. (2012). Only double blind, randomized, placebo-controlled trials were analysed (Begemann et al., 2012). The primary outcome measure was total symptom severity, and in addition positive and negative symptoms were observed as secondary outcome measures. Combined, weighted effect sizes were obtained by compiling effect sizes for individual studies in meta-analyses. The results of the meta-analysis were that adjunctive estrogen treatment in female patients (four RCTs, 214 patients) yielded superior efficacy on total symptom severity (Hedges's g = 0.66) although heterogeneity was moderate to high. Estrogens were also superior in reducing positive (Hedges's g = 0.54) and negative symptoms (Hedges's g = 0.34), with low heterogeneity.

There have been two double blind, randomized controlled trials by Bergemann et al. (2005) and Louza et al. (2004), respectively, that did not find estrogens to be an effective augmentation strategy in the treatment of women with schizophrenia. Neither study reported any significant improvements in psychopathology or relapse rates for estrogen treatment compared with placebo. In addition, despite the high-quality design and reasonable sample size (n = 40) in the study conducted by Louza et al. (2004), women in the estrogen treatment group did not actually display an increase in serum-estrogen levels, which could explain why these women did not improve significantly over the placebo arm. Furthermore, Louza et al. (2004) used conjugated estrogens in their studies, as opposed to 17-β-estradiol, while Bergemann et al. (2005) administered estradiol in combination with a synthetic progestin, targeting this intervention towards relapse prevention. These factors are noteworthy, given that conjugated estrogens do not have the same potency as 17-β-estradiol in the brain (McCarthy, 2008), and the concomitant administration of a synthetic progestin has been suspected to have negative effects on the mental state (Riecher-Rössler and Kulkarni, 2011; L'Hermite, 2013). Such differences in hormonal preparations between studies could explain the positive results of some compared with the negative results of others. Importantly, the four RCTs identified had only examined women of the reproductive age group, although this kind of augmentation seems especially promising in peri- and postmenopausal women with physiologically low estrogen levels.

Meta-analyses and reviews done to date (Begemann et al., 2012; Craig, 2013) conclude that estrogens, especially estradiol, could be an effective augmentation strategy in the treatment of women with schizophrenia. The broader use of estrogens in clinical psychiatric practice may be hampered by concerns about the safety of adjunctive estradiol treatment, which is considered below.

1.3. Concerns about estrogen treatment in general

The Women's Health Initiative (WHI) study was a clinical trial to study the effects of estrogen plus progestin in post-menopausal women (Rossouw et al., 2002). The study was stopped at 5.2 years (instead of continuing for the planned 8.5 years) because of an early evaluation that the risks of breast cancer were purportedly increased and other health risks of hormone treatment were greater than the benefits (National Heart, 2002). The conclusions drawn were initially widely accepted as demonstrating that combined estrogen plus progestin (E + P: 'Prempro': 0.625 mg conjugated estrogens and 2.5 mg medroxyprogesterone acetate) treatment in postmenopausal women increased the risk of invasive breast cancer, (Chlebowski et al., 2003), coronary heart disease (Fletcher and Colditz, 2002) stroke and venous thromboembolism (Wassertheil-Smoller et al., 2003) The media attention surrounding the publication of the initial results of WHI in 2002 led to fear and confusion regarding the use of hormonal therapy (HT) after menopause. This led to a dramatic reduction in prescriptions for HT around the world.

Criticisms of the WHI study include concerns that although the study was meant to be a primary prevention trial, it did not study primary prevention in that most women were largely asymptomatic and were many years past menopause. Women up to the age of 79 years were included, and the average age of the participants was 63 years, which was on average approximately 12 years past menopause (Lobo, 2013).

A detailed critique of the methodology of the WHI has revealed several flaws, with subsequent re-analyses and reversal in many of the safety concerns reported (Clark, 2006). Subsequent studies using data collected from the WHI and other data have shown that there is a beneficial risk- to –benefit for women close to menopause.

In 2011, a consensus statement by the International Menopause Society (IMS) regarding HT stated the following: "The excessive conservatism engendered by the presentation to the media of the first results of the WHI in 2002 has disadvantaged nearly a decade of women who may have missed the therapeutic window to reduce their future cardiovascular, fracture, and dementia risk" (Sturdee et al., 2011). Overall, the current advice is to individualize hormone therapy for those women with symptoms, with a return to the view that in young healthy women (aged 50–60), (Lobo, 2016) there may be role for hormone treatment to prevent cardiovascular disease, fractures and cognitive decline.

2. Selective estrogen receptor modulators (SERMs)

The concerns about potentially adverse impacts of estrogen plus progestin treatment, has led to a growing interest in the development of SERMs as a potentially safer alternative to standard hormone treatment. Selective estrogen receptor modulators (SERMs) act as partial estrogen receptor agonists in bone tissue and the CNS, while at the same time acting as estrogen receptor antagonists in breast tissue, with variable impact on uterine and vaginal tissue. Tamoxifen is a first generation SERM used clinically in the treatment of breast cancer. It is an estrogen agonist in both uterine and bone tissue, with noted adverse, depressive impacts in the CNS (Denk et al., 2015).

The second-generation SERM, raloxifene was developed to treat osteoporosis. Raloxifene is an estrogen receptor antagonist and, unlike tamoxifen, it has 'anti-estrogen like' effects on uterine tissue and was approved by the Food and Drug Administration to treat osteoporosis (An, 2016).

The exact actions of raloxifene in the CNS are not entirely known, however its actions on mood and cognition may also be related to pre- and post-synaptic modulation of cholinergic, serotonergic, and dopaminergic neurotransmission (Cyr et al., 2000; Smith et al., 2004; Sanchez et al., 2010).

Raloxifene may also regulate opiate and GABAergic

neurotransmission by the modulation of the levels of b-endorphin and neuroactive steroids respectively (Florio et al., 2001; Genazzani et al., 2003).

A third-generation SERM, bazedoxifene, has also been developed to treat osteoporosis and has similar effects to that of raloxifene (Silverman et al., 2012). Bazedoxifene is a selective estrogen receptor modulator (SERM), which binds to both α and β intracellular estrogen receptor subtypes. It was developed using raloxifene as a template, but rather than having a benzothiophene core, bazedoxifene is an indole-based SERM with a 2-phenyl ring system serving as a core-binding unit. This difference results in bazedoxifene having improved tissue selectivity compared to the other SERMs (Vestergaard and Thomsen, 2010). *In vitro* studies have shown that bazedoxifene has a 4-fold higher affinity for the human estrogen receptor (ER) type α (IC50 = 26 nM) than for type β (IC50 = 99 nM) (Silverman et al., 2008). In immature or ovariectomized animals (where endogenous estrogen is lacking) bazedoxifene, like raloxifene, displayed estrogen-agonist activity whereas it had an anti-estrogen effect when estradiol was present (Silverman et al., 2008). Bazedoxifene acts like estrogen on the skeletal system and, at least in the rat on lipid metabolism, while exhibiting only minimal to negligible action on breast and uterine tissues (Silverman et al., 2012). A recent systematic review and meta-analysis indicates that bazedoxifene has significant bone/osteoporosis benefits with no increase in adverse or, serious adverse events including myocardial infarction, stroke, venous thromboembolic event, or breast carcinoma (Peng et al., 2017).

Other SERMs in development include arzoxifene – a benzothiophene, similar to raloxifene, and lasofoxifene – a naphthalene SERM (Silverman, 2010). Arzoxifene and lasoxifene have been trialled for efficacy in osteoporosis, but unlike raloxifene, they have not been examined for their effects on cognition. In the Multiple Outcomes of Raloxifene Evaluation (MORE) study, Yaffe et al. (2005) described that in 5386 women, those receiving 120 mg raloxifene per day had a 33% lower risk of cognitive impairment. The cognitive impairment risk was not found when raloxifene 60 mg per day was used.

Therefore, following on from the important positive responses seen in schizophrenia patients treated with adjunctive estradiol, trialling a SERM in schizophrenia seems a logical next step. Given the good safety profile and CNS impact of raloxifene, its use in schizophrenia as an adjunctive treatment is now considered.

2.1. Intervention studies in schizophrenia with selective estrogen receptor modulators (SERMs)

The selective estrogen receptor modulator (SERM), raloxifene, has been trialled in the treatment of postmenopausal women with psychosis. Kulkarni et al. (2010) performed the first ever pilot study of a SERM in schizophrenia and also conducted a dose-finding study in a randomized, double-blind, placebo-controlled trial comparing the efficacy of 60 and 120 mg/day of adjunctive oral raloxifene in the treatment of 35 women with acute postmenopausal schizophrenia. The participants randomized to the 120 mg/day raloxifene arm, had a significantly more rapid recovery in total and general psychopathological symptoms compared with both the 60 mg/day raloxifene hydrochloride and placebo ($p < 0.0005$) groups. Cognition was not tested in this study which was a shortcoming.

Usall et al. (2011) then compared the addition of 60 mg raloxifene per day as an adjunct to regular antipsychotic treatment with placebo in a trial of 33 post-menopausal women with schizophrenia. In this study, the treatment group of 16 women was found to have significantly reduced negative ($p = 0.04$), positive ($p = 0.03$), and general psychopathological ($p = 0.045$) symptoms compared with women receiving placebo. However, on further analysis, average decreases in symptoms from baseline in the treatment group were clinically modest at less than 15%. The results of these two trials are consistent with those of a small study by Good et al. (1999), who found that administering hormone replacement therapy to postmenopausal women with a psychotic disorder led to a significant improvement in negative symptoms over 6 months.

In a more recent study of peri and postmenopausal women, Kulkarni et al. (2016) reported that in 56 participants, the women administered 120 mg daily raloxifene had a greater reduction in the PANSS total and general scores compared to placebo. Change in mood, cognition, and reproductive hormone levels and the rate of adverse events did not differ between groups.

There have been further conflicting results for the use of raloxifene in women with schizophrenia. In a 16-week long study of 200 postmenopausal women with severe persistent schizophrenia, who were given 60 mg of raloxifene twice daily in addition to antipsychotic medications, compared to placebo adjunct in addition to raloxifene, Weiser et al. (2017) reported that patients taking adjunctive placebo in fact had significantly improved PANSS total scores compared to the adjunctive raloxifene group. Weickert et al. (2015) combined data from both men and women with schizophrenia and described cognitive improvement in the group receiving 120 mg raloxifene, but no improvement in psychosis symptoms. The use of a crossover design and combined sex data added significant confounding factors to these reported findings (see Table 1).

In summary, there are conflicting reports about the use of adjunctive raloxifene in treating people with schizophrenia, which is to be expected when developing a new approach for the management of schizophrenia – a heterogeneous condition with many putative etiological and moderating factors. Sex is clearly an important issue in considering gonadal hormone treatment, as is the patient's age, severity of illness and physical health. Factors in the use of raloxifene include the dose and timing of medication delivery as well as the interaction between the primary antipsychotic and raloxifene.

Raloxifene is rapidly absorbed after oral administration, but its bioavailability is only 2%. Hence, the critical difference between the study by Weiser et al. (2017) that found no effect of raloxifene is most likely due to the split dose used (60 mg raloxifene administered morning and night), whereas Kulkarni et al. (2016) administered

Table 1
Summary of adjunctive raloxifene treatment in schizophrenia.

Author	N Group	Raloxifene Dose	Cognition outcome	Psychopathology Outcome
Kulkarni et al. (2010)	21 Postmenopausal	120 mg oral bolus	Not tested	Raloxifene significantly* improved symptoms
Kulkarni et al. (2010)	14 Postmenopausal	60 mg oral bolus	Not tested	Raloxifene moderately** improved symptoms
Usall et al. (2011)	33 Postmenopausal	60 mg oral bolus	Not tested	Raloxifene significantly* improved symptoms
Kulkarni et al. (2016)	56 peri and post menopausal	120 mg oral bolus	No difference in cognition between raloxifene and placebo	Raloxifene significantly* improved symptoms
Weickert et al. (2015)	79, male, pre and post menopausal	120 mg oral bolus	Raloxifene improved cognition	No difference between raloxifene group and placebo
Weiser et al. (2017)	200 postmenopausal	60 mg twice per day	No difference between groups	Placebo adjunct better than raloxifene

* Significant denotes statistical significance.
** Moderate clinical improvement but not statistically significant.

120 mg in one morning dose. The maximum plasma concentration of 0.5 ng/ml is reached after 6 h, and a concentration required to impact on the CNS is likely to require higher dosing than 60 mg/day, in two divided doses. Raloxifene is more than 95% bound to plasma proteins, and less than 0.2% of an oral dose is excreted unchanged in the urine (Heringa, 2003). Also the population studied by Weiser et al. (2017) was a chronically unwell group of older women. This would most likely further contribute to the lack of efficacy of raloxifene.

Another set of studies, not in schizophrenia, considering the impact of diurnal variation on raloxifene dosing in postmenopausal women with osteoporosis. They described that the plasma concentration of plasminogen activator inhibitor (PAI)-1 increased in the group receiving a morning dose of raloxifene but not in the groups receiving an evening dose. The authors concluded that the findings of their study suggest that the dosing time of raloxifene influences its safety and effects (Ando et al., 2013).

Raloxifene is not established as an effective treatment for acute psychosis symptoms or to improve cognition. However, there is some indication that the bigger oral bolus dose of 120 mg might improve psychosis in peri- and postmenopausal women with schizophrenia (Kulkarni et al., 2016). The lower 60 mg dose, in the same age group of women, appears to improve cognition (Huerta-Ramos et al., 2014). Raloxifene does not appear to improve psychosis symptoms in men or in younger women with schizophrenia (Weickert et al., 2015). The main serious side effect of raloxifene is thromboembolic phenomena – which need to be carefully monitored for, particularly in heavy cigarette smokers, which people with chronic schizophrenia often are.

Women with schizophrenia who also have low bone density or osteoporosis, particularly related to hyperprolactinemia, may benefit from adjunctive raloxifene treatment for the indication of bone health improvement.

Recent meta-analyses of raloxifene treatment in schizophrenia were done by Wang et al. (2018) in postmenopausal women with schizophrenic psychoses and by de Boer et al. (2018) in a more heterogeneous population. The study analysed 440 patients across six studies, including 225 patients treated with raloxifene and 215 patients on placebo. Wang and colleagues reported beneficial effects of raloxifene treatment on psychotic symptoms in postmenopausal women with schizophrenia. De Boer and colleagues reported moderate, but significant positive effects of raloxifene on total symptom severity, as well as on positive, negative, and general PANSS subscales but no significant effect on cognitive symptoms. Dosage or treatment duration did not influence these effects.

Clearly, more clinical trials examining the dosing, timing, symptom response, patients' sex and menopausal status need to be conducted to clarify the role of adjunctive raloxifene in treating people with schizophrenia. Kulkarni and colleagues are about to begin a new trial examining the impact of bazedoxifene as an adjunct treatment in the treatment of women with schizophrenia.

2.2. Clinical precautions in the use of estrogens and SERMS in women with schizophrenia

Assessments of breast health with regular ultrasound examination (in women younger than 50 years of age) and mammograms (in women older than 50) as well as cervix cell examination with Pap Smears are essential. Checking for blood clotting disorders that may predispose the patient for deep vein thrombosis or pulmonary embolism is critical – as is ceasing estradiol treatment if long periods of inactivity are expected – such as air travel or surgery. Estradiol treatment given as an adjunct to antipsychotic medications for more than 5–6 months needs to be supplemented with a progestogen, to minimize the risk of endometrial hyperplasia. The best progestogen here seems the natural, body-identical progesterone because it has the least side effects (L'Hermite, 2013).

Clinically it is important to distinguish between younger women without estrogen deficiency and elderly peri-/postmenopausal women with estrogen deficiency.

In younger women (post puberty and up to the mid-forties), estrogen treatment may be delivered in an ongoing treatment manner by using a combined oral contraceptive pill. This should preferably contain 17-β-estradiol and a progestin of the second generation with few side effects, which may provide some augmentation of antipsychotic medication as well as contraception. Of course, all safety issues of hormonal contraception have to be considered and managed.

In women after age 45, physiological estrogen production starts to decline. Here hormonal replacement seems especially promising. In this group of women, estradiol might not only augment the effect of antipsychotics but also reduce perimenopausal complaints, such as night sweats with sleep disturbances, hot flushes and irritability, which can possibly provoke psychotic relapses (Riecher-Rössler, 2017). Furthermore, the positive influence on bone mineral density and potentially also on cognition is most welcome in this age group.

There has been a lot of controversy about the pros and cons of estrogen replacement in the peri-/post menopause (Riecher-Rössler, 2017) which has led to new guidelines for the prophylactic use of estrogens in otherwise healthy women (Riecher-Rössler, 2017). In women with psychosis, estradiol would not be used prophylactically but therapeutically; potential side effects would have to be outweighed by the benefits and would have to be compared with the side effects of other medications. Of course, standard health monitoring practices need to be adhered to, particularly being aware of any special risk factors that contraindicate the use of estrogen therapies in middle-aged women (Riecher-Rössler, 2017). Thus, in women without hysterectomy estrogens have to be combined with progesterone in order to prevent endometrial carcinoma. Estrogens should not be given to patients with a familial or own risk of breast cancer and usually not for longer than seven years. Patients with a risk of thrombosis, cerebral insult or coronary heart disease should not take estrogens. Generally, estrogen treatment should be started as early as possible and not later than within the first ten years after menopause and should not be applied after age 60. A recent meta-analysis also suggested an enhanced risk for ovarian cancer (Beral et al., 2015). On the other hand, a meta-analysis (Benkhadra et al., 2015) found no increased mortality with menopausal hormone therapy, neither all cause nor cardiac deaths nor those from stroke or cancer. In any case, the indication should be carefully assessed for each woman individually, and an informed decision should be made by the woman herself. In peri-/postmenopausal women the natural 17-β-estradiol certainly is preferable, since it is the most active in the brain and has the best benefit/risk profile. Transdermal application (patches or gel) seems to have fewer side effects than oral application (L'Hermite, 2013).

Of interest is recent evidence suggesting that the use of transdermal estradiol plus micronized progesterone also improves depressive symptoms in perimenopausal women (Gordon et al., 2018), which is an important comorbidity to avoid in women with schizophrenia. The use of SERMs in men with schizophrenia is still unclear with respect to psychosis symptom outcomes (Weickert et al., 2015). However, the potential side effects of venous thromboembolic phenomena are of concern, particularly in men who smoke cigarettes. Hence a blood clotting profile needs to be conducted as a screening measure plus smoking cessation advice.

3. Discussion

3.1. The relative lack of use of adjunctive estrogens and SERMS in clinical practice for people with schizophrenia

After more than three decades of research exploring the theory of the 'estrogen hypothesis' and the conduct of many clinical trials of adjunctive hormone treatment, the translation of this treatment approach into mainstream psychiatric practice for people with schizophrenia is still uncommon (Craig, 2013). This is surprising given the

large number of patients with schizophrenia who do not respond completely to antipsychotic medication treatment, and the need for additional interventions (Torrey and Davis, 2012).

There are many contributing factors to the poor uptake of hormone treatments in schizophrenia – perhaps the first and foremost being a need for further, larger global, clinical trials with longer follow up of patients. The more 'standard HRT' treatments – estradiol + progestin - with its feminizing effects, are not a long term or even medium term option for men with schizophrenia. However, the use of standard hormone treatment may be a reasonable option to maximise outcomes in women with schizophrenia. The use of SERMs in men with schizophrenia may avoid feminization, but the clinical efficacy of this adjunctive treatment remains to be further tested in men. Women with schizophrenia appear to respond favourably to raloxifene, but the definitive dose is still unclear as described in the clinical trials performed to date.

Even once further trials are done, in order to utilize hormone treatments; clinicians will need to conduct extensive physical health assessments and ongoing screening for their women patients. Historically, practicing psychiatrists have been somewhat reluctant to take an active role in physically examining their patients and monitoring their general health (Bobes et al., 2011; Parameswaran et al., 2013).

Adding to the problem of poor physical health monitoring is that many guidelines providing advice for psychiatrists on physical health monitoring of patients with severe mental illness, understandably focus on cardiovascular and metabolic disorders and largely ignore specific women's health issues. The recognition of menopause status in women is not mentioned as an area for examination or monitoring in many key practice guidelines drawn up to encourage psychiatrists to monitor the physical health of their patients (Marder et al., 2004; Excellence, 2014; Lambert et al., 2017).

Using estrogens as a treatment adjunct would require psychiatrists to have a working knowledge of the types of hormone treatments, dosing and possible effects and side-effects. This raises the issue experienced by many specialist medical practitioners where a 'silo mentality' or disengagement from other areas of medicine exists. In psychiatry the 'silo mentality' precludes enhancing knowledge about endocrinology including menopause hormone treatments, preferring to focus only on the mental health aspects of patients (McCartney, 2016). A 'shared care' model of holistic healthcare for people with schizophrenia could provide a solution for this 'silo' problem. Psychiatrists working closely with primary care physicians could ensure that female patients receive good physical health care including menopause assessment and appropriate hormone treatments, plus ongoing physical screening tailored for the use of hormone treatment. Of course, this model entails visits to both medical practices by the patient, which may be difficult for people who are very unwell and therefore non-adherent with clinical appointments.

A further possible reason for the low uptake of adjunctive estrogen treatment in schizophrenia is the lack of support from the pharmaceutical industry that develop, patent and distribute their own new drugs. Repurposing old drugs or 'off-label' use of drugs, does not add to the business model for the pharmaceutical industry. Without the educational and marketing support of the influential pharmaindustry, the use of 'old' products such as estradiol, or the newer SERMs in a schizophrenia population, remains rare.

Nonetheless, estrogen treatment is a viable, available adjunctive option for women with persistent schizophrenia. More clinical trials are required before the safety and efficacy of adjunctive SERM treatment in men with schizophrenia is clarified. We now present clinical recommendations for the use of estrogen therapy in women with schizophrenia.

3.2. Clinical recommendations

The following are practice suggestions based on human trials data and our clinical observation work.

(a) Reproductive Age Women with Schizophrenia (Post puberty – 45 years) If the patient is resistant to standard antipsychotic therapies as outlined in treatment guidelines, then a trial of adjunctive estrogen therapy may be warranted.
The oral contraceptive pill, especially types containing 30 or more mcg of estradiol are a relatively simple, first line form of estrogen treatment. The contraceptive effect of this must be discussed with the patient and her consent obtained.
Physical Health Monitoring
Prior to commencing the oral contraceptive pill, a thorough physical health screen needs to be performed and include assessment of breast health (family history, physical examination, ultrasound, BRCA gene testing if needed), cervix smear test (sexually active women), clotting profile on full blood examination, cholesterol levels in women over 30, blood pressure and if indicated an electrocardiogram. Regular six- monthly health monitoring visits are a positive way to ensure the patient's physical and mental health are maintained.

(b) Perimenopausal Women with deteriorating schizophrenia (45–52 years)
In this age group, as has been highlighted in the literature (Seeman, 2012), deterioration in mental health can be common. Often due to fluctuating gonadal hormones, it may be an important treatment strategy to augment antipsychotic medication with estrogen therapy.
First line estrogen treatment in this group may be the addition of transdermal estradiol (50mcg or 100mcg) + progestin (if the woman has a uterus). The progestin should preferably be one of the micronized, more natural types such as prometrium (100 mg oral or per vagina).
If estrogen therapy is contraindicated because of breast or uterine pathology – it may be useful to try raloxifene treatment (120 mg oral per day).
Physical Health Monitoring
Detailed physical health screening must be done before considering estrogen hormone augmentation. In this older age group, in addition to the physical health tests detailed above for younger women, it is important to test thyroid function, full cardiac function (especially if the patient is taking clozapine), liver and renal function, breast ultrasound + mammogram (every 2 years after age 50 years) and cancer markers (CA125). Regular monitoring of the patient is critical. Patients who smoke more than 20 cigarettes per day are at greater risk of thromboembolism and should not receive estrogen treatment. Very sedentary, overweight women similarly should not receive estrogen therapy.

(c) Postmenopausal Women with Schizophrenia (52–65 years old)
Women with schizophrenia in this older age group may have achieved some stability, once the perimenopausal process has settled. However, in the patients who have improved with adjunctive estrogen treatment, it is important to maintain the hormone therapy.
Physical Health Monitoring
The same physical health monitoring described for perimenopausal women must be done regularly (at a minimum, every 6 months). It is not recommended (Sturdee et al., 2011) to begin estrogen treatment after 60 years of age, but to continue it with safety monitoring is acceptable.
The timing of cessation of hormone therapy is a difficult clinical decision and the individual woman's health plus mental health needs to be assessed. There is no definite consensus that hormone therapy must be ceased with advancing age (Sturdee et al., 2011,

Lobo, 2016).

4. Conclusion

The use of estrogen and SERM treatments in women with schizophrenia requires recognition and consideration of the sex and gender differences in the patient's experience of schizophrenia in clinical practice. The broad concept of women's mental health as a distinct and worthy area of therapeutic endeavour is required to encourage specific new treatments to be tailored for women with severe mental illness. Adjunctive SERMs are promising treatments for women with schizophrenia. However, further clinical trials are needed, plus subsequent widespread translation into treatment guidelines. Including estrogen and SERM treatment in mainstream clinical work as a treatment for schizophrenia will require a paradigm shift in the current culture of psychiatric practice, which hopefully will not take another thirty years.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2019.03.002.

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