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Sex hormones and oxytocin augmentation strategies in schizophrenia: A quantitative review

Sophie M. Heringa [a,*,1], Marieke J.H. Begemann [a,1], Angelique J. Goverde [b], Iris E.C. Sommer [a]

[a] University Medical Center Utrecht, Brain Center Rudolf Magnus, Department of Psychiatry, PO Box 85500, 3508 GA Utrecht, The Netherlands
[b] University Medical Center Utrecht, Department of Reproductive Medicine and Gynecology, PO Box 85500, 3508 GA Utrecht, The Netherlands

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ABSTRACT

Introduction: Sex differences in incidence, onset and course of schizophrenia suggest sex hormones play a protective role in the pathophysiology. Such a role is also proposed for oxytocin, another important regulator of reproduction function. Evidence on the efficacy of sex hormones and oxytocin in the treatment of schizophrenia is summarized.

Methods: Double-blind, placebo-controlled, randomized studies were included, examining augmentation with estrogens, selective estrogen receptor modulators (SERMs), testosterone, dehydroepiandrosterone (DHEA), pregnenolone, and oxytocin. Outcome measures were total symptom severity, positive and negative symptom subscores, and cognition. In meta-analyses, combined weighted effect sizes (Hedges' g) per hormone were calculated.

Results: Twenty-four studies were included, examining 1149 patients. Significant effects were found for estrogen action ($k = 10$), regarding total symptoms (Hedges' $g = 0.63$, $p = 0.001$), positive (Hedges' $g = 0.42$, $p < 0.001$), and negative symptoms (Hedges' $g = 0.35$, $p = 0.001$). Subgroup analyses yielded significant results for estrogens in premenopausal women ($k = 6$) for total, positive, and negative symptoms, and for the SERM raloxifene in postmenopausal women ($k = 3$) for total and negative, but not positive symptoms. Testosterone augmentation in males ($k = 1$) was beneficial only for negative symptoms (Hedges' $g = 0.82$, $p = 0.027$). No overall effects were found for DHEA ($k = 4$), pregnenolone ($k = 4$), and oxytocin ($k = 6$). Results for cognition ($k = 12$) were too diverse for meta-analyses, and inspection of these data showed no consistent benefit.

Conclusions: Estrogens and SERMs could be effective augmentation strategies in the treatment of women with schizophrenia, although potential side effects, partially associated with longer duration use, should be taken into account. Future trials are needed to study long-term effects and effects on cognition.

1. Introduction

Schizophrenia is a chronic disease that significantly impacts psychological, social and cognitive functioning. Positive symptoms of schizophrenia can be effectively reduced with antipsychotic medication in the majority of patients. Yet, a significant minority remains symptomatic despite optimal therapy. Furthermore, negative and cognitive symptoms are persistent and, importantly, are strongly correlated with functional outcomes (Fervaha et al., 2014; Lepage et al., 2014). Hence, it remains important to improve treatment strategies, for instance by means of augmenting antipsychotic pharmacotherapy with hormones.

The possibility of hormonal treatment for schizophrenia patients was initially driven by the observation of robust sex differences in onset and course of the disease (Riecher-Rössler and Häfner, 2000). Men are more likely to develop schizophrenia than women, with an incidence risk ratio of 1.4 (Slotema et al., 2012). Furthermore, in men, age of onset is lower and the course of the disease is more severe than in women (Aleman et al., 2003; Halbreich and Kahn, 2003). Also, women, but not men, show a second incidence peak around the age of 50 (Häfner, 2003). Finally, female patients show better treatment response than men (Riecher-Rössler and Häfner, 2000; Grigoriadis and Seeman, 2002) and approximately 50% less hospitalizations (Desai et al., 2013).

A possible explanation for these sex differences is the involvement of gonadal hormones (Halbreich and Kahn, 2003), with estrogens playing a protective role against the schizophrenia pathogenesis (Riecher-Rössler and Häfner, 1993). The second incidence peak in women after menopause is in line with this suggestion. Indeed, female patients with schizophrenia in the low estrogen phase of their menstrual cycle have more severe symptoms (Grigoriadis and Seeman, 2002), and

* Corresponding author at: University Medical Center Utrecht, Brain Center Rudolf Magnus, Department of Psychiatry (A01.126), PO Box 85500, 3508 GA Utrecht, The Netherlands. Tel.: +31 88 7557468.
E-mail addresses: s.m.heringa@umcutrecht.nl (S.M. Heringa), m.j.h.begemann@umcutrecht.nl (M.J.H. Begemann), a.j.goverde@umcutrecht.nl (A.J. Goverde), i.sommer@umcutrecht.nl (I.E.C. Sommer).
[1] Both authors contributed equally.

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studies controlling for estrogen plasma levels demonstrate a negative correlation between 17β-estradiol levels and severity of schizophrenia symptoms in women (Gattaz et al., 1994; Riecher-Rössler et al., 1994; Bergemann et al., 2007), as well as in men (Kaneda and Ohmori, 2005). In a previous review article, we performed a meta-analysis of five randomized controlled trials (RCTs) on the efficacy of estrogen augmentation in premenopausal women with schizophrenia and found a significant mean effect on total, positive, and negative symptom severity (Begemann et al., 2012). However, estrogens exert risk of endometrial hyperplasia if not combined with progestogens and cancer in women (Beral et al., 2002), and in male patients, feminizing effects. Selective estrogen receptor modulators (SERMs) do not carry these side effects, as they have agonistic action on estrogen receptors in the brain and bones, but not in the sexual organs (Gizzo et al., 2013). SERMs could thus have therapeutic benefits in schizophrenia patients of both sexes without the associated side effects of estrogens.

In parallel to the potential role of estrogen, low levels of testosterone appear to be associated with more severe symptoms, although results are less consistent than for estrogens (Ritsner et al., 2006a; Ko et al., 2007). Serum concentrations of testosterone are lower in adolescent boys with prodromal psychotic symptoms than in controls (van Rijn et al., 2011), and also in patients with schizophrenia at admission and during treatment, while levels appear to normalize after remission (Taherianfard and Shariaty, 2004). Furthermore, testosterone levels are lower in patients with predominantly negative symptoms compared to patients with mainly positive symptoms (Shirayama et al., 2002; Goyal et al., 2004; Ko et al., 2007), and testosterone levels are associated with a greater severity of negative symptoms (Sisek-Šprem et al., 2014). In addition, testosterone levels predict cognitive functioning in men with schizophrenia (Moore et al., 2013). These results suggest that augmentation with testosterone could be especially effective in improving negative and cognitive symptoms in male patients. Testosterone is partly converted into estradiol to influence cerebral target sites (Fink et al., 1998; Ko et al., 2007) and may therefore have similar neuroprotective capacities as estrogens in women (Huber et al., 2005).

In addition to the possible therapeutic effects of sex hormones in schizophrenia, precursors of these sex hormones, such as dehydroepiandrosterone (DHEA; a precursor for both testosterone and estrogen) and pregnenolone, may have neuroprotective properties as well and could therefore play a modifying role in the pathophysiology of schizophrenia (Ritsner et al., 2008; Ritsner, 2010). These precursors have many functions of their own, including mood regulation, cognitive performance, and response to stress (Mellon, 2007; Maninger et al., 2009). Although findings on blood levels of DHEA and its sulfate (DHEAS) in schizophrenia are inconsistent, high levels of DHEA appear to be related to lower symptom severity (Harris et al., 2001; Marx et al., 2004). In addition, serum concentrations of pregnenolone are found to be lower in schizophrenia patients compared to healthy controls (Ritsner et al., 2007).

Finally, the pituitary hormone oxytocin has gained much interest as a potential therapeutic option in schizophrenia. Oxytocin, like sex hormones, is an important regulator of reproductive function. It is known for its role in social behavior (Lee et al., 2009) and may therefore have a promising influence on social deficits. The oxytocin system is altered in patients with schizophrenia (Mai et al., 1993; Goldman et al., 2008). Oxytocin is thought to regulate central dopamine, and might therefore exhibit antipsychotic effects (Feifel, 2011). Several studies suggest that higher plasma oxytocin levels in patients with schizophrenia correlate with fewer psychotic symptoms (Sasayama et al., 2012; Cochran et al., 2014), improved cognition (Frost et al., 2014) and pro-social behavior (Rubin et al., 2010).

In order to evaluate the potential beneficial effects of hormonal augmentation in reducing schizophrenia symptoms, we conducted a quantitative review of all available randomized placebo-controlled trials (RCTs) on estrogens, SERMs, testosterone, DHEA(S), pregnenolone, and oxytocin in patients with a schizophrenia spectrum disorder. Secondarily, we investigated the impact of these hormones on cognitive functioning in these patients.

2. Materials and methods

2.1. Literature search

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Liberati et al., 2009). An electronic search was conducted using Medline (Pubmed), Embase, National Institutes of Health ClinicalTrials.gov, and the Cochrane Database of Systematic Reviews. No year or language restrictions were applied. Combinations of the following keywords were used in the search: “schizophrenia”, “antipsychotic”, “augmentation”, “cognition”, together with the names of the specific hormones. Additionally, the reference lists of the identified papers, previous reviews and meta-analyses were screened for cross-references. The search cut-off date was the last day of November 2014. When necessary, corresponding authors were contacted to provide full details of study outcomes. Two reviewers independently extracted data from the papers; any disagreements were resolved by consensus.

2.2. Inclusion

Candidate studies had to meet the following inclusion criteria:

1. Randomized, double-blind, placebo-controlled studies regarding antipsychotic augmentation using estrogens, SERMs, testosterone, DHEA(S), pregnenolone, or oxytocin.
2. Patients had a diagnosis of a schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, schizophreniform disorder or psychotic disorder NOS), according to the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR) (APA, 1994), or the *International Classification of Diseases* (ICD-9 or ICD-10) (WHO, 1992).
3. Studies were published in a peer-reviewed journal.
4. Sufficient information was reported in the article to compute common effect size statistics, i.e. means and standard deviations, exact *p*-, *t*- or *z*-values (Lipsey and Wilson, 2001), or corresponding authors could provide these data upon request. For cross-over studies, first stage data were used in order to avoid carry-over effects (Sibbald and Roberts, 1998).

2.3. Clinical outcome measures

The primary outcome measures were the mean change in total, positive, and negative symptom severity. Total scores and scores on positive and negative subscales were included of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1981), or the Negative Symptoms Rating Scale (NSRS) (Iager et al., 1985). SANS or SAPS scores were preferred over PANSS subscales, in case both were provided. Secondary outcome measure was cognitive functioning. Results were grouped for the domains memory, attention, processing speed, language, visuospatial, constructional and movement skills, verbal fluency, and social cognition.

In most trials, data were analyzed with mixed models. The outcomes of these analyses were used in the meta-analyses to calculate weighted effect sizes. When authors used methods other than mixed models to analyze their data and deal with missing data, last observation carried forward (LOCF) data were preferred over per protocol data.

Side effects were compared between augmentation and placebo group on various side effect scales.

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