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# Estrogen augmentation in schizophrenia: A quantitative review of current evidence

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ABSTRACT

*Background:* Sex differences in the incidence, onset and course of schizophrenia have led to the hypothesis that estrogens play a protective role in the pathophysiology of this disorder. Several trials have assessed the potential of estrogens in reducing schizophrenia symptoms, showing inconsistent results. This quantitative review summarizes available evidence on the efficacy of estrogens in the treatment of schizophrenia.
*Methods:* Only double-blind, placebo-controlled, randomized studies were included. Primary outcome measure was total symptom severity, secondary outcome measures were subscores for positive and negative symptoms. Effect sizes were calculated for individual studies and, if possible, pooled in meta-analyses to obtain combined, weighted effect sizes (Hedges's $g$).
*Results:* Superior efficacy was found for estrogen treatment in female patients (four RCTs, 214 patients) 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. As the included studies applied different forms of estrogens, a separate analysis was conducted on the trials applying estradiol (three RCTs, 170 patients). Even larger effect sizes were found for total symptom severity (Hedges's $g = 0.79$), positive (Hedges's $g = 0.57$) and negative symptoms (Hedges's $g = 0.45$), with reduced heterogeneity. Estrogen treatment in male patients (one study, 53 patients) was not superior to placebo.
*Conclusions:* Our results suggest that estrogens, especially estradiol, could be an effective augmentation strategy in the treatment of women with schizophrenia. However, future larger trials are needed before recommendations on clinical applications can be made.



## 1. Introduction

Schizophrenia is a chronic disease that significantly impacts psychological, social and cognitive functioning. Although antipsychotic medication effectively reduces positive symptoms of schizophrenia, negative and cognitive symptoms are frequently persistent. As these latter two symptom groups are strongly correlated with functional outcome (Green, 2006; Buchanan, 2007), it remains important to improve treatment strategies. One direction for the development of new treatments currently under interest comprises additional pharmacotherapy with hormones.

The possibility of hormonal treatment for schizophrenia patients was initially driven by observed sex differences in incidence, onset and course of the disease (reviewed by Riecher-Rössler and Häfner, 2000). It is now consistently reported that males are more likely to develop schizophrenia than females, with an incidence risk ratio of 1.4 (Aleman et al., 2003; McGrath et al., 2004). In addition, age of onset is younger in men (Leung and Chue, 2000) while women, but not men, show a second incidence peak after the age of 50 (Riecher-Rössler and Häfner, 2000; Häfner, 2003). It has also been noted that premenopausal women experience a more favorable course with fewer negative symptoms and show better treatment response than men (Morgan et al., 2008; Cotton et al., 2009). These observations provide compelling evidence to suggest that estrogens have a protective role in the pathophysiology of schizophrenia (Grigoriadis and Seeman, 2002, Markham, 2011; Kulkarni et al., 2012). The potential involvement of estrogens in schizophrenia was already recognized in the nineteenth century, when an association was noticed between phases of the menstrual cycle and changes in psychopathology (Von Krafft-Ebing, 1878; Riecher-Rössler, 2002). More recent studies have indeed confirmed that female schizophrenia patients tend to have more severe symptoms in the low estrogen phase of the menstrual cycle (Riecher-Rössler et al., 1994; Grigoriadis and Seeman; 2002; Riecher-Rössler, 2002; Bergemann et al., 2007), and estrogen plasma levels are found to be correlated with the therapeutically required dose of antipsychotic medication (Gattaz et al., 1994).

Although estrogens are originally known for their regulation of endocrine and reproductive functions, they are now extensively studied for their profound actions in the central nervous system. Estrogen receptors have been found in various brain areas including the neocortex, hippocampus, hypothalamus, and limbic system, indicating a vital importance in brain functioning (Österlund and Hurd, 2001). The primary forms of estrogen are 17β-estradiol ($E_2$) and estrone ($E_1$), with estradiol being

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the most potent activator of estrogen receptors in the brain (Turgeon et al. 2004). Accumulating evidence indicates that estrogens also have neuroprotective and neurotrophic properties (Wise et al., 2001). Given the numerous brain abnormalities found in schizophrenia patients, it is often proposed that the pathogenesis involves a progressive neurodegenerative component (Iritani, 2007) and estrogens could therefore have a modifying role in the development of schizophrenia. Furthermore, estrogens are found to be significantly involved with dopaminergic, serotonergic and glutamatergic systems, possibly giving them properties similar to those of atypical antipsychotic medications (Hughes et al., 2009; Taylor et al., 2009; Kulkarni et al., 2012).

These indications for a potentially ameliorating role of estrogens in schizophrenia have provided a lead for new treatment. Several clinical trials have assessed the therapeutic potential of estrogen augmentation therapy, showing inconsistent findings. In order to evaluate the current prospects of estrogens in reducing schizophrenia symptoms, we conducted a quantitative review of all available randomized placebo-controlled trials (RCTs).

## 2. Methods

### 2.1. Literature search

This quantitative review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2009). An electronic search was conducted using PubMed, Embase, National Institutes of Health ClinicalTrials.gov, Cochrane Schizophrenia Group entries in PsiTri (http://psitri.stakes.fi), and Cochrane Database of Systematic Reviews. No year or language restrictions were applied. The following keywords were used in the search, both alone and in combinations: "schizophrenia," "antipsychotic," "augmentation," "estrogen," "(17β-)estradiol," "estrone." Additionally, the reference lists of identified papers, previous reviews and meta-analyses were screened for cross-references. When necessary, corresponding authors were contacted to provide full details of study outcomes.

### 2.2. Inclusion

Candidate studies had to meet the following inclusion criteria:

1. Randomized, double-blind, placebo-controlled trials, published in a peer-reviewed journal.
2. Patients had a diagnosis of a schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder or schizophreniform disorder), according to the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR; American Psychiatric Association, 1994), or the *International Classification of Diseases* (ICD-9 or ICD-10; World Health Organization, 1992).
3. Included patients were treated with a stable dose of antipsychotic medication before the trial started, which did not change during the augmentation period. Patients were not receiving any hormonal treatment prior to study onset, including the oral contraceptive pill.
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 (cf. Lipsey and Wilson, 2001), or corresponding authors could provide these data upon request.

### 2.3. Clinical outcome measures

Primary outcome measure was total symptom severity as measured with the Positive and Negative Syndrome Scale (PANSS [Kay et al., 1987]) or the Brief Psychiatric Rating Scale (BPRS [Overall and Gorham, 1962]), secondary outcome measures were the subscores on positive and negative symptom severity. Patient data of the last observation carried forward (LOCF) were used for analysis. When not provided by the article nor by the corresponding author, the data of completers were used.

### 2.4. Statistical analysis

Two reviewers independently extracted data from the papers, any disagreements were resolved by consensus. Effect sizes were calculated for the mean differences (placebo versus augmentation) of the change score (end of treatment minus baseline) means and standard deviations. Change scores were used instead of pre- and post-treatment scores in order to avoid overestimation of the true effect size caused by pre-post treatment correlation (Dunlap et al., 1996). All effect sizes were calculated twice independently from the original articles to check for errors. When more than one RCT on a particular augmentation strategy was available, effect sizes of studies were pooled in meta-analyses to obtain a combined, weighted effect size for primary and secondary outcome measures. The effect size estimate used was Hedges's *g*, applying a random effects model (Shadish and Haddock, 1994). Effect sizes with a *p*-value smaller than 0.05 were considered significant. A homogeneity statistic, $I^2$, was calculated to determine whether the studies could be taken together to share a common population effect size (Higgins et al., 2003). High heterogeneity (i.e. $I^2$ of 50% or higher) indicates heterogeneity of the individual study effect sizes, which poses a limitation to reliable interpretation of the results. Values of $I^2$ between 30 and 50% were considered moderate. When interpreting meta-analytic outcomes, the possibility of an upward bias of the calculated effect sizes due to the omission of unpublished, nonsignificant studies must be taken into account. The phenomenon of studies with null effects not to be published in the literature generates a publication bias, also called the 'file drawer problem' (Rosenthal, 1979). Therefore, in addition to an inspection of the funnel plot, the fail-safe number of studies ($N_R$) was calculated which provides an estimation on how many nonsignificant or missing studies would be needed to reduce an observed overall significant result to nonsignificance. All calculations were executed using Comprehensive Meta Analysis Version 2.0 (Borenstein et al., 2005).

## 3. Results

Five RCTs (Kulkarni et al., 2001; Akhondzadeh et al., 2003; Louzã et al., 2004; Kulkarni et al., 2008, 2011) with a total of 267 patients could be included. Four trials included women of childbearing age (with the study of Kulkarni et al. 2001 comparing two different dosages), and one study included men (Kulkarni et al., 2011). Effect sizes calculated for the individual studies are summarized in Table 1.

We performed a meta-analysis on the four trials that included female patients ($N = 214$; Table 1). Estrogens were found to be superior to placebo in reducing total symptom severity (Hedges's $g = 0.66$; 95%CI:0.21 to 1.11; $p = 0.004$; see Fig. 1), but heterogeneity was moderate to high ($I^2 = 58\%$). The relatively small fail-safe $N_R$ of 21 is indicative of a potential file drawer problem, as Rosenthal (1984) suggests $5\ k + 10$ ($k$ = number of studies in review) as a guideline for ruling out such effects.

Furthermore, estrogens were superior to placebo for positive symptoms (Hedges's $g = 0.54$; 95%CI:0.27 to 0.82; $p = 0.002$; see Fig. 2) and negative symptoms (Hedges's $g = 0.34$; 95%CI:0.01 to 0.67; $p = 0.04$; see Fig. 3). Heterogeneity was low, $I^2 = 0\%$ and $I^2 = 25\%$, respectively. Again, the fail-safe numbers of these analyses ($N_R = 13$ for positive symptoms and $N_R = 3$ for negative symptoms) suggest the possibility of a file drawer problem.

Three of the studies included applied the estrogen (ethinyl) estradiol, one study administered estrone. As estradiol is the more potent agonist of the estrogen receptors (Turgeon et al., 2004), a separate analysis was conducted on the estradiol trials ($N = 170$; Table 1). Even larger mean weighted effect sizes were found for estradiol addition on all