# Combination of Estrogen and Antipsychotics in the Treatment of Women with Chronic Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial

*Emel Ghafari [1], Mohammad Fararouie [2], Hamidreza Ghafarian Shirazi [3], Arazm Farhangfar [4], Fateme Ghaderi [5], Ali Mohammadi [6]*

## Abstract

**Introduction:** Gender differences in schizophrenia include the age of onset, better treatment response, a better outcome, and the peak of the disease in postmenopausal women. Some evidence indicates that these variations are due to estrogen's effect. The intention of this study was to evaluate the effectiveness of estrogen as an adjuvant agent in the treatment of women with chronic schizophrenia. **Methods:** Study participants were 32 women of childbearing age with chronic schizophrenia. These patients were hospitalized in an institute for the chronically mentally ill. Participants were randomized into two groups: the first group (16 cases) received conjugated estrogens 0.625 mg/day 4 weeks with their previous antipsychotic treatment, while the second group (16 cases) received placebo booster and antipsychotics. The Positive and Negative Syndrome Scale (PANSS) was used as a measurement tool for assessing psychopathology. **Results:** The combination of conjugated estrogens with antipsychotic treatment showed a significant decrease in positive ($p=0.003$), negative ($p<0.001$), general ($p<0.001$) and total ($p<0.001$) PANSS scores over 4 weeks. **Conclusions:** Estrogen may be an effective adjuvant agent in the treatment of women with chronic schizophrenia.

**Key Words:** Schizophrenia, Estrogen, PANSS

[1] *Faculty of Medicine, Yasouj University of Medical Sciences, Yasouj, Iran*
[2] *Department of Epidemiology, Yasouj University of Medical Sciences, Yasouj, Iran*
[3] *Department of Biostatistics, Yasouj University of Medical Sciences, Yasouj, Iran*
[4] *Department of Agricultural, Food and Nutritional Sciences, University of Alberta, Edmonton, Canada*
[5] *Department of Internal Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*
[6] *Department of Psychiatry, Yasouj University of Medical Sciences, Yasouj, Iran*

*Address for correspondence: Ali Mohammadi, MD, Department of Psychiatry, Yasouj University of Medical Sciences, Motahari Street, Yasouj, Iran Phone: +98-9171198320; Fax: +98-7412230290; E-mail: amohammadi@hotmail.com*

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## Introduction

For the century since Kraepelin proposed gender differences in schizophrenia (1, 2), several epidemiological and clinical studies have supported this theory. The first episode of schizophrenia begins at a later age in women than in men (3-5) and the rate of relapse of the disease increases in postpartum (6) and during postmenopause (3, 7, 8), which may require higher doses of antipsychotic medication (8). Antipsychotic response and prognosis of the disease among women of childbearing age is generally better than men (8, 9), and estrogen was reported to reduce psychotic symptoms in women with schizophrenia during the luteal phase of menstruation, when estrogen is at its highest level (10, 11). The cause of these variations of sex has been attributed to the effect of estrogen (12).

## Clinical Implications

Estrogen plays a role in a number of processes that regulate synaptic plasticity including synaptogenesis and neurogenesis (26). It has been suggested that estrogen may be neuroprotective (27); it is also clear that estrogen affects the majority of neurotransmitters in the brain. Estrogen provides a significant reduction of both dopamine agonist- and dopamine antagonist-induced behavior (28, 29). Moreover, it is reported that estrogen mediates inhibition of dopamine transport (30). It is clear that serotonin (5HT) can also be influenced by estrogen. Estrogen regulates serotonin transporter activity (31, 32), integrates sensorimotor gating mediated by 5-HT1A receptors (33), and increases 5-HT(2A) receptor binding in human prefrontal areas (34). The effect of estrogen on glutamate appears to prevent glutamate-induced neurotoxicity (35-37) and increasing glutamate release from presynaptic sites (38). Moreover, effects of estrogen on GABA (39-41) and noradrenaline have been shown in a number of studies (42, 43).

Despite all these studies, human clinical trials showed controversial results. Some researchers have reported positive results (12, 14, 15, 18), while others indicated negative (14, 17, 18). Although these studies used different estrogen compounds, it does not seem that the results were affected by this factor. This study provides further evidence on the efficacy of estrogen in the treatment of patients with schizophrenia.

Following these observations, several clinical trials have been conducted to evaluate the effect of estrogen in the treatment of schizophrenia. Kulkarni et al. (13) in an open trial added estradiol (0.02 mg/day) to the neuroleptic regimen of 11 schizophrenic women for 8 weeks and compared the results to 7 women receiving only antipsychotic drugs. They found that the group receiving estradiol showed more elimination of psychotic symptoms compared with the control group. Lindamer et al. (14) reported lower negative symptoms and lower average daily doses of antipsychotic medication in a group of postmenopausal women (n=24) who received hormone replacement therapy compared with the control group (n=28) which didn't go through the specified treatment. Kulkarni et al. (15) investigated the addition of 100 mcg (first group) and 50 mcg (second group) of transdermal estradiol and placebo (control group) to antipsychotic drugs in women of childbearing age. It was reported that the groups receiving transdermal estradiol had more improvement in their psychotic symptoms compared with the control group. Akhondzadeh et al. (16) reported a better response in a group that had received a combination of 0.05 mg/day of ethinyl estradiol and 15 mg/day of haloperidol compared with another group that only received 15 mg haloperidol in the total score, general psychopathology score and positive symptoms score of PANSS. Louza et al. (17) conducted a clinical trial of 44 women with acute schizophrenia and found no significant differences between the case group (combination of 0.625 mg/day of conjugated estrogen plus 5 mg of haloperidol per day) and the control group (placebo plus 5 mg of haloperidol). Also, Bergemann et al. (18) could not recognize any significant difference between an estrogen plus antipsychotic treatment group and a group with antipsychotic treatment alone. And finally, Kulkarni et al. (19), in their study of 102 women with schizophrenia, described a better response in the group with transdermal estradiol treatment versus the placebo group (see Table 1).

Because of the lack of adequate clinical trials and controversial results of existing studies, we designed this study to evaluate the effectiveness of adding estrogen and antipsychotics in women with chronic schizophrenia.

## Methods

Participants in this study were 32 childbearing-age women with chronic schizophrenia. All patients were kept in an institution for chronic mental illness patients in Yasouj, Iran and met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* (20) criteria for chronic schizophrenia. The diagnosis was made by a professional psychiatrist with the Structured Clinical Interview for DSM-IV.

The patients were randomized into two groups receiving either adjuvant conjugated estrogen (16 women) or adjunctive placebo (16 women) according to a computer-generated randomization list. Women in the estrogen group received 0.625 mg/day oral conjugated estrogen tablets and women in the placebo group were given placebo tablets orally every morning at eight o'clock for the trial period of 4 weeks. All participants remained on their current antipsychotic medication. Women were excluded if they received concomitant hormonal therapy or if they were pregnant or lactating, had positive history of deep venous thrombosis or other thrombotic disorders, or if they had abnormal uterine bleeding or severe neurological disorders. Psychopathological symptoms were assessed at baseline and after 4 weeks using the Positive and Negative Syndrome Scale (PANSS) (21), and all participants scored 60 or higher (indicative of severe illness).

Quantitative data were expressed by absolute and relative frequencies. Mean and standard deviation were used to show the distribution of quantitative data. One-way repeated measures ANOVA was used to measure the association between the nature of the treatment and the PANSS total and subscales. A p-value $<0.05$ was considered a statistically significant association. The study was approved by the Yasouj

**Table 1** Some Characteristics of Previous Clinical Trials Using Estrogen for Schizophrenia

| Authors | Number of Subjects | Year | Dose | Improvement | Estrogen Type |
|---|---|---|---|---|---|
| Kulkarni et al. | 11 | 1996 | 0.02 mg/day | + | estradiol |
| Lindamer et al. | 52 | 2001 | unknown | negative symptoms improvement | unknown |
| Kulkarni et al. | 24 | 2001 | 50 and 100 mcg | + | transdermal estradiol |
| Akhondzadeh et al. | 32 | 2003 | 0.05 mg/day | + | ethinyl estradiol |
| Louza et al. | 44 | 2004 | 0.625 mg/day | – | conjugated estrogens |
| Bergemann et al. | 46 | 2005 | 1–3 mg | – | 17beta-estradiol + norethisterone acetate |
| Kulkarni et al. | 102 | 2008 | 100 mcg | + | transdermal estradiol |

Medical University ethics committee, and was performed in accordance with the Helsinki Declaration and subsequent revisions (22). Informed consent was obtained from the patients' caregivers to enroll in the study.

## Results

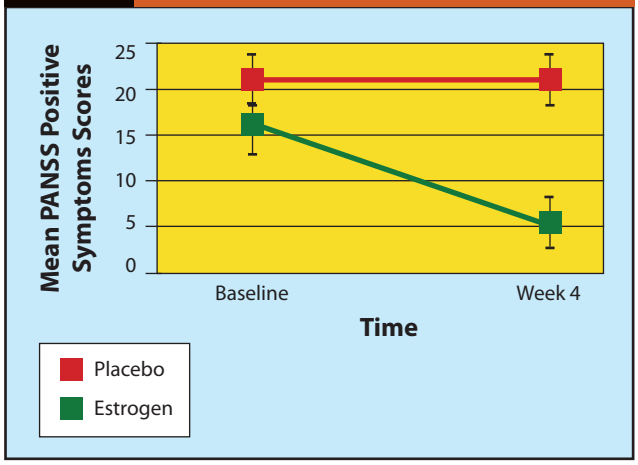
At baseline, no significant differences were found between the two treatment groups (see Table 2). During the trial, one patient withdrew from the estradiol group and one was removed from the placebo group at the request of the patient's caregivers. There were no significant differences between the two treatment arms at baseline for the positive (t=1.35, df=28, p=0.19), negative (t=0.99, df=28, p=0.33), general (t=1.97, df=28, p=0.06) and total (t=1.89, df=28, p=0.07) PANSS scores. One-way repeated measure ANOVA showed that the estrogen group had significantly greater improvements over time than the placebo group in the positive (F=10.97, df=1, p=0.003), negative (F=18.18, df=1, p<0.001), general (F=34.11, df=1, p<0.001) and total (F=109.1, df=1, p<0.001) PANSS scores (see Figures 1–4). According to the results, patients in the estrogen arm had a greater improvement in general scores compared to the other PANSS syndrome subscales.

**Table 2** Baseline Data for Patients in the Estrogen and Placebo Groups

| | Estrogen (n=15) | Placebo (n=15) | P-Value |
|---|---|---|---|
| **Age** | 34.2 (9.1) | 34.8 (8.3) | ns |
| **Number of previous hospital administrations** | 7.4 (9.4) | 6.8 (10.7) | ns |
| **Antipsychotic medication: n** | | | |
| | Haloperidol: 4 | Haloperidol: 5 | ns |
| | Trifluoperazine: 2 | Trifluoperazine: 1 | ns |
| | Chlorpromazine: 1 | Chlorpromazine: 1 | ns |
| | Fluphenazine: 2 | Fluphenazine: 2 | ns |
| | Clozapine: 1 | Clozapine: 1 | ns |
| | Risperidone: 4 | Risperidone: 3 | ns |
| | Olanzapine: 1 | Olanzapine: 2 | ns |

ns = not significant

**Figure 1** Mean PANSS Positive Symptoms at Baseline (Week 0) and Week 4 for the Estrogen and Placebo Groups




## Discussion

In this study we found that the group that received 4 weeks of conjugated estrogen plus antipsychotic drugs showed better results in positive, negative and general psychopathology PANSS scores as compared with the group receiving just a placebo and antipsychotic medications.

The effect of estrogen on the brain has been demonstrated in a series of animal and human studies. It seems that the main effect of estrogen on schizophrenia is the modulating effect of this hormone on dopamine receptors. The presence of estrogen receptors in the limbic system, reduction of dopamine concentration in the striatum by estrogen, enhancement of neuroleptic-induced catalepsy in animal

**Figure 2** Mean PANSS Negative Symptoms at Baseline (Week 0) and Week 4 for the Estrogen and Placebo Groups

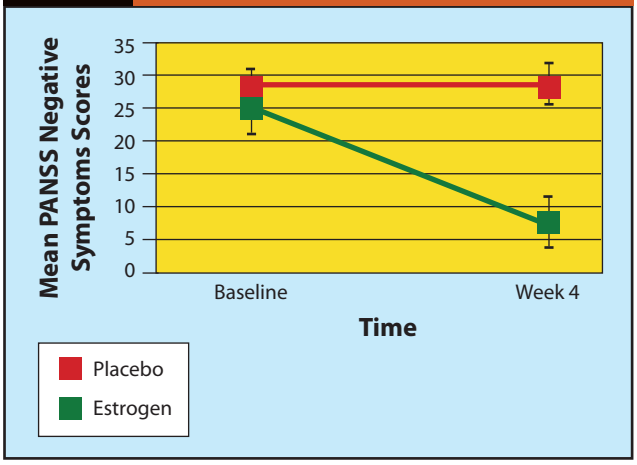



**Figure 3** Mean PANSS General Psychopathology Symptoms at Baseline (Week 0) and Week 4 for the Estrogen and Placebo Groups

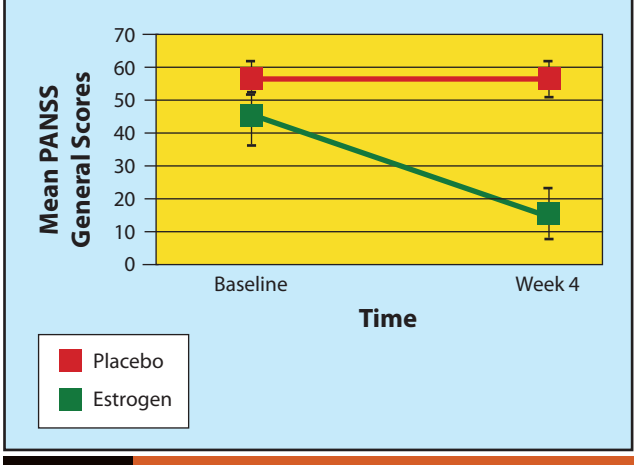
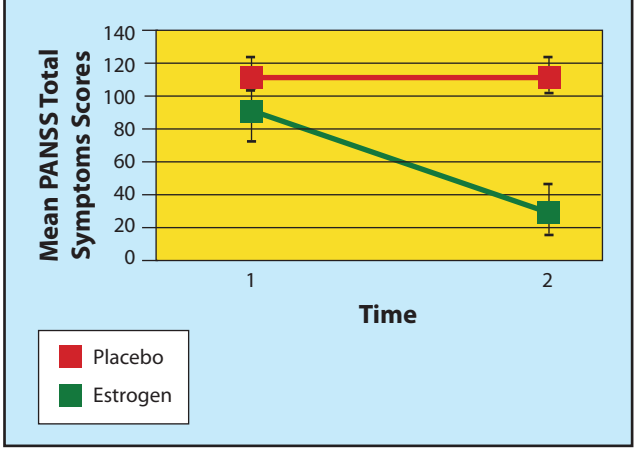



**Figure 4** Mean PANSS Total Psychopathology Symptoms at Baseline (Week 0) and Week 4 for the Estrogen and Placebo Groups




models, and positive clinical effect of estrogen in neuroleptic-induced dyskinesia support this hypothesis (23).

The variation in the estrogen receptor alpha (ESR1) gene and cortical ESR1 mRNA is associated with schizophrenia (24). An animal study showed that estrogen blocks dopamine agonist- and serotonin agonist-mediated prepulse inhibition (25).

Estrogen plays a role in a number of processes that regulate synaptic plasticity including synaptogenesis and neurogenesis (26). It has been suggested that estrogen may be neuroprotective (27); it is also clear that estrogen affects the majority of neurotransmitters in the brain. Estrogen provides a significant reduction of both dopamine agonist- and dopamine antagonist-induced behavior (28, 29).

Moreover, it is reported that estrogen mediates inhibition of dopamine transport (30). It is clear that serotonin (5HT) can also be influenced by estrogen. Estrogen regulates serotonin transporter activity (31, 32), integrates sensorimotor gating mediated by 5-HT1A receptors (33), and increases 5-HT(2A) receptor binding in human prefrontal areas (34). The effect of estrogen on glutamate appears to prevent glutamate-induced neurotoxicity (35-37) and increasing glutamate release from presynaptic sites (38). Moreover, effects of estrogen on GABA (39-41) and noradrenaline have been shown in a number of studies (42, 43).

Despite all these studies, human clinical trials showed controversial results. Some researchers have reported positive results (12, 14, 15, 18), while others indicated negative (14, 17, 18). Although these studies used different estrogen compounds, it does not seem that the results were affected by this factor.

This study provides further evidence on the efficacy of estrogen in the treatment of patients with schizophrenia.

## Conclusions

In this study, the estrogen group was associated with better outcome in terms of reducing total PANSS score, the PANSS positive subscale score, the PANSS negative subscale score and the PANSS general psychopathology subscale score.

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