Estrogen in Severe Mental Illness

A Potential New Treatment Approach

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Context: Accumulating evidence suggests that estrogens may have therapeutic effects in severe mental illnesses, including schizophrenia, via neuromodulatory and neuroprotective activity.

Objective: To compare the efficacy of adjunctive transdermal estradiol with that of adjunctive placebo in the treatment of acute psychotic symptoms.

Design: Randomized, double-blind study.

Setting: Patients were recruited from inpatient acute hospital wards and outpatient clinics of 2 metropolitan Melbourne general hospitals.

Participants: One hundred two women of childbearing age with schizophrenia. All participants were in an acute or chronic phase of their illness; 73 participants were outpatients and the rest were inpatients.

Intervention: Patients were randomized to receive 100 µg of transdermal estradiol (n=56) or transdermal placebo (n=46) for 28 days.

Main Outcome Measures: Psychopathological symptoms were assessed weekly with the Positive and Negative Syndrome Scale.

Results: The addition of 100 µg of transdermal estradiol significantly reduced positive (P<.05) and general psychopathological (P<.05) symptoms during the 28-day trial period compared with women receiving antipsychotic medication alone.

Conclusion: Estradiol appears to be a useful treatment for women with schizophrenia and may provide a new adjunctive therapeutic option for severe mental illness.

Trial Registration: clinicaltrials.gov Identifier: NCT00206570

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Accumulating evidence from clinical data and basic and experimental research, as well as epidemiologic studies, describes the effects of estrogen and other gonadal hormones on the central nervous system and, in particular, on the mental state of women. Although the link between estrogen and mental illness was recognized more than a century ago (see Riecher-Rossler and Hafner1 for a review), scientific evidence supporting the pharmacotherapeutic effects of exogenous estrogen has only started to emerge during the past 2 decades. Although findings are still preliminary, there is now a growing appreciation for the positive effect estrogen treatment can have on symptoms of severe mental illnesses, including schizophrenia.

Epidemiologic observations of sex differences in the onset and course of schizophrenia prompted exploration of estrogen’s role in schizophrenia.2,3 Women with schizophrenia present with their first episode on average about 5 years later than their male counterparts.4-7 Life cycle studies have shown that women are more vulnerable for either a first episode or a relapse of existing illness at 2 major periods of hormonal change: during the postpartum period (associated with a decrease in estrogen levels)8 and during menopause (when estrogen production decreases).9-11 Conversely, chronic psychoses and relapse rates improve during pregnancy, when estrogen plasma levels are high.8,12 Levels of psychopathological symptoms have also been observed to fluctuate with menstrual cycle phases. Exacerbation or recurrence of psychosis is observed during low-estrogen phases of the menstrual cycle, and psychopathological behavior improves during high-estrogen phases.13,14 Collectively, these findings have contributed to
the hypothesis that estrogen has a protective effect in women vulnerable to schizophrenia.

Intervention studies using estrogen as a therapeutic agent have provided further support for the estrogen protection hypothesis. The pilot study by our group found that 11 childbearing-aged women with schizophrenia who were given 2 mg of oral estradiol valerate as an adjunct to antipsychotic medication made a significantly more rapid recovery from acute psychotic symptoms than did 7 similarly aged and unwell women who received antipsychotic medication alone. We next conducted a dose-finding, double-blind, placebo-controlled study of adjunctive transdermal estradiol, 50 and 100 µg, in a comparable cohort of 36 women with schizophrenia. The 12 participants receiving 100 µg of transdermal adjunctive estrogen had a significant improvement in psychotic symptoms compared with the 50-µg or placebo adjunct groups. Similar benefits of adjunctive estrogen therapy were shown by Akhondzadeh and colleagues17 in a double-blind, placebo-controlled study in 32 women of childbearing age with schizophrenia. Despite these positive findings, a recent review on the effects of estrogen as sole treatment or adjunctive therapy for schizophrenia highlighted the need for adequately powered, well-designed studies. Hence, the aim of the present study was to compare 100 µg of transdermal adjunctive estrogen with a placebo adjunct in childbearing-aged women with schizophrenia. The 12 participants receiving 100 µg of transdermal adjunctive estrogen had a significant improvement in psychotic symptoms compared with the 50-µg or placebo adjunct groups. Similar benefits of adjunctive estrogen therapy were shown by Akhondzadeh and colleagues17 in a double-blind, placebo-controlled study in 32 women of childbearing age with schizophrenia. Despite these positive findings, a recent review on the effects of estrogen as sole treatment or adjunctive therapy for schizophrenia highlighted the need for adequately powered, well-designed studies. Hence, the aim of the present study was to compare 100 µg of transdermal adjunctive estrogen with a placebo adjunct in childbearing-aged women with schizophrenia.

METHODS

PARTICIPANTS

Approximately 400 women who met DSM-IV criteria for schizophrenia, schizoaffective disorder, or schizoaffective disorder were invited to take part in the trial during a 3-year period (from January 1, 2001, to April 30, 2004). One hundred two women met inclusion criteria and provided written informed consent (according to the guidelines of the Australian National Health and Medical Research Council). Diagnosis was made by treating psychiatrists and confirmed by research psychiatrists with the Structured Clinical Interview for DSM-IV. All women were in an acute or chronic phase of their illness, and a significant number were treatment resistant. Women with schizoaffective disorder, depressed type, were included and women with schizoaffective disorder, bipolar subtype, were excluded. Women were excluded if they were currently receiving any hormonal treatment, including the oral contraceptive pill; if they were pregnant or lactating; if they had experienced perimenopause or menopause; if they had a history of hyperthyroidism or any unstable neurologic or other serious medical condition; or if they were in a manic phase of their illness. Screening blood tests were conducted to determine hormone levels and general health status.

INTERVENTIONS: ESTRADIOL AND PLACEBO TRANSDERMAL PATCHES

One hundred two participants commenced trial medication. They were individually randomized by the Alfred Clinical Trials Pharmacy to receive either adjunctive estradiol (56 women) or adjunctive placebo (46 women) according to a computer-generated randomization list. All study personnel and participants remained blind to treatment assignment for the duration of the study. Women in the estradiol condition received a 100-µg estradiol transdermal patch, which delivers 100 µg of estradiol per day at a constant rate. Placebo patches were adhesive and identical in appearance but had no active substance. The commencement of treatment was independent of menstrual cycle phase. Both types of patches were changed every 3.5 days (eg, on a Monday morning and a Thursday night) for the trial duration of 28 days. All participants remained on their current antipsychotic medication regimen. After the antipsychotic medications were subclassified as typical or atypical, there was no significant difference between the groups in the number of women using both types (Table 1). Specifically, the distributions were as follows:

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Medication Data Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>52</td>
<td>4 patients</td>
</tr>
<tr>
<td>Placebo</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

Typical agents

- Haloperidol, 1.9% (n=1)
- Flupenthixol, 3.8% (n=2)
- Chlorpromazine hydrochloride, 1.9% (n=1)
- Fluphenazine decanoate, 1.9% (n=1)
- Zuclophenthixol, 1.9% (n=1)

Atypical agents

- Olanzapine, 28.8% (n=15)
- Clozapine, 34.6% (n=18)
- Quetiapine fumarate, 7.7% (n=4)
- Risperidone, 17.3% (n=9)

OBJECTIVES AND OUTCOMES

Psychopathological symptoms were assessed at baseline and days 7, 14, 21, and 28 by means of the Positive and Negative Syndrome Scale (PANSS). All participants scored 60 or higher (indicative of severe illness). A Menstrual Cycle Questionnaire and Abnormal Involuntary Movement Scale. During the course of the trial, 2 participants withdrew from the estradiol group (owing to menstrual bleeding) and 1 participant was removed from the placebo group after becoming lost to follow-up. At day 28, there were 54 participants in the estradiol group and 45 participants in the placebo group. For PANSS ratings, there were incomplete data sets for 3 participants in the estradiol group and 9 participants in the placebo group; hence, for data analysis of psychopathology ratings, 51 participants were included in the estradiol group and 36 in the placebo group.
**Statistical Analysis**

A series of repeated-measures analyses of variance (ANOVAs) were conducted to compare psychopathological symptom ratings (PANSS subscale scores) and adverse effects (Adverse Symptoms Checklist, Abnormal Involuntary Movement Scale, and Simpson Angus Rating Scale for Extrapyramidal Side Effects) at baseline and at days 7, 14, 21, and 28. Because hormone data were not normally distributed, hormone levels were analyzed as change from baseline scores, with the use of repeated-measures ANOVAs. Baseline comparisons were made with χ² tests for equal proportion, unpaired t tests, and Wilcoxon rank-sum tests where appropriate. \( P = .05 \) was considered to be statistically significant for all main effects and interactions (effect size interpretation was based on Cohen's classification).

**Results**

**Demographics**

Demographic information is shown in Table 1. There were no statistically significant differences between the 56 women in the estradiol group and the 46 women in the placebo group in terms of age, age at illness onset, or medication dosage.

**Hormone Results**

Hormone levels are presented in Table 2. For all hormone analyses, cycle phase at baseline (follicular or luteal) was included in the multivariate models as a covariate. Although mean estradiol levels increased from baseline in the active treatment group (but not the placebo group), this difference did not reach significance. Of note, there was a large amount of variability in scores, and this may explain the nonsignificant findings. The change from baseline in LH levels was significantly greater in the estradiol group than in the placebo group (\( P = .05 \)). For the estradiol group, the LH, follicle-stimulating hormone, and progesterone levels significantly decreased from baseline.

**Estradiol and Psychotic Symptoms**

The estradiol group exhibited a significantly greater improvement in psychotic symptoms over time than did the placebo group. As demonstrated in Figure 2, for total PANSS scores, the repeated-measures ANOVA demonstrated a significant group \( \times \) time interaction (\( F_{4,340} = 4.88, P = .002 \), partial \( \eta^2 = 0.054 \)), reflecting the greater improvement over time for the estradiol group. Similarly, for positive symptoms, there was a significant group \( \times \) time interaction (\( F_{4,340} = 41.84, P = .005 \), partial \( \eta^2 = 0.048 \)), indicating that the estradiol group demonstrated a significantly greater improvement over time than did the placebo group (Figure 3). There was a similar pattern of findings for general psychopathological symptoms: a significant group \( \times \) time interaction (\( F_{4,340} = 84.61, P = .01 \), partial \( \eta^2 = 0.041 \)) (Figure 4). In contrast, for negative symptoms, there were no significant main effects of time (\( F_{4,340} = 1.57, P = .20 \)) or group (\( F_{4,340} = 0.01 \); \( P = .92 \)), nor was there a group \( \times \) time interaction (\( F_{4,340} = 1.36, P = .20 \)) (Figure 5).

**Adverse Effects**

Repeated-measures ANOVAs assessing possible adverse effects with the Adverse Symptoms Checklist showed a significant main effect for time (\( F_{4,202} = 6.56, P < .001 \)) for both groups, adverse effects were significantly reduced from baseline (mean \( \pm \) SE, 16.02 [1.05]) to day 28 (12.54 [1.12]).

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**Table 1. Demographic Data for the Women in the Estradiol and Placebo Groups**

<table>
<thead>
<tr>
<th></th>
<th>Estradiol (n = 56)</th>
<th>Placebo (n = 46)</th>
<th>( P ) Value (^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>33.5 (8.8)</td>
<td>33.8 (7.7)</td>
<td>.85</td>
</tr>
<tr>
<td>Age at illness onset, y</td>
<td>22.3 (7.6)</td>
<td>23.3 (7.4)</td>
<td>.53</td>
</tr>
<tr>
<td>Medication dose, risperidone equivalents (^{c})</td>
<td>7.5 (5.0)</td>
<td>6.8 (3.9)</td>
<td>.44</td>
</tr>
<tr>
<td>Participant medication type, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st-Generation antipsychotics</td>
<td>8</td>
<td>10</td>
<td>.27</td>
</tr>
<tr>
<td>2nd-Generation antipsychotics</td>
<td>48</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>No. of hospital admissions since illness onset</td>
<td>6.8 (9.5)</td>
<td>7.5 (7.2)</td>
<td>.65</td>
</tr>
<tr>
<td>Baseline PANSS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>77.48 (20.0)</td>
<td>73.40 (12.5)</td>
<td>.24</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>19.79 (7.1)</td>
<td>19.00 (6.0)</td>
<td>.56</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>17.11 (5.7)</td>
<td>16.82 (5.2)</td>
<td>.80</td>
</tr>
<tr>
<td>General psychopathological symptoms</td>
<td>40.59 (10.8)</td>
<td>37.58 (6.5)</td>
<td>.10</td>
</tr>
<tr>
<td>Patient status at baseline, No.</td>
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<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td>15</td>
<td>14</td>
<td>.85</td>
</tr>
<tr>
<td>Outpatient</td>
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<td>32</td>
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<tr>
<td>Menstrual cycle phase at baseline, No.</td>
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<td></td>
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<tr>
<td>Follicular</td>
<td>24</td>
<td>24</td>
<td>.46</td>
</tr>
<tr>
<td>Luteal</td>
<td>26</td>
<td>20</td>
<td>.92</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>2</td>
<td>.41</td>
</tr>
<tr>
<td>Diagnosis, No.</td>
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<td></td>
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<tr>
<td>Schizophrenia</td>
<td>45</td>
<td>38</td>
<td>.97</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>10</td>
<td>8</td>
<td>.84</td>
</tr>
<tr>
<td>Schizophreniform disorder</td>
<td>1</td>
<td>0</td>
<td>.92</td>
</tr>
</tbody>
</table>

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**Abbreviation:** PANSS, Positive and Negative Syndrome Scale.

\(^{a}\)Values are mean (SD) unless otherwise stated.

\(^{b}\)Values from 1-way analyses of variance.

\(^{c}\)Risperidone equivalents were determined by means of the computer program Switching to Risperdal, Version 1 (Tim Lambert, MBBS, Multimedia in Psychiatry Unit, Melbourne University, Parkville, Victoria, Australia, 1999).

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**Figure 1.** Flowchart of participant random allocation, follow-up, and analysis.

65 Allocated to estradiol

56 Allocated to placebo

2 Discontinued intervention

Reason: menstrual bleeding

3 Incomplete data

Reason: participants unable or unwilling to complete questionnaires

1 Lost to follow-up

Reason: participants unable or unwilling to complete questionnaires

51 Analyzed

36 Analyzed
There was no main effect for group ($P = .49$), nor was the group/time interaction significant ($P = .74$), suggesting that adverse symptoms did not differ between the groups. For adverse effects measured with the Simpson Angus Rating Scale for Extrapyramidal Side Effects, there were no significant main effects for time ($P = .57$) or group ($P = .68$), nor was the group/time interaction significant ($P = .57$). Similarly, for adverse effects measured with the Abnormal Involuntary Movement Scale, there were no significant main effects for time ($P = .91$) or group ($P = .27$), nor was the group/time interaction significant ($P = .98$).

The key finding from this large-sample study of women with schizophrenia was that the addition of 100 µg of transdermal estradiol significantly reduced positive and general psychopathological symptoms during the 28-day trial period compared with women receiving antipsychotic medication alone. The prominent improvement in symptoms of schizophrenia with 100 µg of adjunctive estradiol extends and confirms...
Estrogen's neuroprotective and psychoprotective actions may be mediated by a variety of routes, ranging from rapid actions, including antioxidant effects and enhancement of cerebral blood flow and cerebral glucose utilization, to slower, genomic mechanisms, which may include permanent modification of neural circuits. There are at least 2 forms of the estrogen receptor (α and β), and imaging techniques have mapped their widespread distribution to brain areas including the hypothalamus, amygdala-hippocampal area, substantia nigra and subthalamic nucleus, cerebellum, and various areas of the cerebral cortex. Estrogen modulates multiple neurotransmitter systems, including the dopaminergic, serotonergic, cholinergic, and γ-aminobutyric acid–ergic pathways. Given that dopaminergic and serotonergic neurotransmitter systems are implicated in the efficacy of antipsychotic agents and thus the pathogenesis of schizophrenia, it is possible that the antipsychotic effects of adjunctive estradiol are also explained by estrogen's modulatory role in these neurotransmitter systems. Although no human studies have been performed to date, evidence from animal studies involving ovariectomy have shown that long-term estradiol treatment may preserve striatal dopamine concentrations by decreasing the affinity of the transporter for dopamine. Animal studies also have shown that long-term estradiol treatment can modulate brain serotonergic activity by increasing serotonin synthesis and release in the dorsal raphe, increasing serotonin type 2A receptor messenger RNA binding in the cortex and dorsal raphe, and decreasing serotonin type 1A receptor messenger RNA binding in the amygdala, hippocampus, and cerebral cortex. The lack of effect for negative symptoms is consistent with literature reporting that negative symptoms are less responsive to treatment than other symptoms of schizophrenia. It is possible that longer-term treatment is required for negative symptoms to respond to treatment. Alternatively, brain regions implicated in negative symptoms may be less responsive to gonadal hormone effects.

Our hormone analyses indicated that, although mean plasma estradiol levels increased from baseline in the estradiol group (but not the placebo group), this difference did not reach significance. Although the large amount of variability in scores may explain the nonsignificant findings, discrepancies between circulating estrogen levels and brain levels of estrogen have been described previously. A significant decrease from baseline in LH levels was observed in the estradiol group but not in the placebo group, suggesting that adjunctive estradiol treatment has a suppressing effect on LH. Estradiol is known to be a negative feedback regulator of gonadotropin secretion; thus, the decline in LH levels is a useful indicator of the fact that estradiol levels have been increased. In line with the well-reported modulatory effects of estrogen on the dopaminergic system, research suggests that LH is under inhibitory control by dopamine. Therefore, estradiol treatment may increase dopamine concentrations, which, in addition to contributing to the anti-psychotic effects, may decrease LH levels, influencing the activity of the hypothalamic-pituitary-gonadal axis.

The lack of long-term follow-up is a potential limitation of this study. Given the acute nature of adjunctive estradiol as a treatment, we can only speculate that the anti-psychotic effects of estradiol would not be lasting. Future studies could investigate a longer treatment period with estradiol, as well as longer-term follow-up to determine whether the therapeutic effects may be lasting. Other potential limitations of this study include the large amounts of variability in baseline hormone levels and the variation in menstrual cycle phase at baseline. Future research is needed to address these shortcomings.

There are several avenues for potential estrogen treatment in schizophrenia. For example, estrogen may have a preventive role in women with schizophrenia whose condition has been known to deteriorate in periods of hormonal change, including postpartum periods, menopause, and low-estrogen phases of the menstrual cycle. There are also preliminary results to suggest that estrogen may protect men against psychotic symptoms. Beyond schizophrenia, there are also a number of reports of the potential benefits of estrogen treatment in hormone-related affective disorders. Although short-term use of transdermal estradiol is a safe therapeutic option, the future of estrogen treatment may also include further developments of selective estrogen receptor modulators, which are estrogen compounds that have differential tissue-dependent effects on estrogen receptor functions.

In conclusion, results from this large-sample study of 102 women showed that the addition of 100 µg of transdermal estradiol significantly reduced positive and general psychopathological symptoms. Estrogen treatment is a promising new area for future treatment of schizophrenia and potentially for other severe mental illnesses.

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