Estrogen as an adjuvant therapy to antipsychotics does not prevent relapse in women suffering from schizophrenia: results of a placebo-controlled double-blind study

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Abstract

The expected therapeutic effect of estrogen as an adjunct treatment to antipsychotics in women suffering from schizophrenia for relapse prevention was to be tested under real-life conditions. A multicenter, randomized, placebo-controlled, double-blind, cross-over study based on an A–B–A–B (and/or B–A–B–A) design was applied. Forty-six hypoestrogenic women with schizophrenia hospitalized for the first time or repeatedly were included in the study. Their average age was 37.9 and they had been suffering from schizophrenia for 8.4 years. During the drug treatment phases, they received a three-phase estrogen–gestagen combination drug (17β-estradiol + norethisterone acetate) in addition to an antipsychotic drug. Significant effects of the adjuvant hormone replacement therapy on the estradiol levels could be observed, and high and low levels of estradiol prevailed in the active drug and placebo phases, respectively. We did not find any difference either in defined relapse events or in the psychopathology between estradiol replacement and placebo phases. Neither did the required antipsychotic doses or the tolerance data differ between the two phases. Thus, the results of our study do not confirm the hypothesis that a combined estradiol/antipsychotic therapy is superior to an antipsychotic monotherapy for relapse prevention.

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1. Introduction

Besides the genuine hormonal functions on the gonadal axis, estrogens have multiple effects on brain function. In the past it could be demonstrated that estrogens have an influence on major neurotransmitter systems and brain regions affecting cognitive, emotional, and vegetative functions (e.g., Fink et al., 1996; Halbreich et al., 1995; Morissette and DiPaolo, 1993; DiPaolo, 1994; Gordon et al., 1988). Estrogens also exert neurotrophic and neuroprotective effects which are mediated by nongenomic as well as by direct and indirect genomic pathways (for review, see McEwen and Alvers, 1999; Lee and McEwen, 2001; Garcia-Segura et al., 2001; Behl, 2001). How estrogen influences the course of various diseases of the nervous system has been the focus of research in the neural sciences for the past few years. In addition to stroke, Parkinson’s disease, Alzheimer’s disease, and depression, schizophrenia is also included among these diseases.

In schizophrenia research, the estrogen protection hypothesis has been being investigated for the past 20 years. It assumes a protective effect of estrogen in women vulnerable to schizophrenia. Evidence for this hypothesis is based on epidemiologic, neurochemical, animal, and clinical data (for review, see, e.g., Häfner et al., 1992, Häfner, 2003; Seeman, 1996; Cyr et al., 2002; Riecher-Rössler, 2003; Halbreich, 2003; cf. Bergemann and Riecher-Rössler, 2005).

Analyses of sex differences in schizophrenia were an important starting point of research in this field. They focused on differences in the age at onset and the course of illness which were attributed to the protective effect of higher plasma concentrations of estradiol in women compared to men (e.g., Sartorius et al., 1978; Salokangas, 1983; Seeman, 1982, 1985; DeLisi et al., 1989; Häfner et al., 1992, 1998; Angermeyer and Kühn, 1988).

Several clinical studies or case reports show a correlation between low estrogen plasma concentrations and an increase in the risk for schizophrenic symptoms occurring in women after giving birth or after the menopause (Nott, 1982; Kendell et al., 1987; Seeman, 1997). Further studies have shown more severe psychotic symptoms and a higher risk for the exacerbation of schizophrenic symptoms or for hospitalization in low than in high estradiol phases of the menstrual cycle (for review, see Bergemann et al., 2002).

Besides the numerous investigations which could prove that estrogen has a protective effect in schizophrenia, some reports have postulated an association between schizophrenia and a chronic estrogen deficiency in schizophrenic women called hypooestrogenism. Low estrogen levels leading to an elevated rate of menstrual dysfunction, such as amenorrhea and irregular menstruation, have been described in schizophrenic women.

Studies on hypooestrogenism carried out in the pre-antipsychotic era are of particular interest. They demonstrated different types of menstrual cycle disorders in schizophrenic psychoses, anomalies of secondary sexual features, and an increased rate of virilization (e.g., Häfner, 1912; for review, see Bleuler, 1943; Reiss, 1958). Diczfalusy and Lauritzen (1961) reviewed the few studies on low plasma concentrations of estrogen directly measured in urine and/or blood in schizophrenic women in the pre-antipsychotic era between 1933 and 1955. In later years, hypooestrogenism and, subsequently, irregular menstrual cycles and amenorrhea were usually attributed to antipsychotic-induced hyperprolactinemia, mediated by hypothalamic-pituitary-gonadal feedback mechanisms, although irregular menstruation had already been observed in schizophrenic women before antipsychotics were introduced in the therapy of patients suffering from psychoses. More recently, however, some studies have provided evidence for hypooestrogenism in women suffering from schizophrenia based on analyses of estradiol plasma concentrations (Riecher-Rössler et al., 1994; Choi et al., 2001; Huber et al., 2001; Hoff et al., 2001; Canuso et al., 2002; Bergemann et al., 2002, 2005) and indicate that hypooestrogenism occurs in schizophrenic women with and without antipsychotic-induced hyperprolactinemia, a fact which supports the hypothesis of primary hypooestrogenism.

Hypooestrogenism in women suffering from schizophrenia is not only of particular interest from a theoretical point of view, but also considering the therapeutic implications. The protective effect of estrogen in schizophrenia suggests that it be used for treatment and prophylaxis. Thus, estrogen replacement
therapy could be particularly effective in those women with schizophrenia suffering from hypoestrogenemia. However, very few studies addressing an estrogen medication in schizophrenia have been conducted to date. Mall (1958, 1960) seems to be the first to have administered estrogen to women suffering from schizophrenia. He recommended an estrogen replacement therapy in those patients suffering from “post-menstrual psychosis” and “hypofollicular psychosis” – classified by quantitative analyses of estrogen in the urine – simultaneously. It should be noted that the author provides only little information on the results of his trials. More recently, in various experimental trials, Kulkarni et al. (1996, 2001, 2002) showed a beneficial effect of estradiol on the course of illness in the acute phase. In a post-hoc analysis covering postmenopausal women with schizophrenia, Lindamer et al. (2001) showed that an estrogen replacement therapy in conjunction with antipsychotic medication helped to reduce negative but not positive symptoms.

The aim of the present study was to verify the estrogen hypothesis under naturalistic conditions in women suffering from schizophrenia. Emphasis was placed on the prevention of relapse in order to obtain further clinical evidence for the hypothesis, and to evaluate the practical implications of an adjuvant estrogen treatment in these patients. In particular, the question was to be addressed as to whether antipsychotics plus estrogen (and/or a combination of estrogen and gestagen) is superior to antipsychotic monotherapy. A more favorable course of illness or a lower antipsychotic drug requirement and a better tolerance were expected from an adjuvant therapy with estrogen compared to an antipsychotic monotherapy.

2. Methods

2.1. Study design and procedure

To answer these questions, a multicenter, randomized, placebo-controlled, double-blind, cross-over study based on an A–B–A–B (and/or B–A–B–A) design was applied. Sample size calculations required a total of 40 schizophrenic women between 16 and 67 years of age to be included in the study. Ultimately, 46 patients were recruited. The estrogen replacement was administered as an adjuvant therapy to routine antipsychotic relapse prevention. For 8 months, the patients received the drug regimen and placebo for 2 months each. The patients were placed together randomly in group A–B–A–B or B–A–B–A (Fig. 1).

In the first complete menstrual cycle after hospital admission, the sexual hormone levels were analyzed in detail, three times during the menstrual cycle: in the follicular (proliferative) phase at cycle days 2–4 (t1), in the peri-ovulatory phase at cycle days 10–12 (t2), and in the luteal phase at cycle days 20–22 (t3). Only after hypoestrogenism was observed and the inclusion and exclusion criteria were double-checked were patients included in the study. After sufficient remission and having reached the following menstrual cycle, the study medication was started on day 5.

In parallel to determining the laboratory parameters, the patients’ psychopathological condition was assessed according to the rating scales described under Section 2.4, and the side effects were monitored. The patients were examined three times a month. One session took place face-to-face in the hospital (t1) and two sessions were carried out by way of a telephone interview (t2 and t3). During the prevention phase, the hormone levels were measured at the hospital sessions.

2.2. Subjects

Women either suffering from schizophrenia for the first time or from a relapse that had sufficiently remitted after the acute phase were included in the study. The earliest point of sufficient remission was reached 6 weeks after the acute exacerbation of the schizophrenic disorder and when the patient achieved a sum score of <30 on the Brief Psychiatric Rating...
In particular, they had to meet the following criteria: schizophrenia according to ICD 10- and DSM-IV-criteria, hypoestrogenism (estradiol serum level <30 pg/ml on days 2–4 of the menstrual cycle and estradiol serum level <100 pg/ml on days 10–12), age 16–67, as well as cooperation and informed consent. Exclusion criteria were: heavy alcohol or drug abuse, family history of breast cancer, mastodynia, intake of oral contraceptives in the year preceding the study, estrogen therapy for more than 3 months in the year preceding the study, relevant co-morbidity (Parkinson’s disease or severe respiratory, renal, hepatic, hematological, or endocrinological disease), pregnancy or lactation, and unsuccessful treatment with at least three different antipsychotics in the 2 years preceding the study.

According to the inclusion and exclusion criteria, a total of 46 patients were admitted to the study. Their average age was 37.9 (S.D.=9.8, range 21–60 years) and they had been suffering from schizophrenia for 8.4 years (S.D.=7.4 years; ICD-10 F20.0, F20.1, F20.5). The average rate of hospitalization was 3.3 (S.D.=4.3).

All but two patients were diagnosed with paranoid schizophrenia, one with hebephrenia, the other with a schizophrenic residual state. Thirteen patients were unemployed, eight were fully employed, three were employed part-time, five were housewives, four were students, and five were retired. Twenty-seven patients were single, nine married, seven divorced, and three widowed. Thirty-four patients lived in normal living conditions at home, five lived in therapeutic settings, and six had been hospitalized for a longer period of time.

In total, the data of 39 patients were included in the study after seven patients had dropped out. The most common reason for drop-out was a lack of compliance (in three cases); other reasons for drop-out were weight gain, breast tension, headache, as well as sickness and vomiting. At the time of drop-out, five of the patients were going through the drug treatment phase, two through the placebo phase.

2.3. Laboratory parameters

Blood samples were taken in the morning between 8.00 and 9.00 a.m. In addition to the routine parameters for safety reasons, the following laboratory parameters were assessed: 17β-estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, testosterone, progesterone, and dehydroepiandrosterone sulfate (DHEA-S). For laboratory analysis of all the parameters, an electro-chemical luminescence immunoassay was used (Roche Elecsys 2010 immunoassay analyzer).

2.4. Effectiveness and outcome measures

The target parameter of the investigation was the improved therapeutic effectiveness of a combination of antipsychotics and estradiol versus an antipsychotic monotherapy for relapse prevention. To assess the state of psychopathology, the German versions or translations of the following standard rating scores and/or self-rating scales were applied: The Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987), Brief Psychiatric Rating Scale (BPRS, Overall and Gorham, 1962), Clinical Global Impressions (CGI, Guy, 1976), Beck Depression Inventory (BDI, Beck and Steer, 1987; German version by Hautzinger et al., 1995). The overall condition was assessed by using an 100-mm-Analogue-Scale.

The main variable of the study was the relapse frequency and/or the “survival time” during the prevention phase while administering a combined estradiol/antipsychotic therapy versus an antipsychotic monotherapy. A relapse was defined as a hospitalization, a 3-point lower score on the BPRS Score 3 (“Thought Disturbance”), a deterioration of the CGI-score down to 7 or 8 (condition is “much worse” or “very much worse”), or a 20% lower score within the “100-mm Scale”. The BPRS Score 3 (“Thought Disturbances”) includes items 4 (“Conceptional Disorganization”), 8 (“Grandiosity”), 12 (“Hallucinatory Behavior”), and 15 (“Unusual Thought Content”).

2.5. Side effects

Side effects were monitored by way of open responses and standardized questionnaires. For this purpose, German versions of the Extrapyramidal Symptom Scale (EPS, Simpson and Angus, 1970), the Barnes Akathisia Scale (BAS, Barnes, 1988) as well as the Abnormal Involuntary Movement Scale (AIMS, Guy, 1976) were applied. In addition, a German translation of the Menstrual Distress Questionnaires (MDQ, Moos, 1968) was used.
2.6. Study medication

During the drug treatment phases, in addition to the antipsychotic medication, a relatively high dose of 17β-estradiol was given. To meet this requirement, Trisequens® plus Estrifam® (both by Novo Nordisk Pharma) were administered. Trisequens® is a three-phase estrogen/gestagen combination with the following compounds adapted to the different phases of the cycle:

- blue-coated tablet 17β-estradiol 2 mg (follicular phase)
- white-coated tablet 17β-estradiol 2 mg norethisterone acetate 1 mg (peri-ovulatory phase)
- red-coated tablet 17β-estradiol 1 mg (luteal phase)

Estrifam® contains 2 mg of 17β-estradiol as the medically active component. It was added in the follicular and peri-ovulatory phase only. In combining Trisequens® and Estrifam®, a relatively high dose of 4 mg was reached during the follicular and peri-ovulatory phase.

A dose of 4 mg could have also been achieved by administering Trisequens forte® (Novo Nordisk Pharma). The decision in favor of the dual medication was made in view of potential side effects. In this case the dose could be lowered by omitting Estrifam®. This turned out to be necessary in two cases only. The post-hoc analysis of the plasma concentrations indicated that the estradiol levels in these two patients were still comparable to those of the other subjects in the sample.

During the placebo phases, a placebo medication of the same appearance and feel was administered.

In accordance with a naturalistic study design, the antipsychotic medication was given without predefining the drug or dose. It included clozapine in nine cases, flupenthixol in seven, olanzapine in five, and amisulpride and perazine in four cases each; fluphenazine, perphenazine, or zotepine was administered in three cases each, bromperidol in one case only. The patients received this non-standardized antipsychotic medication as required by the individual psychopathological condition and all other state-of-the-art interventions in terms of care, diagnosis, and therapy.

2.7. Good clinical practice

The study was performed in accordance with the Declaration of Helsinki of 1964 (in the edition of the 52nd World Medical Assembly in Edinbaugh, Scotland, October 2000), the Good Clinical Practice for Trials on Medicinal Products in the European Community (“EG-GCP-Note for Guidance” July 1990), Germany’s Guidelines for Clinical Trials (“Grundsätze für die ordnungsgemäße Durchführung der klinischen Prüfung von Arzneimitteln”, Bundesanzeiger 243: 16618; 1987) and the stipulations of German Law on Medicinal Products (“Arzneimittelgesetz”, AMG §§40–42). The protocol was approved by the local Research Ethics Committee at the University of Heidelberg.

2.8. Statistical analyses

Besides standard descriptive statistics, various inference statistical procedures were applied. To test for the effects of estrogen on the hormone levels, a 3-factor analysis of variance for repeated measurements was performed with plasma concentrations of hormones as dependent variables, estrogen replacement as an inner-subject factor, and age (age ≤45 versus 45+) and medication (clozapine as a prolactin-sparing antipsychotic versus various prolactin-elevating antipsychotics) as within-subject factors. To test for the difference between the psychopathology assessment scores and the side effects under active drug (estrogen replacement) versus placebo, linear regression analyses with a robust standard error were conducted. To test for the difference between the required mean daily dose of antipsychotics, the t-test for dependent samples was conducted. To make the various antipsychotics comparable, the haloperidol equivalences were calculated. To test the number of increases and/or decreases in the antipsychotic medication, and the relapse events under drug versus placebo, Fisher’s exact test was performed. The statistical analyses were calculated using the statistical program Stata 8 (Stata, 2003).

3. Results

3.1. Endocrinological effects of estrogen replacement

Fig. 2 shows the course of estradiol levels of all patients in the two randomized groups (A–B–A–B and B–A–B–A) assessed monthly during the peri-ovulatory phase. The 2-month estrogen replacement...
phases can be easily recognized: during these periods, the estradiol levels correspond more or less to normal for premenopausal women (>150 pg/ml); in the placebo phases, the levels are visibly and significantly below the norm.

Furthermore, the endocrinological data were analyzed by age groups (29 patients aged ≤45, 10 patients 45+) to take potential age effects into account. Table 1 shows the effect of estrogen replacement on the plasma concentrations of 17β-estradiol, prolactin, LH, FSH, progesterone, testosterone, and DHEA-S for both age groups. As expected, the age group 45+ shows a menopausal hormone profile with low estradiol and elevated gonadotropins levels under placebo conditions.

As expected, the estrogen replacement led to a significant increase in the estradiol plasma concentration in both age groups, significantly more so in the age group 45+ (analysis of variance for repeated measurements). LH was significantly higher in the group 45+ before intervention; under estrogen replacement, the decrease in LH was significantly higher in this group. As also expected, FSH shows significantly higher values in the 45+ group than in the younger group; estrogen replacement led to a decrease in both age groups, significantly more so in the patients 45+.

No significant effect of estrogen replacement could be seen in serum levels of prolactin, testosterone, and DHEA-S. However, as is known, the different medications had an effect on prolactin: the group of patients receiving clozapine in monotherapy as a prolactin-sparing atypical antipsychotic drug showed significantly lower prolactin levels than the group of patients receiving other antipsychotic drugs, most of them typical antipsychotics. Regarding testosterone and DHEA-S, the patients 45+ show significantly lower plasma levels than the group below 45. The same is true for the group receiving clozapine compared to those receiving other medications.

In further analyses age, medication, or other factors were not considered as their significance for cerebral effects in this context has not yet been established.

Table 1

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<tr>
<th>Hormone parameters in age group ≤45 and 45+ under drug (estrogen replacement) and placebo conditions</th>
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<td>Age groups</td>
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<td>DHEA-S (ng/ml)</td>
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* Mean±standard deviation.
3.2. Relapses

The adjuvant estradiol therapy does not decrease the risk of relapse according to the definitions provided earlier. Table 2 shows the proportion of the different relapse events in active drug versus placebo; no significant difference between the hormone replacement and the placebo phase could be observed for any of the defined relapse events (Fisher’s exact test). Whether the obvious tendency towards slightly higher values in the drug treatment phase has any significance remains to be analyzed.

3.3. Psychopathology

No significant difference in the mean and/or the average sum scores or sub-scales of the BPRS, PANSS, BDI, CGI, and the 100-mm-Analogue-Scale during drug treatment and placebo conditions could be seen (random effect regression with respect to the co-variates “haloperidol equivalence” and “time” and/or “trend”).

In addition, an analysis of the PANSS data of individual symptoms was carried out, also based on a random effect regression and with respect to the co-variates haloperidol equivalence and time and/or trend. This analysis did not yield any significant results indicating the expected effect either. Surprisingly, the item “Uncooperativeness” was rated significantly lower during drug treatment. As the difference in score was half a rating point, this result cannot be considered clinically relevant.

In terms of an explorative analysis of the data, calculations hypothetically assuming a delayed effect of estradiol were conducted. In this case the results of the first hormone assessment of the subsequent active drug or placebo phase were included in the analysis. This change in formula did not show the expected effect either.

In a further analysis, we investigated the relationship between the absolute estradiol serum level and the psychopathology, irrespective of the drug and/or placebo phases. In terms of the BPRS scale “Hostile-Suspiciousness“ (HOST), a significant influence of estradiol could be identified; however, the HOST-score under drug was higher than under placebo (random effect regression with respect to the co-variates haloperidol equivalence and time and/or trend p=0.004). According to this result, 100 pg/ml of estradiol induced a change of 0.2 points on the rating scale, an effect which cannot be considered to be clinically relevant.

3.4. Side effects

The average sum scores and/or sub-sum scores of the scales assessing possible side effects – EPS, BAS, AIMS, MDQ – in the active drug versus placebo phase did not show any significant difference (random effect regression with respect to the co-variate haloperidol equivalence).

3.5. Medication

The adjuvant estradiol administration in our study did not affect the antipsychotic dose. For analysis, the mean daily doses of the various antipsychotics were transformed into haloperidol equivalents. There was no difference between the haloperidol equivalence in drug versus placebo (t-test for dependent samples). In addition, the number of times the dose was either increased and/or decreased was calculated. No significant differences were found here either.

4. Discussion

This study represents the first clinical intervention study to empirically verify the estrogen hypothesis in
schizophrenic women for relapse prevention. The potential therapeutic value of estrogen in treating schizophrenia was to be investigated under naturalistic conditions. It was expected that an adjuvant estrogen therapy in addition to an antipsychotic treatment versus an antipsychotic monotherapy would lead to a more favorable course of illness and reduce the required dose of antipsychotics for relapse prevention.

As far as the hormone parameters are concerned, estradiol replacement showed the expected effects, although to a different extent in the groups of patients under 45 years of age and the group 45+. In particular, a significant increase towards the normal estradiol level could be observed during replacement. However, neither the relapse rate nor the sum or sub-sum scores of the psychopathology scales used revealed any significant difference between drug and placebo. In terms of the required dose of antipsychotics, a difference could not be found either. Thus, the results of the present study do not confirm the hypothesis assuming that a combined estradiol/antipsychotics therapy for relapse prevention is superior to an antipsychotic monotherapy. Furthermore, the results do not provide evidence for an effect of estrogen on the negative symptoms in particular, i.e., an effect on the serotonergic transmission as described by Fink et al. (1996) and as concluded by Lindamer et al. (2001).

Critically reviewing the results from a methodological standpoint, one might argue that the phases of active drug and placebo treatment were too short. In response to this concern, we refer to Riecher-Rössler et al. (1994), who showed changes in psychopathology based on physiological fluctuations during the menstrual cycle that were much smaller than in the present study. Furthermore, the women included in the study by Riecher-Rössler et al. – as well as in the studies by Kulkarni et al. (1996, 2001) – were experiencing the acute phase of schizophrenia, which differs from the group of women in our study. It is remarkable that in the open intervention trial by Kulkarni et al. (1996), the superiority of a combined treatment also wanes after about 3 weeks.

Although the adjuvant estradiol medication does not cause any significant difference in the risk of relapse according to the definitions provided above, an obvious tendency towards slightly higher relapse events in the drug phases can be observed (cf. Table 2). Whether this tendency has any relevance needs to be discussed.

Assuming that the influence of hormones is different in different groups of patients as the results of Albus and Maier (1995) as well as those of Könnecke et al. (2000) indicate, the group of women falling ill in the perimenopause represents a particularly interesting subject for further intervention studies. In this group, estrogens could have played a decisive role in suppressing the symptoms until the onset of schizophrenia; the physiological decrease in the estrogen serum level might play a key role in the etiopathogenesis of the illness. Interventional trials should be carried out, ideally with a double-blinded and placebo-controlled design and that take the estrogen status of the patients into consideration. However, due to potential side effects and contraindications, the individual risk and benefit of such estrogen treatment should be analyzed and taken into account (cf. Notman and Nadelson, 2002; Writing Group for the Women’s Health Initiative Investigators, 2002; The North American Menopause Society, 2003; Writing Group of the International Menopause Society Executive Committee, 2004; Turgeon et al., 2004).

Furthermore, research in this area should not only focus on the potential therapeutic effects of estrogen and/or other estrogenic compounds in schizophrenia, but also on providing more insight into the currently poorly understood relationship between hypoestrogenism and/or disturbances of the hypothalamic-pituitary-gonadal axis and schizophrenia. Thus, further endocrinological studies in schizophrenic patients should contribute to understanding hormonal disorders and investigate the interdependency of the different hormones relevant in this context as well as their role in the pathogenesis and the course of schizophrenia.

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