Raloxifene as an Adjunctive Treatment for Postmenopausal Women With Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Trial

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ABSTRACT

Objective: The potential therapeutic utility of estrogens in schizophrenia is increasingly being recognized. Raloxifene, a selective estrogen receptor modulator, appears to act similarly to conjugated estrogens on dopamine and serotonin brain systems and may be a better option since it lacks the possible negative effects of estrogen on breast and uterine tissue. In this study, we assess the utility of raloxifene as an adjunctive treatment for negative symptoms and other psychotic symptoms in postmenopausal women with schizophrenia.

Method: This was a 12-week, double-blind, randomized, placebo-controlled study. Patients were recruited from both the inpatient and outpatient departments of Parc Sanitari Sant Joan de Déu, Barcelona, Spain, and Corporació Sanitària Parc Taulí, Sabadell, Spain. Thirty-three postmenopausal women with schizophrenia (*DSM-IV* criteria) who exhibited prominent negative symptoms were randomized to either adjunctive raloxifene (16 women; mean age = 60.14 years, SD = 6.41 years) or adjunctive placebo (17 women; mean age = 62.66 years, SD = 4.54 years) for 12 weeks. The period of recruitment lasted from January 2005 through June 2009. Psychopathological symptoms were assessed at baseline and weeks 4, 8, and 12 by means of the Positive and Negative Syndrome Scale.

Results: The addition of raloxifene (60 mg/d) to regular antipsychotic treatment significantly reduced negative ($P = .044$), positive ($P = .031$), and general psychopathological ($P = .045$) symptoms during the 12-week trial as compared with women receiving placebo.

Conclusions: Raloxifene as an adjuvant treatment in postmenopausal women with schizophrenia who exhibit prominent negative symptoms appears to be useful in improving negative, positive, and general psychopathological symptoms. If more extensive and longer-term studies confirm and expand upon these positive results, the use of raloxifene could be recommended in postmenopausal patients with schizophrenia.

Trial Registration: clinicaltrials.gov Identifier: NCT01041092

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A number of studies have found gender differences in the epidemiology, clinical presentation, course, and response to treatment of schizophrenia.[1,2] Findings showing that, in women, schizophrenia is less common, has a later onset, and tends to have a less severe course[3,4] have given rise to the "estrogen hypothesis" of schizophrenia, which posits that estrogen has a protective effect in women who are susceptible to presenting with this illness.[5]

Animal research has shown that estrogen has a modulating effect on the dopaminergic system in the brain.[6,7] The schizophrenia estrogen hypothesis has been confirmed in several studies,[8–11] which have found that estrogen levels in schizophrenic women are significantly lower than in healthy women[8] and that illness onset or relapses most often occur during phases of the menstrual cycle with low levels of estrogen.[9–11]

The finding that estrogen has a modulating effect on the dopaminergic system has led researchers to study the therapeutic use of estrogen in subjects with schizophrenia. Several double-blind studies[12–14] have found that estrogens are effective in improving psychotic symptoms. These later studies have assessed the efficacy of estrogens at 1 or 2 months—and mainly for positive symptoms in acutely ill patients. However, in older patients with schizophrenia, it is the severity of negative symptoms—not the severity of positive symptoms—that appears to correlate with worse social and cognitive functioning.[15] Moreover, positive symptoms tend to become less severe with age, while negative symptoms tend to persist.[16] In addition, the introduction of atypical antipsychotic medication provided additional hope in the management of negative symptoms; however, success remains limited.[17]

The use of estrogen as adjuvant treatment appears promising, but its use in long-term treatment has the disadvantage of the potential negative effect estrogen can have on breast and uterine tissue.[18,19] For this reason, we chose a selective estrogen receptor modulator (SERM) for our study since SERMS do not affect breast or uterine tissue and may therefore be a better option. Raloxifene is a first-generation SERM that is used in the preventive treatment of postmenopausal osteoporosis.[20] Raloxifene can act as an agonist or antagonist of the estrogen receptors in different tissues. It appears to act in a similar way to conjugated estrogens on dopamine and serotonin in the brain.[21,22] There is some evidence that raloxifene may be useful for treating some mental disorders in postmenopausal women.[23,24] Recently, Kulkarni et al[25] reported preliminary data that also seem to support the usefulness of raloxifene in the treatment of patients with schizophrenia.

The aim of our study was to assess the utility of 60 mg/d of raloxifene as an adjunctive treatment for negative symptoms and

other psychotic symptoms in postmenopausal women with schizophrenia in a 12-week, double-blind, randomized, placebo-controlled study.

METHOD

Sample

Women participants were recruited from both the inpatient (nonacute) and outpatient departments of Parc Sanitari Sant Joan de Déu, Barcelona, Spain, and Corporació Sanitària Parc Taulí, Sabadell, Spain. Thirty-five patients were randomized (sample size calculations based on the primary objective required a total of 36 patients, since the calculated minimum sample size was 30 and we assumed a 20% dropout rate). The period of recruitment lasted from January 2005 to July 2009.

The inclusion criteria required that women (1) meet *DSM-IV*[26] criteria for schizophrenia, (2) be in postmenopausal period (postmenopause is defined as a period of 1 year of spontaneous amenorrhea and a serum follicle stimulating hormone level > 20 IU/L), (3) have been receiving stable doses of their current antipsychotic medication for at least a month prior to study initiation, and (4) have significant negative symptoms (defined as 1 or more negative symptom scores greater than 4 on the Positive and Negative Syndrome Scale [PANSS]).[27]

Women were excluded if there was a substance abuse/dependence diagnosis in the previous 6 months; a diagnosis of mental retardation, endocrine abnormalities, acute or chronic liver disease, or impaired kidney function; a history of thromboembolism, breast cancer, abnormal uterine bleeding, or cerebrovascular accident; current administration of hormone replacement therapy; or current medication with a mood stabilizer that could not be discontinued.

Screening blood tests were conducted to determine the level of follicle stimulating hormone and general health status.

The study (clinicaltrials.gov Identifier: NCT01041092) received institutional review board approval. The patients provided informed consent in accordance with the procedures outlined by the local institutional review board and were informed that they could withdraw from the study at any time. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions.[28]

Interventions

Thirty-five subjects were initially randomized, of whom 33 started the trial. One of the initial subjects finally did not meet inclusion criteria, and another was excluded due to psychopathological imbalance. Therefore, 33 subjects were randomized by the Parc Sanitari Sant Joan de Déu trial pharmacy to 1 of the 2 treatment groups in a proportion of 1:1 (blocks of 4 patients, 2 for group 1 and 2 for group 2) on the basis of a random number list. Participants received either adjunctive raloxifene (16 women; mean age = 60.14 years, SD = 6.41 years) or adjunctive placebo (17 women; mean age = 62.66 years, SD = 4.54 years). All study personnel and participants remained blind to treatment assignment for the duration of the study. Women in the raloxifene group received 60 mg/d raloxifene hydrochloride. Placebo tablets were prepared that were identical in appearance to raloxifene. Patients were required to continue taking their regular medications throughout the study. No changes in dose were permitted during the study period. Double-blind treatment continued for 12 weeks.

Other psychotropic medications that were permitted were biperiden (to prevent antipsychotic side effects), benzodiazepines, and antidepressants. The antipsychotics were subclassified as typical, atypical, or combinations. The antipsychotic drug doses are expressed in terms of their risperidone equivalence.[29]

One of the 16 patients in the raloxifene group decided not to complete the baseline evaluation; therefore, she was not included in the analysis. Of the 15 remaining patients, 1 could not be assessed at 12 weeks due to psychopathological worsening. Also, in the placebo group, 1 patient could not be assessed at 12 weeks due to family problems. The last 2 patients mentioned were included in the analysis since the analysis was carried out in accordance with intention to treat.

Outcomes

Diagnoses were established by means of the Structured Clinical Interview for *DSM-IV* Axis I Disorders,[30] which was conducted by a research fellow and reviewed by the principal investigator. A sociodemographic and clinical history questionnaire (J.U.; M. Barceló, MA; S.O., unpublished questionnaire, 2004; available from the authors upon request) was also administered. Psychopathological symptoms were assessed at baseline and weeks 4, 8, and 12 using the PANSS.[27] Side effects were assessed at each visit using the Simpson-Angus Scale[31] and the UKU Side Effect Rating Scale.[32] We also assessed effects on breast and uterine tissue.

Treatment compliance was controlled by counting the number of remaining tablets between evaluations. The adherence (percentage of tablets taken) was estimated for each evaluation, and the total adherence was calculated by averaging the 3 study evaluations and for all patients in each group. A minimum of 80% adherence was required for participants to be part of the study.

Clinical Points

- Drugs with estrogen activity in the brain seem to improve the outcome of subjects with schizophrenia.
- Use of raloxifene as an adjuvant treatment in postmenopausal women with schizophrenia is very promising.

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Statistical Analysis

Homogeneity of the sample baseline characteristics was tested with the Student *t* test or χ^2 test depending on the type of variable. The differences from baseline to final evaluation between the placebo and raloxifene groups for the 3 scales surveyed were also compared using the Student *t* test. To assess effect of treatment group and time interaction, a series of repeated-measures analyses of variance (ANOVAs) were conducted. Since there were only 2 patients with missed assessments (1 in each group), the last-observation-carried-forward method was applied.

RESULTS

Demographics

Demographic information is shown in Table 1. There were no statistical differences between the 16 women in the raloxifene group and the 17 women in the placebo group in terms of age, age at illness onset, or years of education. We found no significant differences between the raloxifene and placebo groups with regard to regular antipsychotic medication and other medications. There was no significant difference in mean daily dose of antipsychotic medication between the 2 groups (Table 1). The raloxifene and placebo groups showed no difference in terms of treatment adherence (mean = 99.82%, SD = 6.71; and mean = 95.12%, SD = 8.37, respectively; $P = .143$).

Table 1. Baseline Demographic and Clinical Characteristics for Women in the Raloxifene and Placebo Groups (N = 33)[a]

Characteristic	Raloxifene (n = 16)	Placebo (n = 17)	*P* Value[b]
Age, mean (SD), y	60.14 (6.41)	62.66 (4.54)	.20
Education, mean (SD), y	7.00 (3.40)	7.25 (3.69)	.66
Age at onset of disease, mean (SD), y	27.69 (6.97)	25.24 (11.12)	.41
Baseline PANSS score, mean (SD)			
Positive subscale	10.57 (3.56)	12.25 (5.04)	.27
Negative subscale	22.53 (4.73)	21.63 (5.34)	.69
General psychopathological subscale	30.80 (4.98)	31.63 (8.32)	.81
Total	62.64 (8.60)	65.50 (14.55)	.52
Participant medication, n (%)			
Antipsychotic			
First-generation antipsychotic	4 (12.12)	4 (12.12)	.61
Second-generation antipsychotic	9 (27.27)	7 (21.21)	
Combination	3 (9.09)	6 (18.18)	
Antidepressant, yes	5 (15.15)	4 (12.12)	.71
Antidepressant, no	11 (33.33)	13 (39.39)	
Biperiden, yes	4 (12.12)	3 (9.09)	.68
Biperiden, no	12 (36.36)	14 (42.42)	
Dosage of antipsychotic, median, mg/d[c]	4.25	6.00	.19
Patient status at baseline, n (%)			
Inpatient	4 (12.12)	4 (12.12)	1.00
Outpatient	12 (36.36)	13 (39.39)	

[a]Percentages are based on the total N of 33.
[b]*P* values are derived from 1-way analyses of variance.
[c]Antipsychotic drug doses are expressed as risperidone equivalence.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Symptoms

The raloxifene group obtained significantly better scores on all PANSS subscales than the placebo group. On the positive PANSS subscale, with respect to the difference between baseline and final mean scores, there was a significant difference ($P = .008$) between the raloxifene group (mean difference = −1.42, SD = 2.31) and placebo group (mean difference = 0.81, SD = 2.00). There was also a significant difference in the negative PANSS subscale ($P = .048$) from baseline to final mean scores between the raloxifene group (mean difference = −3.50, SD = 2.13) and placebo group (mean difference = −1.81, SD = 2.66). Regarding the general psychopathological PANSS subscale, a significant difference was also found ($P = .04$) between the raloxifene group (mean difference = −2.53, SD = 5.71) and placebo group (mean difference = 1.62, SD = 5.07). Similarly, the total PANSS score showed a significant difference ($P = .009$) in the mean baseline-to-final scores between the raloxifene group (mean difference = −6.85, SD = 7.57) and placebo group (mean difference = 0.62, SD = 18.24).

Figures 1 through 4 show the course of psychotic symptoms during the treatment period. In Figure 1, we observe a better course of positive symptoms in the raloxifene group. The ANOVA results also show significant differences in the time × group interaction ($F = 3.704$, $P = .031$), but the main effect for the group variable was not significant ($F = 3.208$, $P = .084$).

In Figure 2, we can also observe a better course of negative symptoms for the raloxifene group, although there is an improvement in both groups. The results from the ANOVA show differences in the time × group interaction ($F = 3.292$, $P = .044$), whereas the main effect for the group variable did not appear to be significant ($F = 0.008$, $P = .930$).

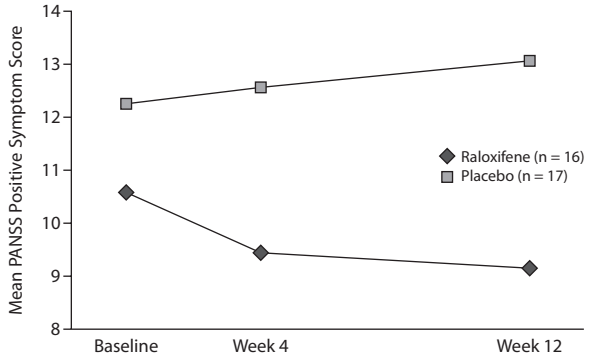
In Figure 3, we again find a better course of general psychopathological symptoms in the raloxifene group. We obtained significant differences in the time × group interaction ($F = 3.263$, $P = .045$). The main effect for the group variable was not found to be significant ($F = 1.870$, $P = .182$).

As can be observed in Figure 4, the repeated-measures ANOVA of total PANSS scores showed significant differences in the time × group interaction ($F = 4.635$, $P = .014$), a finding that indicates a better time course for the raloxifene group. The main effect for the group variable did not appear significant ($F = 2.282$, $P = .142$).

Adverse Effects

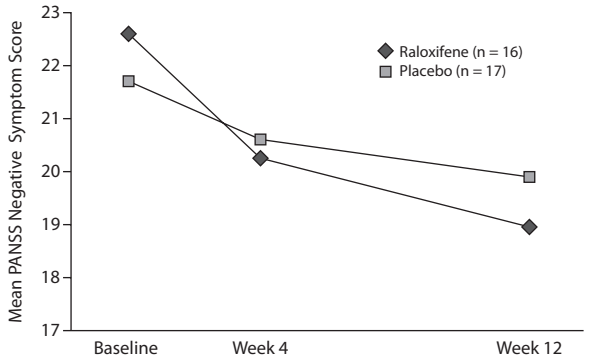
Differences for the UKU Side Effect Rating Scale and Simpson-Angus Scale values between baseline and last evaluation, compared for the placebo and raloxifene groups, were not significant. Repeated-measures ANOVA showed no significant main effect for treatment group ($F = 1.842$, $P = .19$), nor was there a significant group × time interaction ($F = 0.098$, $P = .90$), suggesting that adverse effects measured with the UKU Side Effect Rating Scale did not differ between groups or over time. Moreover, some items on the UKU Side Effect Rating Scale related to menopause, such as weight increase, sexual dysfunction, headache, insomnia, sweating, and palpitations, were analyzed specifically. We observed no

Figure 1. Mean Positive and Negative Syndrome Scale (PANSS) Positive Symptoms at Baseline (day 0) and at Weeks 4 and 12 for Raloxifene and Placebo Groups[a]



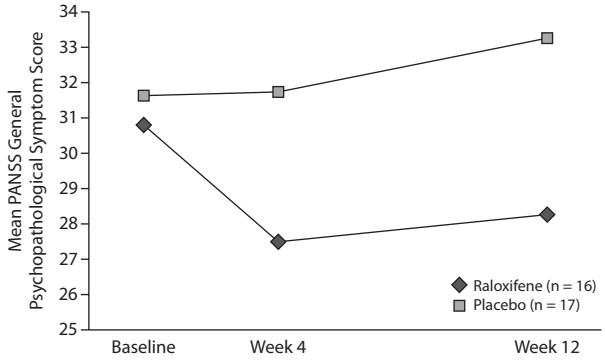
[a]Analysis-of-variance time × group interaction P value = .031.

Figure 2. Mean Positive and Negative Syndrome Scale (PANSS) Negative Symptoms at Baseline (day 0) and at Weeks 4 and 12 for Raloxifene and Placebo Groups[a]



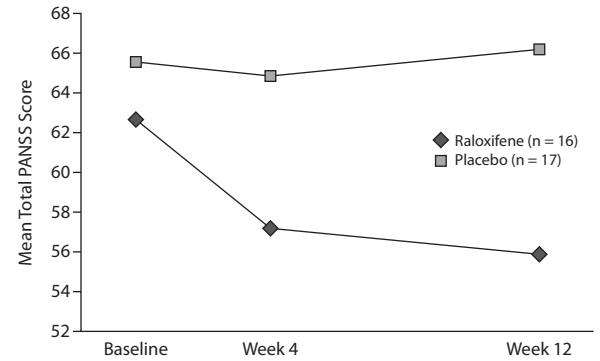
[a]Analysis-of-variance time × group interaction P value = .044.

Figure 3. Mean Positive and Negative Syndrome Scale (PANSS) General Psychopathological Symptoms at Baseline (day 0) and at Weeks 4 and 12 for Raloxifene and Placebo Groups[a]



[a]Analysis-of-variance time × group interaction P value = .045.

Figure 4. Mean Positive and Negative Syndrome Scale (PANSS) Total Scores at Baseline (day 0) and at Weeks 4 and 12 for Raloxifene and Placebo Groups[a]



[a]Analysis-of-variance time × group interaction P value = .014.

significant differences for any of these symptoms between the groups or over time. Similarly, for adverse effects measured with the Simpson-Angus Scale, there was no significant main effect for group ($F = 1.139$, $P = .29$), nor was the group × time interaction significant ($F = 0.109$, $P = .89$). No adverse effects on breast and uterine tissue were found in the entire sample, and no case of thrombophlebitis was reported.

DISCUSSION

The key finding of our study is that the addition of raloxifene, a selective estrogen receptor modulator, to regular antipsychotic treatment in postmenopausal women with schizophrenia who are exhibiting negative symptoms significantly reduced both positive and negative symptoms, as well as general psychopathological symptoms, in comparison with women receiving antipsychotic medication alone.

The main objective of our study was to assess the efficacy of raloxifene for negative symptoms since there is some evidence supporting the possible utility of estrogenic treatment of negative symptoms in postmenopausal women with schizophrenia. The higher rate of late-onset schizophrenia in women (as compared with men)[33] is hypothesized to be related to the decrease in estrogen levels that occurs during menopause. Häfner[34] found that women with late-onset schizophrenia showed greater severity than men with late-onset schizophrenia, especially with respect to negative symptoms. These results also seem to support the hypothesis that estrogen acts as a protective agent, with susceptibility to schizophrenia thus increasing during perimenopause. Moreover, response to treatment with neuroleptics appears to be influenced by menopause: while young women require lower doses of medication than men,[35] postmenopausal women require higher doses than men.[36]

The improvement in negative symptoms is a remarkable finding that is in contrast with the majority of clinical trials with estrogens. This difference could be explained by the shorter duration of other studies (1 to 2 months) or by the clinical characteristics of their samples, which usually include acute patients with prominent positive symptoms.[12,14] Our results on negative symptoms do agree with

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the findings reported by Lindamer et al,[37] who showed in a post hoc analysis of data on postmenopausal women with schizophrenia that patients receiving hormone replacement therapy required lower doses of antipsychotic drugs and presented fewer negative symptoms.

Our finding of a significant effect on positive and general psychopathological symptoms following the addition of raloxifene is in agreement with the results of a number of clinical trials assessing the efficacy of different estrogenic compounds. In their 2-month study, Akhondzadeh et al[14] found improvements in patients' positive and general psychopathological symptoms when 0.05 mg/d of ethinylestradiol was added to patients' treatment. Kulkarni et al[12] reported the results of a double-blind study investigating the utility of adding estrogen, in the form of transdermal estradiol, and also found clinical improvement, especially in positive and general psychopathological symptoms. In a more recent study, Kulkarni et al[13] also found, in a sample of 102 patients with schizophrenia who randomly received transdermal estradiol or placebo added to their regular neuroleptic medication for 1 month, that estradiol was more effective for improving positive and general symptoms.

Our positive results when adding raloxifene to treatment for patients with schizophrenia are in line with the data reported by Kulkarni et al[25] in a very recent publication. In contrast with their finding that a dose of 120 mg/d of raloxifene was more effective than a dose of 60 mg/d of raloxifene or placebo, we found that patients experienced a significant response with the 60-mg/d dose. We chose the 60-mg/d dose because it is the documented dose for the approved indications of raloxifene. We did not carry out a comparison with other doses, so our study cannot establish an optimal dose for raloxifene.

In addition to the better response to raloxifene in comparison with placebo, it should be noted that patients in the raloxifene group did not have more adverse effects than patients in the placebo group; of special interest is the finding that adverse effects on breast and uterine tissue were not different in both groups. The absence of adverse effects on breast and uterine tissue represents an important advantage of raloxifene over estrogens.[18]

The effect of estrogenic compounds on symptomatology in schizophrenia may be mediated by several mechanisms. Estrogen appears to have rapid membrane effects in the short term by altering functional activity in the dopaminergic synapse; it also has genomic effects in the longer term by modifying synthesis in dopamine receptors.[38] There is also evidence to suggest that estrogen alters serotonergic systems.[39] Estrogen can also promote neuronal regeneration and block mechanisms of neuronal death.[40]

As we have previously mentioned, a number of studies seem to indicate that raloxifene acts on brain dopamine and serotonin systems in a way that is similar to that of conjugated estrogens, and some authors propose that conjugated estrogens may exercise their therapeutic potential either by modulating brain neurotransmission or through neuroprotective activity.[20,21] Our results lend support to the potential utility of drugs with estrogen activity in the brain to improve the outcome of subjects with schizophrenia.

The main limitations of the present study are the small number of subjects and the need for a longer follow-up. Our 12-week follow-up was longer than that of other clinical trials, but longer-term studies should be undertaken to assess whether the therapeutic effects are lasting. For example, a study by Bergemann et al,[41] which assessed the effects of estrogenic treatment over 8 months, found no difference in risk of relapse between 2 groups. Finally, we cannot exclude the possibility that the improvement of negative symptoms may be secondary to a positive change in depression, other psychotic symptoms, or extrapyramidal side effects since we did not control for these effects in our study.

In conclusion, our double-blind, placebo-controlled clinical trial found that raloxifene improved all psychotic symptoms in postmenopausal patients with schizophrenia. If more extensive and longer-term studies confirm and expand upon these positive results, the use of raloxifene could be recommended in postmenopausal patients with schizophrenia.

Drug names: biperiden (Akineton), raloxifene (Evista), risperidone (Risperdal and others).

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In memoriam: Dedicated to the memory of Marta Barceló Campaña.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

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