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Raloxifene as an Adjunctive Treatment for Postmenopausal Women With Schizophrenia: A 24-Week Double-Blind, Randomized, Parallel, Placebo-Controlled Trial

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The potential therapeutic utility of estrogens in schizophrenia is increasingly being recognized. Raloxifene, a selective estrogen receptor modulator, appears to act similarly to estrogens on dopamine and serotonin brain systems. One previous trial by our team found that raloxifene was useful to improve negative, positive, and general psychopathological symptoms, without having the negative side effects of estrogens. In this study, we assess the utility of raloxifene in treating negative and other psychotic symptoms in postmenopausal women with schizophrenia exhibiting prominent negative symptoms. This was a 24-week, randomized, parallel, double-blind, placebo-controlled study. Patients were recruited from the inpatient and outpatient departments of Parc Sanitari Sant Joan de Déu, Hospital Universitari Institut Pere Mata, and Corporació Sanitària Parc Taulí. Seventy postmenopausal women with schizophrenia (DSM-IV) were randomized to either adjunctive raloxifene (38 women) or adjunctive placebo (32 women). Psychopathological symptoms were assessed at baseline and at weeks 4, 12, and 24 with the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS). The addition of raloxifene (60 mg/d) to regular antipsychotic treatment significantly reduced negative ($P = .027$), general ($P = .003$), and total symptomatology ($P = .005$) measured with the PANSS during the 24-week trial, as compared to women receiving placebo. Also Alogia SANSS subscale improved more in the raloxifene ($P = .048$) than the placebo group. In conclusion, raloxifene improved negative and general psychopathological symptoms, compared with antipsychotic medication alone, in postmenopausal women with schizophrenia. These data replicate our previous results with a larger sample and a longer follow-up. Trial registration: NCT01573637.

Key words: SERM/negative symptoms/estrogen

Introduction

Research in gender differences in schizophrenia over the past decades has furnished a good number of relevant results. Among these, that in women, schizophrenia is less common, has a later onset, and tends to have a less severe course.[1–3] The estrogen hypothesis concerning schizophrenia posits that estrogen in women who are susceptible to presenting this illness has a protective effect.[4] This hypothesis is supported by several studies. Animal research has shown that estrogen has a modulating effect on the dopaminergic system in the brain.[5] Studies in humans have found that estrogen levels in schizophrenic women are significantly lower than in healthy women,[6] and that the onset of illness or relapses coincide more frequently with the phases of the menstrual cycle when estrogen levels are low.[7] Also, the appearance of late-onset schizophrenia with greater frequency in women than in men[8] seems to be related to the diminution of estrogen levels during menopause.

These data have led researchers to study the therapeutic use of estrogen in patients with schizophrenia. Several double-blind studies have found that estrogens are effective in improving psychotic symptoms.[9–11] These studies have assessed the efficacy of estrogens at 1 or 2-months, and mainly with acutely ill patients.

The use of estrogens as adjunctive therapy in schizophrenia appears promising, but their use in long-term treatment has a potentially negative effect on breast and uterine tissue.[12,13] This has led to investigating the use of selective estrogen receptor modulators (SERM) without these side effects.

Raloxifene is a first-generation SERM used as a preventive treatment for postmenopausal osteoporosis[14] that acts as an antagonist in the reproductive tissue[15] and may, therefore, be a better option than estrogen. Also, raloxifene has agonist actions on AMPA, NMDA, and serotonin receptors in the frontal cortex, striatum, and basal ganglia,[16] brain areas commonly impaired in schizophrenic patients. Raloxifene also has anti-inflammatory activity[17,18] and can act as an agonist of D2 and D3 dopamine receptors.[19,20]

Since there was some evidence that raloxifene could be useful for treating psychotic symptoms in postmenopausal women,[21] but there were no clinical trials exploring this possibility, our team conducted and The Stanley Medical Research Institute (SMRI) funded, a 12-week double-blind, randomized, parallel, placebo-controlled study to assess the utility of 60 mg of raloxifene as adjunctive treatment for negative, positive, and general psychopathological symptoms in postmenopausal women. We found that in our sample of 33 patients, women in the raloxifene group showed greater improvements in both positive and negative symptoms, as well as general psychopathological symptoms, compared with women receiving antipsychotic medication alone.[22]

In recent years, 2 other clinical trials with a follow-up of 3 months or less have assessed the efficacy of 120 mg of raloxifene, and have found that raloxifene could be effective in patients with schizophrenia.[23,24]

Based on the positive results of our previous study, we designed a longer-term clinical trial with a larger sample and the same dose of raloxifene that had proved to be effective. We recruited a sample of 78 postmenopausal women with schizophrenia who received raloxifene in a double-blind, randomized, parallel, placebo-controlled study of 24 weeks' duration.

The objective of our study was to analyze the utility of raloxifene in treating negative, positive, and general psychopathological symptoms in postmenopausal women with schizophrenia and exhibiting prominent negative symptoms. To this end, we conducted a 24-week, multicenter, randomized, double-blind, parallel, placebo-controlled trial.

The main hypothesis underlying this clinical trial is that raloxifene, a selective estrogen receptor modulator, may be an effective adjunctive treatment for negative, positive, and general psychopathological symptoms in postmenopausal women with schizophrenia.

Methods

Sample

Participating women were recruited from mental health centers and various long-stay hospital units (nonacute patients) at Parc Sanitari Sant Joan de Déu, Hospital Universitari Institut Pere Mata, and the Corporació Sanitària Parc Taulí. Seventy-eight patients were randomized (sample size calculation based on primary objective required a total of 80 patients and we assumed a 25% dropout date). The recruitment period began in July 2011 and continued until June 2014.

Inclusion criteria were women with a diagnosis of schizophrenia (DSM-IV-TR criteria),[25] postmenopausal status, receiving stable doses of their current antipsychotic medication for at least a month prior to study initiation, and the presence of prominent negative symptoms defined as 1 or more negative symptom scores greater than 4 on the Positive and Negative Symptom Scale (PANSS) scale.[26] Postmenopausal status was defined as an age over 50 years and at least 1 year of amenorrhea. However, as most women reach menopause between 45 and 55 years, we also considered as postmenopausal those younger women (between 45 and 50 years) with at least 1 year of amenorrhea and FSH levels >20 (which can be considered postmenopausal).[27] Patients gave written informed consent after a complete description of the study was provided.

Exclusion criteria were substance abuse/dependence diagnosis in the previous 6 months, mental retardation, diagnosis of major depression (DSM-IV TR criteria), endocrine abnormalities related with sexual hormones, acute or chronic liver disease, impaired kidney function, history of thromboembolism, breast cancer, abnormal uterine bleeding, history of cerebrovascular accident, and use of hormone replacement therapy.

Blood analysis was performed to determine FSH levels and general state of health. The study received the approval of each institution's review board (IRB) and the Agencia Española del Medicamento. Patients provided informed consent in accordance with procedures established by the local IRB and were informed that they could drop out of the study at any time. The trial was carried out in accordance with the Declaration of Helsinki[28] and subsequent revisions and registered at ClinicalTrials.gov Identifier: **NCT01573637.** The clinical trial was monitored by an external Clinical Research Organization (Sermes CRO).

Interventions

Seventy-eight subjects were initially randomized, of whom 70 started the trial. Six patients dropped out at baseline and 2 patients did not meet inclusion criteria. Both patients were assessed and randomized according to the protocol. At the outset of treatment, one of them began menstruating, despite claiming to have stopped. The claim was borne out by the medical history. This was deemed a screening failure. In another case, at the time when medication was started, it was noted that there had been relevant changes in the antipsychotic medication

some weeks before beginning the study. This was also deemed an error in screening.

Once a patient accepted inclusion in the study and was assessed, the investigator called the pharmacy of the Parc Sanitari Sant Joan de Déu for group assignment. The pharmacy randomly assigned patients to one of the 2 treatment groups with a proportion of 1:1 (blocks of 4 patients, 2 for group 1 and 2 for group 2), based on a random number list. Medication was administered under placebo-controlled, double-blind conditions. Medication was prepared by the pharmacy of the participating hospital. The dose of raloxifene hydrochloride was 60 mg/day. Patients were required to continue taking their regular antipsychotic medications throughout the duration of the study. No changes in dosage were allowed during the study period. Participants received either adjunctive raloxifene (women; mean age = 62.03 years, SD = 9.39) or adjunctive placebo (women; mean age = 61.34 y, SD = 10.31).

All study personnel and participants remained blind to treatment assignment for the duration of the study. Placebo tablets were prepared so as to be identical in appearance to the raloxifene tablets. The compounds from both treatment arms (raloxifene and lactose as placebo) were over-encapsulated in dark green gelatin capsules in order to assure blinding. Placebo capsules contained lactose. Active capsules were prepared by over-encapsulating a raloxifene tablet and filling the empty space with lactose to prevent the tablet from moving. Once the capsule was produced, it was hermetically sealed.

Other psychotropic medications were permitted: 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 chlorpromazine equivalence. Moreover, none of the patients took any sex hormone therapy.

Eight patients in the raloxifene group did not finish the study: 3 patients had changes in medication during the study, 3 refused to participate, 1 suffered a worsening in psychopathology and one decided not to participate due to dizziness. Five patients in the placebo group did not finish the study: 5 refused to participate and one presented 1 unrelated adverse effect. This was a transient ischemic attack. These patients were included in the analysis since it was carried out in accordance with intention to treat (figure 1).

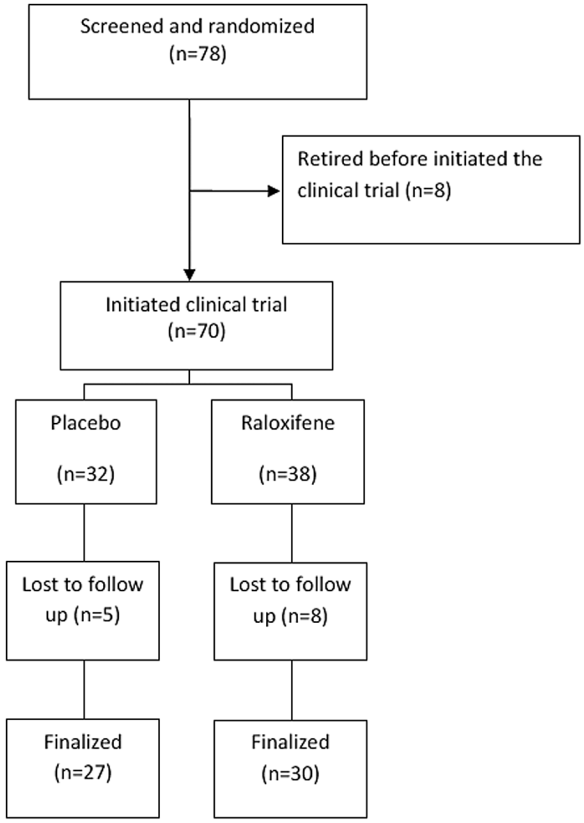

Fig. 1. Flow diagram for patients included in the study.

Outcomes

Diagnoses were established by means of the SCID-IV conducted by a research fellow and reviewed by the principal investigator. A sociodemographic and clinical history questionnaire was also administered. Evaluations were performed by 3 experienced psychologists, who previously performed inter-rater reliability tests. Each psychologist evaluated patients from only 1 center. Psychopathological symptoms were assessed at baseline and at weeks 4, 12, and 24 using the PANSS.[26] Negative symptoms were also assessed with the Scale for the Assessment of Negative Symptoms (SANS).[29] Side effects were assessed at each visit, and the Simpson-Angus Rating Scale[30] was administered for extrapyramidal side effects as was the UKU side effect rating scale.[31]

Treatment compliance was controlled by counting the number of remaining tablets between visits. All patients showed adherence far greater than 80%.

Statistical Analysis

Homogeneity of the sample baseline characteristics between groups was tested with the Student *t* test on continuous variables and/or Mann-Whitney *U* test on ordinal variables and χ^2 test or Fisher's exact test on categorical variables; the appropriate test was chosen according to the variable distribution characteristics. The differences from baseline to final evaluation between the 2 groups for the 4 PANSS and 7 SANS subscales were also compared using the Student *t* test on the scores, and the $\chi 2$ test on the proportion of respondents. To assess effect of treatment group and time interaction, in order to test for differences between the placebo and raloxifene group evolutions over the study time, a repeated-measures analysis of variance (ANOVA) was

conducted for each score of interest at the 4 study timepoints (baseline, and 4, 12, and 24 weeks' follow-up). Only patients with at least baseline and 4 weeks' follow-up data were included (70 patients in total, 32 placebo, 38 raloxifene), and last-observation-carried-forward method was applied to patients with missing data at 12 or 24 weeks' follow-up. SPSS 19.0 (IBM Corp.) was used for statistical analysis; *P*-values <.05 were considered significant.

Results

Demographics

Demographic information is shown in table 1. There were no statistically significant differences between the placebo and raloxifene groups in terms of age, age at illness onset, or years of education. We found no significant differences between the groups regarding regular antipsychotic medication and other medications such as antidepressants and biperiden. There was no significant difference in mean daily dose of antipsychotic medication between the groups (table 1). The raloxifene and placebo groups also showed no significant difference in terms of treatment adherence (mean = 98.27%, SD = 7.40; and mean = 97.04%, SD = 4.43, respectively; $P = .582$).

Symptoms

As shown in table 1, at baseline there were significant differences between the groups in the general psychopathological PANSS subscale ($P = .020$, the raloxifene group scoring higher than the placebo), while the differences were not significant between groups in the positive symptoms ($P = .89$), negative symptoms ($P = .17$) and total ($P = .084$) PANSS scales.

The raloxifene group obtained better mean differences between baseline and final scores on all PANSS subscales than the placebo group, and the results were significant in all PANSS subscales except for the positive symptoms. On the positive PANSS subscale, the mean difference (m.d, with 95% confidence interval) was lower in the raloxifene group (m.d. = −1.63, [−2.60, −0.66]) than in the placebo group (m.d. = −0.41, [−1.82, 1.01]), but the difference was not significant ($P = .141$). However, the difference was significant ($P = .027$) in the negative PANSS subscale between the raloxifene (m.d. = −3.52, [−5.25, −1.80]) and the placebo (m.d. = −0.88, [−2.45, 0.70]) groups. There was also a significant difference ($P = .003$) in the general psychopathological symptoms PANSS subscale between the raloxifene (m.d. = −5.08, [−7.33, −2.83]) and the placebo (m.d. = 1.22, [−2.36, 4.80]) groups. Finally, the total PANSS score also showed a significant difference ($P = .005$) between the raloxifene (m.d. = −10.24,

Table 1. Demographic Data and Baseline for the Women in the Raloxifene and Placebo Groups ($N = 70$)[a]

Characteristic	Raloxifene ($n = 38$)	Placebo ($n = 32$)	*P* Value[b]
Age, mean (SD), y	62.03 (9.39)	61.34 (10.41)	.77
Education y, mean (SD), y	8.13 (3.10)	7.73 (3.26)	.64
Age at onset of disease, mean (SD), y	26.29 (8.64)	27.04 (11.37)	.78
Baseline PANSS score, mean (SD)			
Positive	17.05 (4.53)	17.22 (5.66)	.89
Negative	24.39 (5.32)	22.81 (4.05)	.17
General	39.03 (8.14)	34.63 (7.18)	.020
Total	80.47 (14.30)	74.66 (13.26)	.084
Participant medication type, *n* (%)			
Antipsychotic			
First-generation antipsychotic	2 (3.1%)	4 (6.2%)	.53
Second-generation antipsychotic	28 (43.1%)	21 (32.3%)	
Combination	5 (7.7%)	5 (7.7%)	
Antidepressant, yes	12 (17.6%)	5 (7.4%)	.16
Antidepressant, no	25 (36.8%)	26 (38.2%)	
Biperiden, yes	9 (43.2%)	9 (3.2%)	.78
Biperiden, no	28 (41.2%)	22 (32.4%)	
Dosage of antipsychotic, median, mg/d[c]	750	600	.42
Patient status at baseline, *n* (%)			
Inpatient	27 (38.6%)	29 (41.4%)	.070
Outpatient	11 (15.7%)	3 (4.3%)	

Note: PANSS: Positive and Negative Syndrome Scale
[a]Percentages based on the total *N* of 70.
[b]*P*-values derived from Student *t* Test, Mann-Whitney U test, $\chi 2$ test, or Fisher's Exact Test.
[c]Antipsychotic drug doses are expressed as chlorpromazine equivalence.

[−14.42, −6.05]) and the placebo (m.d. = −0.063, [−6.11, 5.98]) groups.

Additionally, we analyzed response to treatment according to the criterion of a decrease in negative PANSS score of at least 20% or more from baseline, and we found a greater treatment response in those receiving raloxifene when compared to those on placebo (36.8% vs 12.5%, $\chi 2 = 5.39$, $P = .020$).

Figures 2–5 show the evolution of mean psychotic symptom PANSS subscales during the treatment period for both groups. In figure 2, significant differences are not observed between the placebo and raloxifene groups according to the positive PANSS subscale, and in fact the time × group interaction was not significant ($F = 1.387$, $P = .248$) in the ANOVA results. The main effect for the group variables was also not significant ($F = 0.502$, $P = .481$).

In figure 3, we observe a better course of negative PANSS subscale for the raloxifene group, especially between baseline and first follow-up. The results from the ANOVA show a significant time × group interaction ($F = 3.869$, $P = .010$), while the main effect of the group variable was not significant ($F = 0.002$, $P = .969$).

In figure 4, we find significant differences in general psychopathological PANSS subscale over time in the raloxifene group, while the placebo group actually worsens in the same period. The time × group interaction was therefore significant ($F = 5.826$, $P = .001$), and the main effect for the group variable was not significant ($F = 0.135$, $P = .715$).

Finally, in figure 5, there are also significant differences over time in the total PANSS score in the raloxifene group, while the placebo group does not show changes. The ANOVA results show a significant interaction time × group interaction ($F = 5.072$, $P = .002$). The main effect for the group variable was not significant ($F = 0.003$, $P = .958$).

An equivalent analysis of the SANS negative symptoms scale and its subscales (Affective Flattening, Alogia, Avolition–Apathy, Anhedonia–Associality, Attention, Total sum of global scores, Composite score) only showed significant results in the Alogia subscale, where the mean difference between baseline and final Alogia SANSS subscale was lower in the raloxifene group (m.d. = −0.68, SD = 3.02) than in the placebo group (m.d. = 1.25, SD = 3.51). The repeated- ANOVA measures of this subscale showed a significant time × group interaction ($F = 2.674$, $P = .048$), with the raloxifene group improving over time, while the main effect for the variable group was not significant ($F = 0.788$, $P = .378$).

Adverse Effects

In order to check whether there were significant differences between groups in terms of adverse effects, for each patient the difference between baseline and final evaluation in the UKU Side Effect Rating Scale and Simpson-Angus Scale was calculated, but the placebo and raloxifene groups were not significantly different.

In the UKU Side Effect Rating Scale, repeated-measures ANOVA showed no significant time × group interaction ($F = 0.077$, $P = .972$) and the group main effect was also not significant ($F = 0.329$, $P = .568$). Therefore, we may conclude that adverse effects measured by this scale did not differ between groups or over time. In addition, some items on the UKU Side Effect Rating Scale relating to menopause, such as weight increase, sexual dysfunction, headache, insomnia, sweating, and palpitations, were added together to define a new subscale, and we observed no significant differences between groups or over time on this subscale. Finally, for adverse effects measured with the Simpson-Angus scale, there was no significant time × group interaction ($F = 1.102$, $P = .385$) and the group main effect was also not significant ($F = 0.003$, $P = .959$). No adverse effects on breast or uterine tissue and vaginal bleeding were found in the entire sample, and no case of thrombophlebitis was reported.

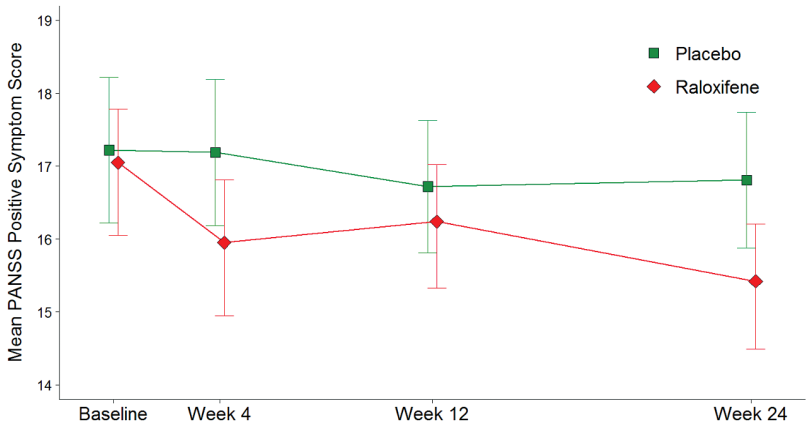

Fig. 2. Mean Positive and Negative Syndrome Scale (PANSS) Positive Symptoms at baseline (d 0) and at 4, 12, and 24 weeks for raloxifene and placebo groups[a].Error bars indicate standard error of the mean.[a]ANOVA time × group interaction *P*-value = .248

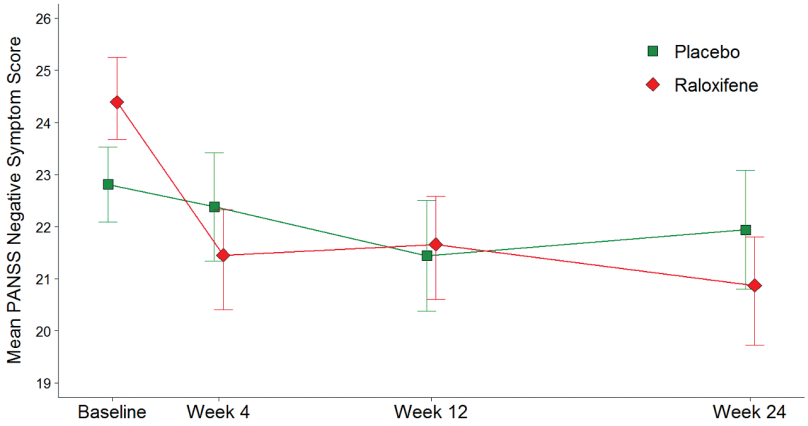

Fig. 3. Mean Positive and Negative Syndrome Scale (PANSS) Negative Symptoms at baseline (d 0) and at 4, 12, and 24 weeks for raloxifene and placebo groups[a].Error bars indicate standard error of the mean.[a]ANOVA time × group interaction *P*-value = .010.

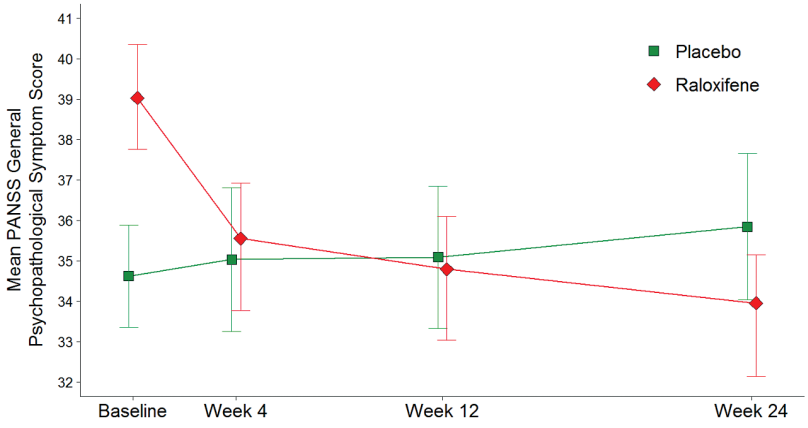

Fig. 4. Mean Positive and Negative Syndrome Scale (PANSS) General Psychopathological Symptoms at baseline (d 0) and at 4, 12, and 24 weeks for raloxifene and placebo groups[a].Error bars indicate standard error of the mean.[a]ANOVA time × group interaction *P*-value = .001.

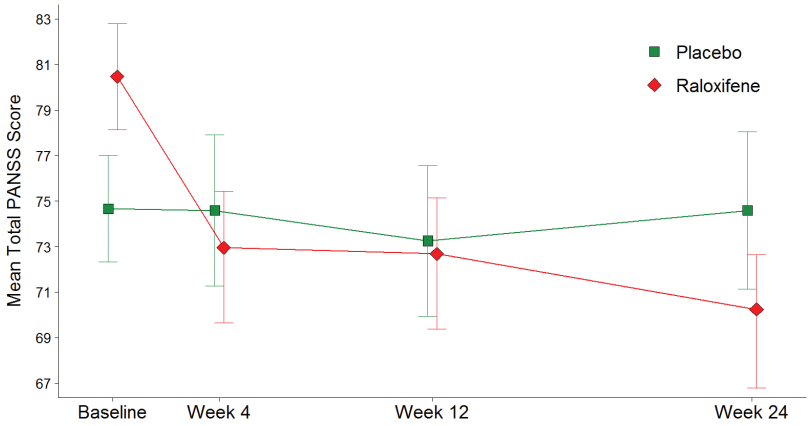

Fig. 5. Mean Positive and Negative Syndrome Scale (PANSS) Total Scores at baseline (d 0) and at 4, 12, and 24 weeks for raloxifene and placebo groups[a]. Error bars indicate standard error of the mean. ANOVA time × group interaction *P*-value = .002.

Discussion

The key finding of our study is that the addition of raloxifene, a selective estrogen receptor modulator (SERM), to regular antipsychotic treatment in postmenopausal women with schizophrenia exhibiting prominent negative symptoms significantly improved the negative symptoms, as well as general psychopathological symptoms, compared with women receiving antipsychotic medication alone.

The main objective of our study was to assess the efficacy of raloxifene for negative symptoms, since negative

symptoms are more resistant to treatment than positive symptoms;[32] in our previous trial[22] the addition of raloxifene to antipsychotic treatment improved negative symptoms. Other recent studies[33,34] have also demonstrated beneficial effects of raloxifene on cognitive symptoms, that may also overlap with negative symptoms. Thus, our trial was focused on negative symptoms rather than positive symptoms, and recruited stabilized patients with schizophrenia and prominent negative symptoms.

Recently, some studies have pointed up the adjunctive efficacy of raloxifene for the treatment of postmenopausal women with schizophrenia. Of all the studies, only 3 were randomized, while the others were case reports.[35]

One of the clinical trials, by Kulkarni et al.,[23] found that raloxifene was only effective for general symptomatology. This clinical trial and ours have some methodological differences that may explain the contrasting results. First of all, we included a larger sample (78 vs 35) with a longer follow-up period (6 vs. 3 months). Second, in the study by Kulkarni et al.,[23] they included patients that were acutely unwell. And third, the presence of prominent negative symptoms was not in the inclusion criteria of the trial of Kulkarni et al.[23]

The other clinical trial was by Kianimehr et al.[24] This team found that raloxifene was only effective for the positive symptomatology. This was an 8-week follow-up study conducted in a sample of 46 patients. The inclusion criteria were closer to those of the Kulkarni trial than to ours.

Another interesting result is that in contrast to our previous trial, we did not find a significant improvement in positive symptoms. Although there are speculative explanations, this discrepancy may be explained by several issues related to sample characteristics, including the smaller sample size of the previous trial ($N = 33$) and differences in the severity of positive symptoms between the 2 studies (mean [SD] 11.88 [4.76] in the first trial vs 17.03 [5.11] in the current trial [$P < .001$]). The previous result on positive symptoms could be a false positive finding that was not replicated (in contrast to the improvement in negative symptoms) when the sample size was increased.

In contrast to our 2 trials, in which we used 60 mg of raloxifene, the other 2 clinical trials[23,24] used 120 mg of raloxifene. We studied the efficacy of 60 mg because it is the recommended dose for use as a preventive treatment of postmenopausal osteoporosis[36] and the tolerance and safety are well known.[37] We did not carry out a comparison with other doses, so our study cannot establish an optimal dose for raloxifene.

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.[5] There is also evidence to suggest that estrogen alters serotonergic systems.[38] Estrogen can also promote neuronal regeneration and block mechanisms of neuronal death.[39]

Specifically, raloxifene appears to influence multiple neurotransmitter pathways including serotonin in the frontal cortex, and striatum and basal ganglia.[16] Raloxifene acts not only through tissue selectivity, but also through cellular selectivity within the brain, and it differentially modulates the activiation of microglia, astroglia and neurons.[39] Also, an interesting study has found that in rats, raloxifene improves the execution of a cognitive task that depends of the prefrontal cortex and also increases the numerical density of dendritic spines in layer III pyramidal neurons from the prelimbic/infralimbic prefrontal cortex. The results of this study could explain the positive effect of raloxifene on negative symptoms found in our trial.[40]

The known actions of raloxifene in preventing osteoporosis[41] may also offer a secondary benefit in these patients. Decreased bone mineral density (BMD) is more common in patients with schizophrenia than in the general population, and it is the case that some antipsychotics reduce BMD.[42]

Among the strengths of our clinical trial is the fact that its methodology follows the consensus of the NIMH-MATRICS: we included only patients with persistent and clinically prominent negative symptoms, and with clinically stable positive symptoms, and we also did not make changes in medication during the 24 weeks of the trial. The length of the follow-up was in the range of 24 weeks in order to better document efficacy. Also, we did not include patients with depression in order to minimize the possibility that the improvement in negative symptoms was secondary to a positive change in depression.[43]

Among the limitations of the trial is the fact that we cannot rule out that the improvement in negative symptoms was secondary to an improvement in other psychotic symptoms, as there was also an improvement in psychopathological symptoms; however, there was no significant improvement in positive symptoms. Also, at baseline, the raloxifene group had significantly higher baseline general symptom scores than the placebo group and, therefore, had more room for improvement in these symptoms. Therefore, interpretation of the results regarding efficacy of treatment for general symptoms must be treated with care.

Given that the effects of raloxifene on positive symptoms were lesser when compared to other symptoms (negative, general psychopathology), the original sample size of our study may be too small for detecting such small differences. In fact, the post-hoc statistical power for each ANCOVA analysis for the time × group interaction effect was 37% for positive symptoms, 82% for negative symptoms, 95% for general psychopathology, and 92% for total PANSS score. This suggests that our sample may be underpowered for detecting changes in positive symptoms but not for other symptoms (negative symptoms or

general psychopathology). However, as observed changes in positive symptoms are small, we also think that these changes are not clinically meaningful.

In conclusion, our double-blind, 24-week, parallel placebo-controlled clinical trial found that raloxifene improved negative and general psychopathological symptoms, measured with the PANNS scale, compared with antipsychotic medication alone in postmenopausal women with schizophrenia exhibiting prominent negative symptoms. These data replicate our previous results on the efficacy of 60 mg of raloxifene on negative symptoms measured with the PANSS with a larger sample and a longer follow-up. If other studies confirm and expand upon these positive results, the use of raloxifene could be recommended in postmenopausal women with schizophrenia.

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