A Placebo-Controlled Study of Raloxifene Added to Risperidone in Men with Chronic Schizophrenia

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Abstract- Selective estrogen receptor modulators (SERMs) such as raloxifene have already shown beneficial effects on negative, positive and general psychopathology symptoms in postmenopausal women with schizophrenia. The purpose of the present investigation was to assess the efficacy of raloxifene as an adjuvant agent in the treatment of men with chronic schizophrenia in an 8-week double-blind and placebo-controlled trial. In a randomized, double-blind and placebo-controlled study, forty-six male patients diagnosed with schizophrenia (DSM-IV-TR), were randomized to either raloxifene (120 mg/day) or placebo in addition to risperidone (6 mg/day) for eight weeks. The assessment was performed using the positive and negative symptom scale (PANSS) at baseline, and at weeks 2, 4, 6 and 8. Extrapyramidal symptom rating scale (ESRS) at baseline, weeks 1, 2, 4, 6, 8 and Hamilton depression rating scale (HDRS) at baseline and week 8 were also used to assess extrapyramidal symptoms and depression simultaneously. Forty-two patients completed the trial. The raloxifene group showed significantly greater improvement on the negative subscale (P<0.001), the general psychopathology subscale (P=0.002) and total PANSS score (P<0.001) in comparison to the placebo group at the endpoint. There was no significant difference in the reduction of positive symptoms score between the two group (P=0.525). Extrapyramidal symptom rating scale and Hamilton depression rating scale and frequency of other adverse effects were comparable between two groups.
This study indicates raloxifene as a potential adjunctive treatment strategy for chronic schizophrenia in men.

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Introduction

Schizophrenia is a chronic and progressively debilitating disease that irreversibly affects cognitive, social, and vocational performance and is one of the leading causes of disability-adjusted life years (DALYs) worldwide (1,2). The disease occurs in all populations with global prevalence in the range of 1.4 to 4.6 per 1,000 and incidence rates in the range of 0.16-0.42 per 1,000 people (3). Despite its lower prevalence in comparison to other psychiatric disorders, it signifies a major burden for families, healthcare systems and societies. The median healthcare cost is estimated to be around 1.1% of the total health care expenditure of a nation (4,5).

Gender differences in epidemiology, incidence and prevalence of schizophrenia are well established (6). Consistently, incidence in males is 1.4 times higher (7), and males experience earlier onset, poorer premorbid function and social course with more severe negative symptoms, cognitive deficits and greater structural brain and neurophysiological abnormalities (8-12). Furthermore, they are indicated to be less responsive to existing antipsychotic treatments (13,14).

Although pharmacologic management with either first or second generation antipsychotics are the basis of schizophrenia treatment, over time clinicians have noticed that classical antipsychotics are mostly ineffective against the negative symptoms and cognitive dysfunctions that are prominent in male patients with chronic course of this disease (15). Therefore, the need for innovative and more effective treatment strategies like poly-pharmacy is absolutely clear (16,17). Recent animal and human studies concerning gender differences

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revealed the substantial impact of estradiol as a sex hormone on the central nervous system and neurotransmitters assumed to be involved in schizophrenia pathogenesis giving rise to the estrogen hypothesis (18,19). It is hypothesized that estradiol has a modulating effect on the dopaminergic and serotonergic system (20-23). Studies reported estradiol levels in schizophrenic women to be significantly reduced in comparison to the normal population (24,25). In addition, patients experience symptom recurrence during low estradiol level phases (26). Accordingly, authors proposed a protective role for estrogen in women (11,27-29). These findings led to the therapeutic use of estradiol. Subsequent clinical trials also proved adjuvant estrogen therapy in schizophrenic women to be promising actually (30-34). Unfortunately, long-term use of estrogen is limited and has the drawback of potential adverse effects on men particularly feminization and infertility (35,36) as it is hazardous to gynecological tissue in women along with higher risk of stroke and coronary heart disease (37,38).

Selective estrogen receptor modulators (SERMs) as estrogen both agonists and antagonists also appeared to have an estradiol-like impact on brain neurochemistry and adjuvant therapy to antipsychotics but without peripheral adverse effects of estradiol (39,40). Raloxifene as a first generation SERM showed efficacy in improving cognition and psychopathologic symptoms in postmenopausal women (41-43).

Thus the development of innovative adjunctive hormone therapies, such as SERMs may offer new strategies for treating men suffering from schizophrenia (36,44).

This study, as an 8-week, double-blind, randomized, placebo-controlled trial, aimed to evaluate the use of raloxifene as an adjunctive treatment for psychotic symptoms in men diagnosed with schizophrenia.

Materials and Methods

Study design

This study was designed as an eight-week, randomized, double-blind, placebo-controlled, and parallel-group clinical trial. The study was conducted in outpatient clinics at Roozbeh Psychiatric Hospital, affiliated with Tehran University of Medical Sciences (TUMS) and Razi Hospital affiliated with University of Social Welfare and Rehabilitation from July 2013 to July 2014. The protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences and carried out in agreement with the declaration of Helsinki and its subsequent revisions. After complete explanation of the study details, written informed consent was obtained from eligible patients and their legally authorized representatives, informing the participants of their rights to withdraw from the trial at any time without any interruption in their healthcare benefits.

This trial was registered at the Iranian Clinical Trials Registry (IRCT201211211556N47; www.irct.ir).

Participants

Patients diagnosed with schizophrenia who met the diagnostic criteria for schizophrenia based on the Diagnostic and Statistical Manual (DSM)-IV-TR were recruited for this study.

Patients were all male within the age range of 18-55 years. The diagnosis was established by means of chart review and semi-structured clinical interview for DSM-IV-TR Axis I disorders (SCID). The patients were included if they (1) met DSM-IV-TR criteria for schizophrenia, (2) had minimum Positive and Negative Symptoms Scale (PANSS) score of 60 and (3) Minimum disease duration of at least 2 years.

Patients were excluded if they had any of the following criteria: (1) additional axis I diagnosis according to the DSM-IV-TR (2), other neurologic or organic illnesses based on clinical examinations or laboratory findings (3), Intelligent Quotient (IQ) of less than 70 (mental retardation) based on clinical judgment (4), any alcohol or substance dependence (except nicotine or caffeine) within past 6 months of screening (5), previous treatment with oral antipsychotics in the past week or long-acting antipsychotics in the past month, 6-ECT therapies in the past 2 weeks (6), endocrine abnormalities (7), acute or chronic liver disease or kidney dysfunction (8), history of thrombosis or thromboembolism (9), history of uncontrolled bleeding (10), or history of cerebrovascular accident. In addition, Patients with a score of $\geq$14 on a 17-item Hamilton Depression Rating Scale (HDRS) or a score of $\geq$4 on depression item of PANSS were excluded from the study since significant depression can cause misinterpretation of the negative symptoms. Suicidal ideation based on clinical judgment or a score of $\geq$2 on suicide item of HDRS was considered as another exclusion criterion.

Interventions

Participants were randomly assigned to receive risperidone (6 mg/day in 3 divided doses) (Janssen Pharmaceuticals, Toronto, Canada; 2mg tablet)

combined with either placebo (N=23) or 120 mg/day of raloxifene (Eli Lilly) (N=23) for 8 weeks.

Placebo tablets were identical in appearance to raloxifene, and no further change in treatment doses was permitted.

Bipyridine up to 6mg/day PO was administered in case of any symptoms of dystonia or Parkinsonism, and Propranolol was prescribed with the needed dose in the case of akathisia.

Outcomes

Patients were evaluated by PANSS total, positive and negative subscales criteria at baseline, and weeks 2, 4, 6 and 8.

Extrapyramidal Symptoms were assessed using Extrapyramidal Symptoms Rating Scale (ESRS) (part 1: Parkinsonism, dystonia, dyskinesia; the sum of 11 items) at baseline, weeks 1,2,4,6 and 8. Prior to initiation of the intervention, all patients were assessed for PANSS and any extrapyramidal side effects at baseline (day 0).

The primary outcome was the difference in PANSS total score reduction between two groups from baseline to week 8. The secondary outcome measures the difference of change in PANSS subscale score between two groups. Depressive symptoms were also checked with HDRS scale at baseline and at week 8.

Adverse events and safety

A thorough physical examination and ECG were performed at screening and each post-baseline visit when vital signs of the participants were recorded and monitored. All patients were encouraged to inform their health care providers and subsequently the research team about any unexpected adverse events at any time during this project. In order to provide more safety, open-ended questioning about any probable side effects followed by completion of a systematic 25-item questionnaire checklist of a broad range of alarming symptoms or complaints were carried out during each visit. Extrapyramidal side effects were also evaluated with ESRS (part 1: Parkinsonism, dystonia, dyskinesia; the sum of 11 items) in addition to a thorough physical examination at baseline and all post-baseline visits. The behavior appraisal and adverse effects checklist were completed by independent raters.

Facing any side effect, an expert psychiatrist was responsible to decide whether the patient is eligible to continue with the same drug dose or continue with reduced dose of drug or discontinuation of the drug is warranted.

Sample size

Based on our previous studies, a difference of 5 on PANSS total score, a standard deviation (SD) of 5, a two-sided significance of 5%, and a power of 80% was considered and a sample size of 32 was first calculated. In consideration of a 20% attrition rate, 40 patients (20 in each group) were targeted as our final sample size.

Randomization and blinding

In order to randomize the enrolled participants, a computer random number generator was used to assign patients randomly and equally in a 1:1 ratio in blocks of four, receiving either raloxifene or placebo. Allocation concealment was done using sequentially numbered, sealed, opaque packages. Both randomization and allocation were carried out by independent persons who were not involved elsewhere in the study. Patients, nurses, and physicians responsible for referring the patients, and the statistician, as well as the investigators who rated the patients and administered the drugs, were all blinded to the allocation. Placebo tablets were identical to raloxifene tablets in shape, odor, size, and color. They were all kept in identical containers and were administered by an investigational drug pharmacist.

Statistical analysis

IBM SPSS Statics version 20 (IBM Corporation) was used for data analysis. Continuous variables are reported as mean (SD) and categorical variables as a number (percent). Mean differences (MD) are described with 95% confidence intervals [MD (95% CI)]. Independent sample T-test was used in order to compare the mean score changes of PANSS, HDRS and ESRS between the two groups from baseline to the trial endpoint. General linear model repeated measures was employed to evaluate the interaction of time X treatment for PANSS and ESRS scores between the two groups, assuming the study groups (raloxifene vs. placebo) as the between-subject variable and study measurements as the within-subject factor (time). In case of significant Mauchly's test of sphericity, Greenhouse-Geisser correction for degrees of freedom was performed. Statistically, significant P-value was defined as <0.05.

Results

Baseline characteristics

From a total of sixty-four patients screened for this study, 46 patients were randomly assigned to this trial of

risperidone plus raloxifene and risperidone plus placebo with 23 patients in each group. Forty-two patients (21 in each group) completed the trial. (Figure 1). Baseline characteristic of patients is summarized in table 1. There was no significant difference in baseline PANSS total and subscale scores, and ESRS and HDRS score between the two groups of patients.

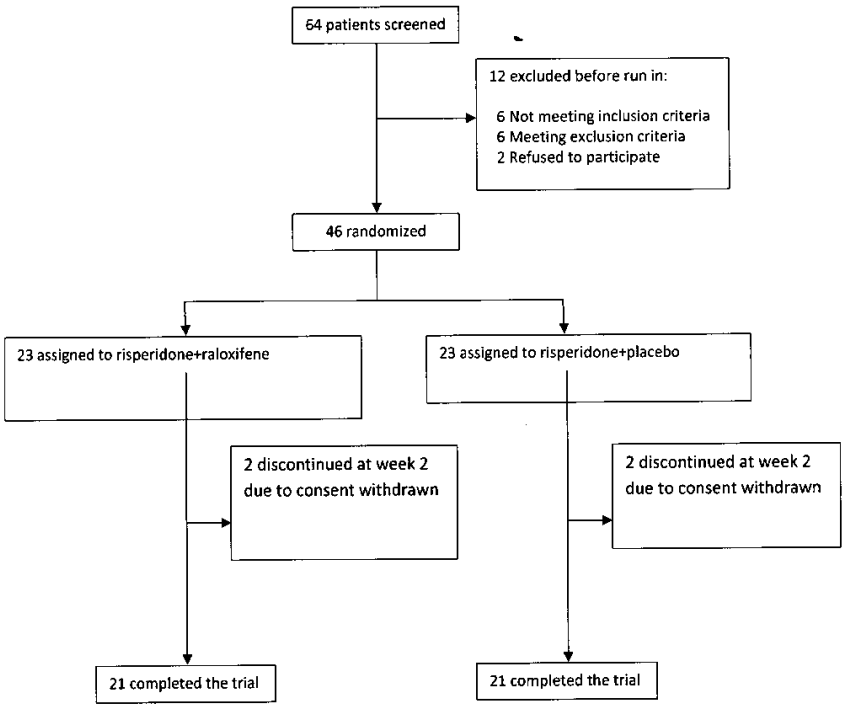

Figure 1. Flow diagram of the trial

Table 1. Demographic characteristics of the patients

Variables		Placebo (n=21)	Raloxifene (n=21)
Age, mean±SD (years)		32.4±7.8	31.4±5.9
Marital status, n, %	**Single**	15 (72%)	17 (80%)
	Married	6 (28%)	4 (20%)
	Divorced	-	-
Level of education, n, %	**Illiterate**	1 (4.7%)	-
	Primary school	15 (71.4%)	18 (85.7%)
	High school diploma	4 (19%)	3 (14.2%)
	University degree	1 (4.7%)	-
Smoking, n, %		18 (85.7%)	20 (95.2%)
Duration, mean±SD (month)		96.2±45.9	89.3±70.9
Type of schizophrenia, n, %	**Paranoid**	14 (66.6%)	13 (61.9%)
	Residual	8 (38%)	10 (47.6%)
	Disorganized	7 (33.3%)	6 (28.57%)
	Undifferentiated	8 (38%)	8 (38%)
Prior antipsychotic medications, n, %	**Risperidone**	14 (66.6%)	13 (61.9%)
	Haloperidol	8 (38%)	10 (47.6%)
	Fluphenazine	7 (33.3%)	6 (28.57%)
	Olanzapine	8 (38%)	8 (38%)
Total PNSS, mean±SD		100.7±15.5	101.6±13.5
Positive mean±SD		30.3±6.7	29.7±5.1
Negative mean±SD		24.1±7.5	23.5±6.1
General Psychopathology, mean±SD		46.3±6.9	48.4±9.0
Extrapyramidal Symptoms Rating Scale, mean±SD		1.1±3.3	1.1±3.0
Hamilton Depression Rating Scale, mean±SD		7.9±1.7	8.0±1.7

PANSS total score

Baseline total score didn't differ significantly between the two groups [MD: (95 %CI) =0.9 (-8.2 to 10), t (40) =0.201, *P*=0.84]. Repeated measures ANOVA indicated a significant effect for time-treatment interaction [Greenhouse-Geisser: F (2.324, 92.957) = 11.980, *P*<0.001] (Figure 2A). By week 8, patients in the raloxifene group experienced significantly greater reduction in their PANSS Total score than the placebo group [MD: (95 %CI) = -15.81 (-22.3 to -9.4), t(40) = -4.972, *P*<0.001] (Table2).

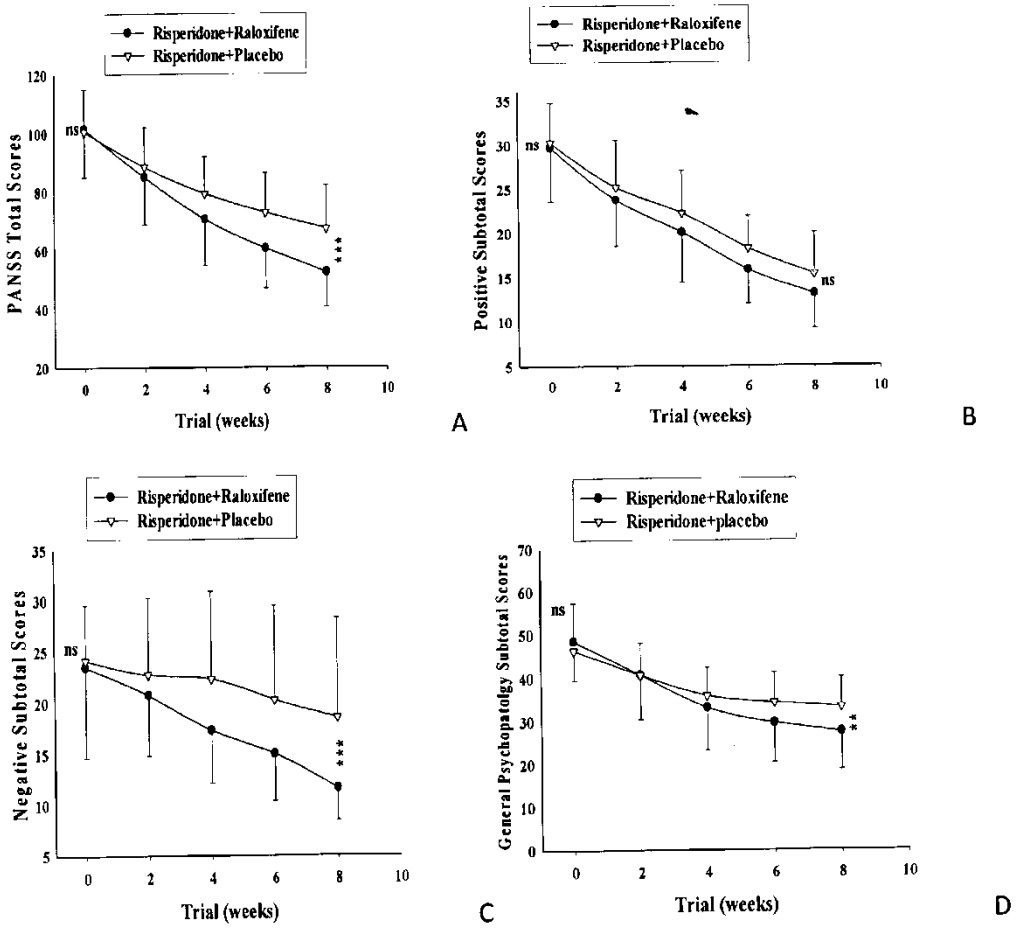

Figure 2. Comparison of PANSS total scores (A), PANSS positive subscale scores (B), PANSS negative subscale scores (C) and PANSS General Psychopathology subscale scores (D) between two groups over time (**=*P*-value<0.01, ***=*P*-value<0.001 and ns= non-significant)

PANSS positive symptoms

Baseline positive subscale score didn't differ significantly between the two groups [MD: (95 %CI) =-0.6 (-4.3 to 3.1), t (40) = -0.312, *P* = 0.756]. Repeated measure ANOVA showed a non-significant effect for time-treatment interaction [Greenhouse-Geisser: F (2.549, 101.95) = 0.678, *P* = 0.544] (Figure 2B). By week 8, patients in the raloxifene group didn't differ significantly in reduction of their positive subscale score than the placebo group [MD: (95 %CI) = -1.6 (-6.5 to 3.4), t (40) = -0.641, *P* = 0.525] (Table2).

PANSS negative symptoms

Baseline negative subscale didn't differ significantly between the two groups. [MD: 95%CI = -0.7 (-4.9 to 3.6), t (40) = -0.315, *P* = 0.754)]. Repeated-measures ANOVA showed significant effect for time-treatment interaction [Greenhouse-Geisser: F (1.766, 70.637) =

12.509, $P<0.001$] ((Figure 2C). By week 8, patients in the raloxifene group experienced a significantly greater reduction in negative subscale score than patients in the placebo group [MD: (95 %CI) = -6.3 (-9.4 to -3.3), t(40) = -4.183, $P<0.001$] (Table2).

When the PANSS negative subscale change was predicted by multiple linear regression analysis, it was found that the treatment group ($\beta = -0.57$, $t = -4.11$, $P < 0.001$) was independent significant predictors. Changes in the PANSS positive subscale ($\beta = 0.19$, $t = 0.69$, $P = 0.49$), Hamilton Depression Score ($\beta = 0.19$, $t = 0.71$, $P = 0.48$) and ESRS ($\beta = 0.01$, $t = 0.11$, $P = 0.91$) scores could not significantly predict the change in PANSS negative subscale. Treatment group (raloxifene or placebo) was the strongest predictor of any negative symptom changes over the course of this trial.

PANSS general psychopathology

The baseline general pathology subscale score didn't differ significantly between the two groups [MD: (95 %CI) = 2.1 (-2.8 to 7.1), t (40) = 0.869, $P = 0.390$]. Repeated measures ANOVA indicated a significant effect for time-treatment interaction [Greenhouse-Geisser: F (1.762, 70.484) =7.017, $P = 0.002$] (Figure 2D). By week 8, patients in the raloxifene group experienced significantly greater reduction in general psychopathology subscale score than the placebo group [MD: (95 %CI) = -7.9 (-12.8 to -3.1), t(40) = -3.327, $P = 0.002$](Table2).

Table 2. Changes from baseline in the PANSS scores at week 8

Scores (mean±SD)		Change	*t*(40)	*P* value	Effect size (Cohen's d)
Negative	**Raloxifene**	12±5.2	-4.183	<0.001	-1.3
	Placebo	5.6±4.5			
Positive	**Raloxifene**	10.4±7.1	-0.641	0.525	-0.2
	Placebo	8.8±8.7			
General psychopathology	**Raloxifene**	20.9±7.8	-3.327	0.002	-1.0
	Placebo	13±7.7			
Total PANSS	**Raloxifene**	49.3±8.4	-4.972	<0.001	-1.5
	Placebo	33.5±11.9			

Table 3. Frequency of the side effects in the two study groups

Side effect	Placebo	Raloxifene
Sweating n, %	5 (23.8%)	3 (14.2%)
Skin Rash n, %	2 (9.5%)	4 (19%)
Dizziness, n, %	2 (9.5%)	5 (23.8%)
Weight gain n, %	5 (23.8%)	6(28.5%)
Headache, n, %	3 (14.2%)	4 (19%)
Dry mouth, n, %	5 (23.8%)	6 (28.5%)
Diarrhea, n, %	1 (4.7%)	2 (9.5%)

Hamilton depression rating scale

Baseline HDRS scores didn't differ between the two groups [MD: (95 %CI) = 0.2 (-0.9 to 1.3), t (40) = 0.360, $P = 0.721$]. By week 8, patients in the raloxifene group didn't differ significantly in HDRS score than the placebo group [MD: (95 %CI) = 0.1 (-0.9 to 1.2), t(40) = 0.283, $P = 0.778$].

Extrapyramidal symptom rating scale

Baseline ESRS scores didn't differ between the two groups [MD: (95 %CI) = 0.0 (-1.9 to 2.0), t (40) = 0.49, $P = 0.961$]. Repeated measures ANOVA showed a non-significant effect for time-treatment interaction [[Greenhouse-Geisser: F (2.518, 100.729) = 0.175, $P = 0.884$]. By week 8, patients in the raloxifene group didn't differ significantly in reduction of their ESRS score than the placebo group [MD: (95 %CI) = -1.1 (-3.2 to 1.0), t (40) = -1.094, $P = 0.281$]

Adverse effects

Other than extrapyramidal symptoms, eight side effects were recognized throughout the study. Applying the fisher's exact test, the frequency of side effects didn't differ significantly between the raloxifene and the placebo group (Table 3).

Discussion

In recent years adjuvant therapy and polypharmacy for schizophrenia has been a major concern while being applied to several other chronic diseases. The results of this study indicate that raloxifene as an add-on to risperidone has significant beneficial effect on the primary negative and psychopathologic symptoms of schizophreniain men. Regarding the primary negative symptoms, we should consider factors like positive, extrapyramidal and depressive symptoms to be confounding to the changes occurring in negative symptoms (45,46). Although the patients should be adequately stabilized before entering the trial, changes in positive, extrapyramidal and depressive symptoms were actually minimal. Therefore, it is safe to attribute

improvement in negative symptoms to a reduction in primary negative symptoms.

Recently, several studies explored raloxifene add-on effect on schizophrenic symptoms mostly in women. Usall *et al*., in a 12-week double-blind, randomized placebo-controlled trial in postmenopausal women, unveiled the addition of 60mg/day raloxifene to regular antipsychotic treatment to be useful in improving negative, positive and general psychopathologic symptoms. Moreover, Kulkarni *et al*., in a combined 12-week double-blind randomized control trial indicated the potential therapeutic dose of raloxifene HCl in postmenopausal women where use of 120 mg/day oral raloxifene HCl led to significantly greater recovery in total and general PANSS psychopathology compared with both 60 mg/ day raloxifene HCl and placebo (39). Kianimehr *et al*., showed in an 8-week, parallel-group, placebo-controlled trial in postmenopausal women that 120 mg/day raloxifene as an adjunctive treatment to risperidone was only superior in improvement of positive symptoms in comparison to placebo group and it was not effective in treating negative and general psychopathology symptoms (41).

Raveendranathan *et al*., also tried adjuvant raloxifene on a 29-year-old menstruating woman with drug-resistant schizophrenia who experienced significant improvement in socio-occupational function, with a reduction in symptom severity, over 7 months (40). The potential therapeutic efficacy of estrogens on schizophrenic symptoms has been already recognized (30-34). Raloxifene also has shown the same neuroprotective effects like estrogen on the central nervous system (47).

In addition, as an estrogen receptor agonist in the brain, raloxifene has the same results on neurotransmitter and neuronal systems including serotonergic and dopaminergic systems in frontal cortex, striatum and basal ganglia, which have been identified to be affected in schizophrenia (22,23,48,49). Elena Huerta-Ramos *et al*., in a 12-week, double-blind, randomized, placebo-controlled study of postmenopausal women indicated that 60mg/day adjuvant raloxifene effect on patient neuropsychological function results denoted significant differences in some aspects of memory, attention and executive functioning (50). Kulkarni *et al*., reported three cases and in each case the woman selected had participated in large, double-blind, randomized controlled trials exploring hormone modulation. There was beneficial effect achieved on cognition, verbal memory and psychomotor speed in one case who had received 120mg/day adjuvant therapy over 12weeks (51). Yaffe *et al*., in a randomized, placebo-controlled trial among postmenopausal women with osteoporosis indicated that raloxifene at a dose of 120 mg/day, but not 60 mg/day, results in reduced risk of cognitive impairment in postmenopausal women (52).

Estrogen Supplementation in men is relatively uncommon, but estrogen augmentation may prove effective and have comparable protective benefits for men as it does for women with schizophrenia (44). Sherwin *et al*., by a 12-week randomized, placebo-controlled, cross-over study in men with mild cognitive impairment (MCI), indicated that treatment with estrogen may improve verbal memory in men with MCI. Kulkarni *et al*., conducted a14-day placebo-controlled trial in 53 men with schizophrenia evaluating the efficacy of 2 mg oral estradiol valerate as an adjunct to atypical antipsychotic treatment, which triggered more rapid reduction in general psychopathology (36).

In the current study, no adverse effect was detected in the raloxifene group compared to the placebo group, but long term estrogen use may have potential risks such as gynecomastia, feminization and infertility (53) in male patients along with venous thromboembolism and lethal stroke in either sex (54).

Conclusively, it is desired that raloxifene, as a selective estrogen receptor modulator (SERM, as tissue-specific estrogen receptor agonists or antagonists, be able to provide men with the benefits of estrogen in the brain without potential peripheral adverse effects. The results of this study should be interpreted with consideration of its limitations. Small sample size and short observation period are the major limitations of this study. These results may be confirmed in more prolonged trials with larger sample sizes to ensure study power. Also, it should be mentioned that PANSS is limited to assessing behavioral problems; therefore, patient cognitive function improvement is not measurable. In conclusion, this double-blind, placebo-controlled clinical trial revealed raloxifene as a tolerable adjunct to risperidone with improvement in primary negative symptoms of schizophrenia in male patients. Additional studies with long-term follow-up periods seem to be essential to reinforce the clinical use of adjuvant raloxifene in male schizophrenic patients.

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References

1. Davidson M, Caspi A, Noy S. The treatment of schizophrenia: from premorbid manifestations to the first episode of psychosis. Dialogues Clin Neurosci 2005;7(1):7-16.
2. Rössler W, Salize HJ, van Os J, et al. Size of burden of schizophrenia and psychotic disorders. Eur Neuropsychopharmacol 2005;15(4):399-409.
3. Jablensky A. Epidemiology of schizophrenia: the global burden of disease and disability. Eur Arch Psychiatry Clin Neurosci 2000;250(6):274-85.
4. Charrier N, Chevreul K, Durand-Zaleski I. The cost of schizophrenia: a literature review. Encephale 2013;39(Suppl 1):S49-56.
5. Carr VJ, Neil AL, Halpin SA, et al. Costs of schizophrenia and other psychoses in urban Australia: findings from the Low Prevalence (Psychotic) Disorders Study. Aust N Z J Psychiatry 2003;37(1):31-40.
6. Jackson D, Kirkbride J, Croudace T, et al. Meta-analytic approaches to determine gender differences in the age-incidence characteristics of schizophrenia and related psychoses. Int J Methods Psychiatr Res 2013;22(1):36-45.
7. McGrath J, Saha S, Welham J, et al. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med 2004;2(1):13.
8. Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. Acta Psychiatr Scand 2000;401(Suppl):3-38.
9. Usall J, Busquets E, Araya S, et al. Gender differences in schizophrenia. A literature review. Actas españolas Psiquiatr 2000;28(3):178-85.
10. Sánchez R, Téllez G JL. Age of onset symptoms and gender in schizophrenia spectrum disorders. Biomedica 2012; 2(2):206-13.
11. Häfner H. Gender differences in schizophrenia. Psychoneuroendocrinology 2003;28(Suppl 2):17-54.
12. Kulkarni J, Gavrilidis E, Worsley R, et al. Role of estrogen treatment in the management of schizophrenia. CNS Drugs 2012;26(7):549-57.
13. Smith S. Gender differences in antipsychotic prescribing. Int Rev Psychiatry 2010;22(5):472-84.
14. Usall J, Suarez D, Haro JM. Gender differences in response to antipsychotic treatment in outpatients with schizophrenia. Psychiatry Res 2007;153(3):225-31.
15. Goldstein JM, Link BG. Gender and the expression of schizophrenia. J Psychiatr Res 1988;22(2):141-55.
16. Zeinoddini A, Ahadi M, Farokhnia M, et al. L-lysine as an adjunct to risperidone in patients with chronic schizophrenia: a double-blind, placebo-controlled, randomized trial. J Psychiatr Res 2014;59:125-31.
17. Hosseini SM, Farokhnia M, Rezaei F, et al. Intranasal desmopressin as an adjunct to risperidone for negative symptoms of schizophrenia: a randomized, double-blind, placebo-controlled, clinical trial. Eur Neuropsychopharmacol 2014;24(6):846-55.
18. Kulkarni J, Riedel A, de Castella AR, et al. Estrogen - a potential treatment for schizophrenia. Schizophr Res 2001;48(1):137-44.
19. Hayes E, Gavrilidis E, Kulkarni J. The role of oestrogen and other hormones in the pathophysiology and treatment of schizophrenia. Schizophr Res Treatment 2012;2012:540273.
20. Kulkarni J. Oestrogen--a new treatment approach for schizophrenia? Med J Aust 2009;190(4 Suppl):S37-8.
21. Akhondzadeh S, Mokhberi K, Amini H, et al. Is there a relationship between estrogen serum level and symptom severity throughout the menstrual cycle of patients with schizophrenia? Therapy 2005;2:745-51.
22. Chavez C1, Hollaus M, Scarr E, et al. The effect of estrogen on dopamine and serotonin receptor and transporter levels in the brain: an autoradiography study. Brain Res 2010;1321:51-9.
23. Landry M, Paolo D. E ffect of chronic estradiol, tamoxifen or raloxifene treatment on serotonin 5-HT 1A receptor. Brain Res Mol Brain Res 2003;112(1-2):82-9.
24. Huber TJ, Rollnik J, Wilhelms J, et al. Estradiol levels in psychotic disorders. Psychoneuroendocrinology 2001;26(1):27-35.
25. Kulkarni J, de Castella A, Smith D, et al. A clinical trial of the effects of estrogen in acutely psychotic women. Schizophr Res 1996;20(3):247-52.
26. Riecher-Rössler A, Häfner H, Dütsch-Strobel A, et al. Further evidence for a specific role of estradiol in schizophrenia? Biol Psychiatry 1994;36(7):492-4.
27. Kulkarni J. Women and schizophrenia: a review. Aust N Z J Psychiatry 1997;31(1):46-56.
28. Riecher-Rössler A, Häfner H. Schizophrenia and oestrogens--is there an association? Eur Arch Psychiatry Clin Neurosci 1993;242(6):323-8.
29. Seeman M V, Lang M. The role of estrogens in schizophrenia gender differences. Schizophr Bull 1990;16(2):185-94.
30. Akhondzadeh S, Nejatisafa AA, Amini H, et al. Adjunctive estrogen treatment in women with chronic schizophrenia: a double-blind, randomized, and placebo-controlled trial. Prog Neuropsychopharmacol Biol Psychiatry 2003;27(6):1007-12.

31. Kulkarni J, de Castella A, Fitzgerald PB, et al. Estrogen in severe mental illness: a potential new treatment approach. Arch Gen Psychiatry 2008;65(8):955-60.
32. Ghafari E, Fararouie M, Shirazi H. Combination of estrogen and antipsychotics in the treatment of women with chronic schizophrenia. Clin Schizophr Relat Psychoses 2013;6(4):172-6.
33. Grigoriadis S, Seeman M. The role of estrogen in schizophrenia: implications for schizophrenia practice guidelines for women. Can J Psychiatry 2002;47(5):437-42.
34. Kulkarni J, Gavrilidis E, Wang W, et al. Estradiol for treatment-resistant schizophrenia: a large-scale randomized-controlled trial in women of child-bearing age. Mol Psychiatry 2014. [Epub ahead of print]
35. Sayed Y, Taxel P. The use of estrogen therapy in men. Curr Opin Pharmacol 2003;3(6):650-4.
36. Kulkarni J, de Castella A, Headey B, Marston Net al. Estrogens and men with schizophrenia: is there a case for adjunctive therapy? Schizophr Res 2011;125(2-3):278-83.
37. Chua WL, de Izquierdo SA, Kulkarni J, et al. Estrogen for schizophrenia. Cochrane database Syst Rev 2005;(4):CD004719.
38. Prentice RL. Postmenopausal hormone therapy and the risks of coronary heart disease, breast cancer, and stroke. Semin Reprod Med 2014;32(6):419-25.
39. Kulkarni J, Gurvich C, Lee SJ, et al. Piloting the effective therapeutic dose of adjunctive selective estrogen receptor modulator treatment in postmenopausal women with schizophrenia. Psychoneuroendocrinology 2010;35(8):1142-7.
40. Raveendranathan D, Shivakumar V, Jayaram N, et al. Beneficial effects of add-on raloxifene in schizophrenia. Arch Womens Ment Health 2012;15(2):147-8.
41. Kianimehr G, Fatehi F, Hashempoor S, et al. Raloxifene adjunctive therapy for postmenopausal women suffering from chronic schizophrenia: a randomized double-blind and placebo controlled trial. Daru 2014;22(1):55.
42. Huerta-Ramos E, Iniesta R, Ochoa S, et al. Effects of raloxifene on cognition in postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. Eur Neuropsychopharmacol 2014;24(2):223-31.
43. Usall J, Huerta-Ramos E, Iniesta R, et al. Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry 2011;72(11):1552-7.
44. Kulkarni J, Gavrilidis E, Worsley R, et al. The Role of Estrogen in the Treatment of Men with Schizophrenia. Int J Endocrinol Metab 2013;11(3):129-36.
45. Kirkpatrick B, Fenton WS, Carpenter WT Jr, et al. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull 2006;32(2):214-9.
46. Murphy BP, Chung Y-C, Park TW, et al. Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review. Schizophr Res 2006;88(1-3):5-25.
47. Littleton-Kearney MT, Ostrowski NL, Cox DA, et al. Selective estrogen receptor modulators: tissue actions and potential for CNS protection. CNS Drug Rev 2002;8(3):309-30.
48. Huang Y, Huang YL, Lai B, et al. Raloxifene acutely reduces glutamate-induced intracellular calcium increase in cultured rat cortical neurons via inhibition of high-voltage-activated calcium current. Neuroscience 2007;147(2):334-41.
49. Iritani S. Neuropathology of schizophrenia: a mini review. Neuropathology 2007;27(6):604-8.
50. Usall J, Huerta-Ramos E, Iniesta R. Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry 2011;72(11):1552-7.
51. Kulkarni J, Gurvich C, Gilbert H, et al. Hormone modulation: a novel therapeutic approach for women with severe mental illness. Aust N Z J Psychiatry 2008;42(1):83-8.
52. Yaffe K, Krueger K, Cummings SR, Blackwell T, et al. Effect of raloxifene on prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. Am J Psychiatry 2005;162(4):683-90.
53. Hayes FJ, Seminara SB, Decruz S, et al. Aromatase inhibition in the human male reveals a hypothalamic site of estrogen feedback. J Clin Endocrinol Metab 2000;85(9):3027-35.
54. Henderson VW, Lobo RA. Hormone therapy and the risk of stroke: perspectives 10 years after the Women's Health Initiative trials. Climacteric 2012;15(3):229-34.