Raloxifene Plus Antipsychotics Versus Placebo Plus Antipsychotics in Severely Ill Decompensated Postmenopausal Women With Schizophrenia or Schizoaffective Disorder: A Randomized Controlled Trial

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ABSTRACT

Objective: Several single-center studies have found raloxifene, an estrogen agonist, to be effective in ameliorating symptoms of schizophrenia in stable patients as augmentation of antipsychotics. This multicenter study assessed whether raloxifene plus antipsychotic treatment, in comparison to placebo plus antipsychotics, improves symptoms or cognition in severely ill decompensated schizophrenia patients.

Methods: In this 16-week, double-blind, randomized, placebo-controlled study, 200 severely ill, decompensated postmenopausal women who met *DSM-IV-TR* criteria for schizophrenia or schizoaffective disorder were recruited from January 2011 to December 2012 and were randomized to receive either raloxifene 120 mg/d plus antipsychotics or placebo plus antipsychotics. The primary outcome measure was Positive and Negative Syndrome Scale (PANSS) total score at the end of the trial.

Results: The placebo plus antipsychotics group experienced statistically significant improvement in PANSS total score ($P < .001$) compared to the raloxifene plus antipsychotics group, using mixed models for repeated measures, with results favoring placebo by 4.5 points (95% CI, 2.3–6.7). These results were clearly outside the 95% confidence interval. This negative effect was more pronounced in patients who had more frequent relapses and in those with baseline PANSS scores of 100 or higher. There were no differences between groups in Clinical Global Impression Scale-Severity scores or Composite Brief Assessment of Cognition in Schizophrenia scores at 16 weeks ($P > .3$). Baseline follicle-stimulating hormone and estradiol levels did not alter the drug-placebo differences.

Conclusions: Individuals in the active treatment arm showed worse outcome than those in the placebo arm, most likely as a result of chance variation, but the results unequivocally show no benefit of antipsychotics plus raloxifene versus antipsychotics plus placebo in this large randomized, double-blind, placebo-controlled trial in postmenopausal women. These data do not support the use of raloxifene in severely decompensated schizophrenia patients until reliable research identifies what subgroup of patients or domain of outcome is benefited.

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The estrogen protection hypothesis of schizophrenia was introduced in the late 1980s to explain the gender-related differences that have been documented regarding the epidemiology and some clinical features of schizophrenia.[1] A consistent observation of 43 independent epidemiologic studies was that the onset of schizophrenia is 2–4 years later in women than in men, with women having a lower incidence of schizophrenia until menopause, when women have an increased incidence, so that the lifetime prevalence is basically the same in both genders.[2,3] Furthermore, women are more likely to have their first schizophrenia episode during an estrogen trough in the menstrual cycle.[4] Furthermore, some,[5–8] but not others,[9–12] indicate that women require lower doses of neuroleptics compared to men to prevent relapse. While most studies found that female patients function better than male patients,[4,13–18] a few failed to demonstrate differences,[19–21] and 1 study on premorbid cognitive functioning reported that females actually functioned worse than males before the onset of psychosis.[22] These gender differences in the natural course of schizophrenia are well replicated and provide a major lead to understanding and treating the illness.

Investigators have hypothesized that the mechanism by which estrogen protects against psychotic illness is related to its ability to interfere with dopamine neurotransmission[23] and its influence on serotonin activity.[24] A second possible mechanism comes from investigations showing that estrogen receptors are altered in postmortem schizophrenic brains.[25,26] In ovariectomized rats, estrogen receptor modulations (including raloxifene) increased the number of dendritic spines and increased working memory.[27] There is evidence that individuals with schizophrenia have reduced numbers of dendritic spine.[28] Since spines occupy space, this may partially be responsible for the

Clinical Points

- Previous small-sample studies in stabilized patients showed improvement in symptoms with administration of add-on raloxifene to antipsychotics in patients with schizophrenia. This large (N = 200) study administered add-on raloxifene to patients with severe symptoms and found that patients receiving raloxifene actually did worse than those receiving placebo.
- While the worsening is probably due to chance, clinicians should carefully consider the possibility of worsening when considering administration of add-on raloxifene.

decrease in gray matter and increased ventricle size observed in schizophrenia, deficits correlated with poor prognosis, negative symptoms, and cognitive impairments. Support for this assumption is found by the observation that estrogen exposure in young adult females with schizophrenia, as measured by bone mineral density, was positively correlated with cortical thickness measured by magnetic resonance imaging.[29] Hence, one can postulate that estrogenic agents could improve positive and/or negative symptoms, cognitive impairment, or combinations of these. Estrogen also plays a role in men,[30] and it is possible that estrogenic drugs could benefit male schizophrenia patients as well.

There is some evidence that estrogen treatment benefits schizophrenia. The efficacy of estrogen is supported by 1, but not all, meta-analyses.[31,32]

Raloxifene is an estrogen-receptor modulator that has been shown to possess an agonist action in the brain.[33] Three recent randomized, placebo-controlled, relatively small studies (n = 33,[34] n = 26,[35] and n = 56[36]) have demonstrated a beneficial role for raloxifene as an add-on treatment to antipsychotics in postmenopausal women with schizophrenia. Huerta-Ramos et al[37] demonstrated that raloxifene produced improvement in several cognitive tasks in postmenopausal women. Weickert et al,[38] in a 13-week randomized crossover trial (6 weeks of drug/placebo, 1-week washout, 6 weeks of placebo/drug) on men and women demonstrated that raloxifene produced substantial improvement in attention, processing speed, and memory in the first phase, with carryover beneficial effects in the second (placebo) arm of the crossover. On the basis of improvement of Positive and Negative Syndrome Scale (PANSS) score in the initial 2 studies[34,35] and in the recently published trial by Kulkarni et al,[36] our aim was to assess the utility of raloxifene 120 mg/d plus antipsychotics versus antipsychotics plus placebo in postmenopausal women with severely decompensating schizophrenia in a large scale, 16-week, multicentered, double-blind, randomized, placebo-controlled study. There is a large literature showing that drug versus placebo changes are higher in patients who are more severely ill at baseline.[39]

METHODS

Study Population

The ClinicalTrials.gov identifier for this study is NCT01280305. Two hundred women, either inpatients (≥ 3 days after admission, n = 13) or outpatients (n = 187), were recruited from 38 sites in Romania and the Republic of Moldova between January 2011 and December 2012. Inclusion criteria required that women (1) meet *DSM-IV-TR* criteria for schizophrenia or schizoaffective disorder, with at least 2 prior schizophrenic episodes, or be continually ill for at least 6 months; (2) be 45–65 years old and be postmenopausal, defined as the lack of vaginal bleeding for at least 2 years prior to randomization, with both serum estradiol < 73 pmol/L (20 pg/mL) and follicle-stimulating hormone (FSH) > 30 IU/L (30 mIU/mL); (3) have been receiving an antipsychotic drug for at least 2 weeks prior to the baseline visit at doses within the Schizophrenia Patient Outcomes Research Team criteria[40]; (4) have symptoms with moderate or above severity, as measured by a 4 or above score on Clinical Global Impression Scale-Severity (CGI-S) and a score of 4 or above on 2 of the following 4 PANSS items: delusions, hallucinatory behaviors, conceptual disorganization, or suspiciousness/persecution and/or a PANSS negative score of 18 or above; and (5) be willing and able to provide informed consent. The study received approval from the institutional review boards of the Ministries of Health of Romania and the Republic of Moldova.

Study participants were randomized to receive either 120 mg/d (60 mg bid) raloxifene hydrochloride tablets or placebo tablets for a period of 16 weeks. Both groups continued to receive antipsychotics.

Symptoms were assessed at baseline and at predetermined intervals using PANSS,[41] CGI-S,[42] and the Brief Assessment of Cognition in Schizophrenia (BACS). The primary outcome measure was PANSS total score at the end of the trial. We present BACS scores normalized relative to a healthy population.[43] BACS version 3.0, which has been validated in a Romanian population by Neurocog, was used in this study. BACS raters were trained by Paull Radu, MD, who was qualified by Neurocog to train raters. Raters were trained and repeatedly tested until they received qualification. PANSS raters also were trained and tested and received qualification by Prophase.

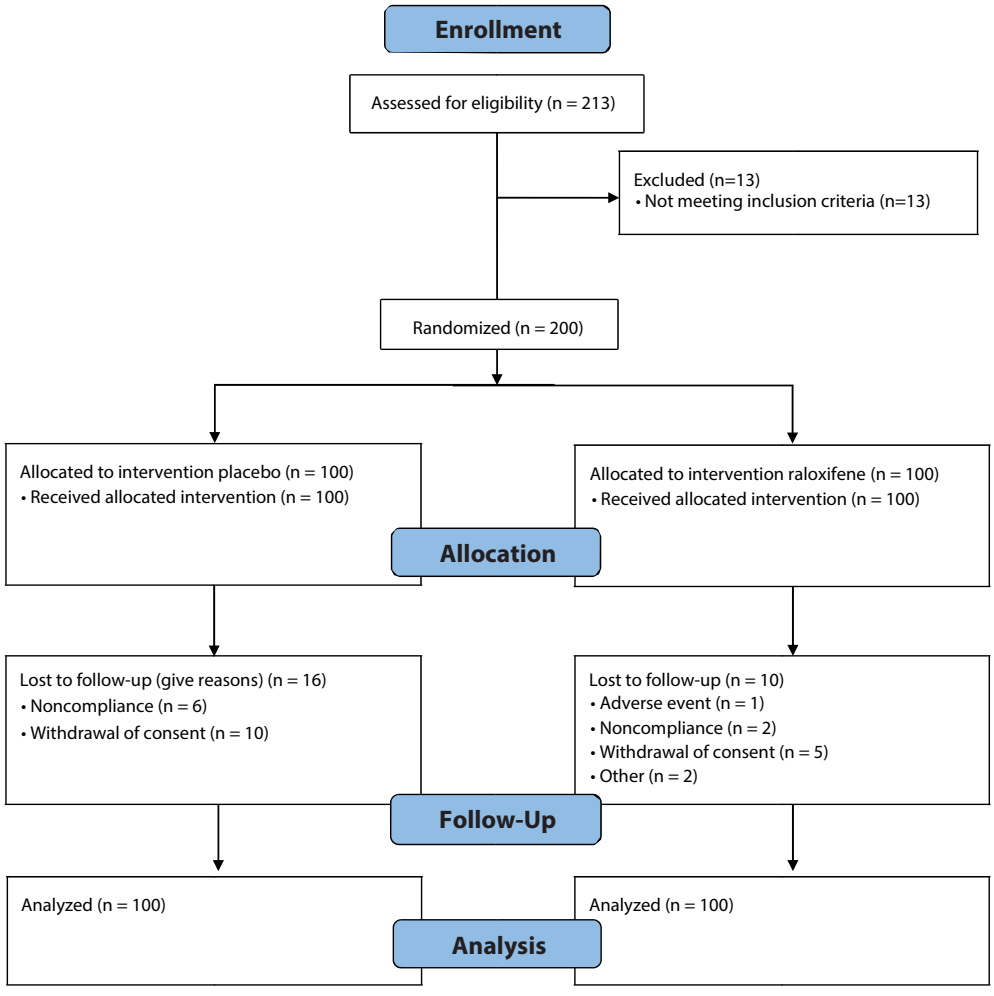
Structured assessments of side effects were performed using the Simpson-Angus Scale[44] and the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating scale.[45]

Demographic characteristics were assessed at baseline based on patients' reports. Plasma FSH and estradiol were assessed based on bloodwork performed during the study.

Statistical Analysis

Data analyses were conducted using STATA version 14 (StataCorp LP, College Station, Texas). The statistical analysis code is available upon request. To determine the effect of the raloxifene group (vs placebo group) on the PANSS, CGI, and BACS outcomes, we used mixed models for repeated measures in which the treatment effect was allowed to differ freely at each postrandomization visit. Models used all available data and included adjustment for clustering by study center. In addition, as a sensitivity analysis, we estimated the effect of the raloxifene plus antipsychotics versus antipsychotics plus placebo group on each outcome at 16 weeks postrandomization

Figure 1. CONSORT Flow Diagram



using analysis of covariance (ANCOVA) with the respective baseline outcome as covariate. This was done in 3 different ways: using an unmodified intention-to-treat approach (last observation carried forward), a modified intention-to-treat analysis using all subjects who had at least 1 follow-up value, and a completers-only approach using data from all subjects with observed data at 16 weeks.

We also used mixed models to conduct exploratory subgroup analyses examining whether baseline PANSS score, plasma estradiol, plasma FSH, demographic factors, and medications used during the study modified the effect of the raloxifene group versus placebo group. Subgroup categories were defined as close to the median value as possible. Likelihood ratio (LR) tests were used to assess the addition of 3-way interactions of time × intervention × modifier. A low LR test *P* value can be interpreted as evidence of a difference between the subgroups.

RESULTS

Demographics

A total of 26 women did not complete the study, and rates of early termination in the placebo group (n = 16) and raloxifene group (n = 10) did not differ significantly between groups ($P = .193$) (Figure 1). Demographic and clinical characteristics of the 200 participants are presented in Table 1, showing no detectable differences between the 2 groups.

Efficacy

All patients had a substantial decrease in PANSS total scores of about 18 points, an expected finding since they were treated for an acute exacerbation of their illness with antipsychotics. We tested the hypothesis that raloxifene augmentation would produce more improvement than placebo. It did not produce more improvement, and, in fact, our findings were in the opposite direction. At 16 weeks postrandomization, the raloxifene group experienced statistically significantly lesser improvement in PANSS total score (difference = 4.46; 95% CI, 2.3 to 6.7) and PANSS subscales for negative symptoms (1.65; 95% CI, 1.01 to 2.29), general psychopathology (2.01; 95% CI, 0.84 to 3.17), and positive symptoms (0.77; 95% CI, 0.12 to 1.42) compared to the placebo group (Figure 2). There was no difference between groups in the CGI and the composite BACS score ($P \geq .1$) (Figure 2). The results for the ANCOVA comparing raloxifene plus antipsychotics versus antipsychotics plus

Table 1. Baseline Demographic and Clinical Characteristics for Women in the Raloxifene and Placebo Groups (N = 200)[a]

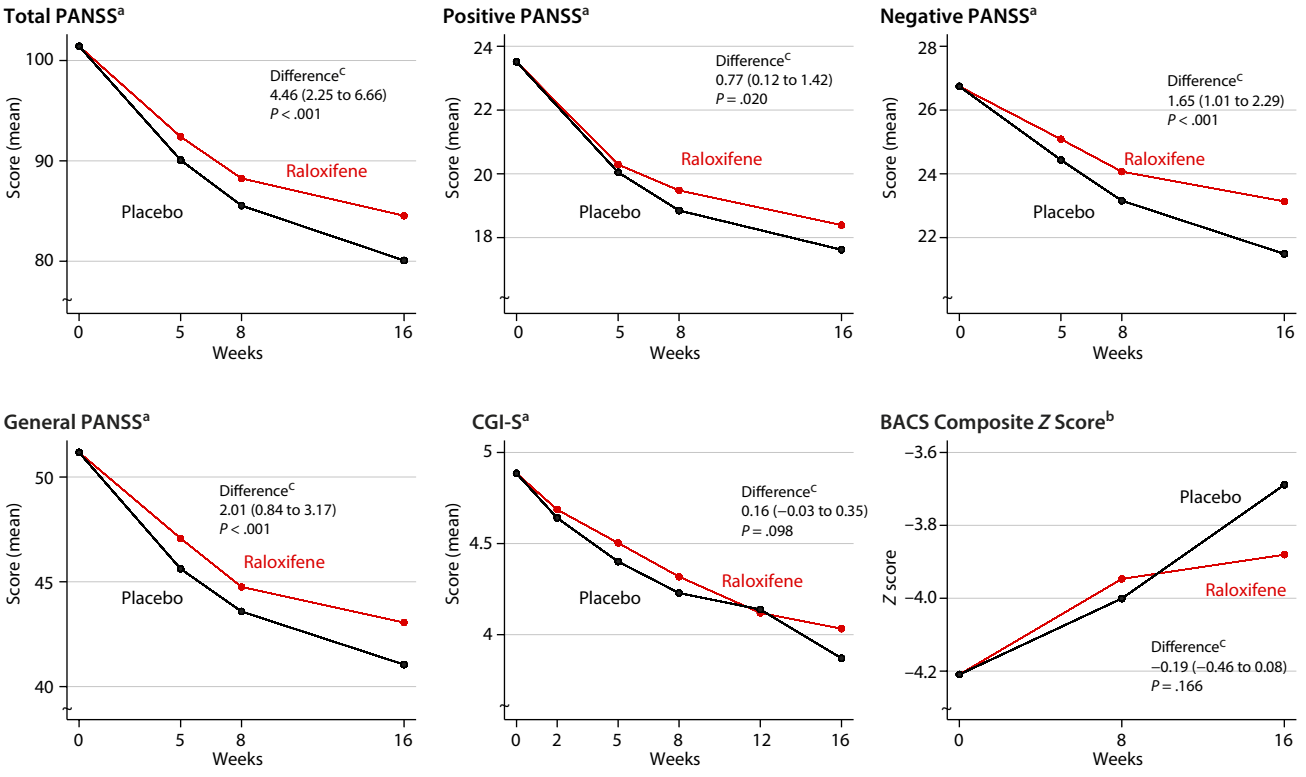
Characteristic	Placebo (n = 100)	Raloxifene (n = 100)	*P* Value
Age, mean (SD), y	55.8 (4.7)	56.6 (4.6)	.211[c]
Marital status, n (%)			.278[b]
Never married (single)	23 (23)	27 (27)	
Presently married	27 (27)	26 (26)	
Divorced/separated	32 (32)	38 (38)	
Widowed	18 (18)	9 (9)	
Formal education, n (%)			.401[b]
1–8 y	30 (30)	22 (22)	
8–16 y	65 (65)	71 (71)	
> 16 y	5 (5)	7 (7)	
Inpatient, n (%)	7 (7)	6 (6)	.185[b]
Psychiatric diagnosis, %			
Schizophrenia	84	91	.134[b]
Schizoaffective disorder	19	12	.171[b]
No. of hospitalizations, mean (SD)	18.0 (17.2)	20.7 (22.8)	.356[c]
Age at onset of psychiatric illness, mean (SD), y	32.0 (9.5)	31.1 (8.6)	.472[c]
Baseline PANSS score, mean (SD)			
Total	101.2 (18.1)	101.7 (18.5)	.835[c]
Positive symptoms	23.4 (3.9)	23.6 (4.3)	.704[c]
Negative symptoms	26.5 (6.3)	27.0 (5.9)	.626[c]
General symptoms	51.2 (10.8)	51.1 (11.4)	.949[c]

[a]Percentage is based on group total (n = 100).
[b]*P* values are derived from 2-tailed χ^2 test.
[c]*P* values are derived from 2-tailed 2-sample *t* test.

placebo at 16 weeks using intention-to-treat and completers-only approaches are in Table 2 and also indicated that raloxifene produced somewhat less improvement than placebo on the PANSS, showing results that are roughly directionally consistent with the results of the mixed models (Table 2).

In an exploratory manner, we searched for insight as to why raloxifene plus antipsychotics should be less effective than antipsychotics plus placebo by examining differences in the effect of raloxifene among different population subgroups. Figure 3 illustrates the difference in PANSS total score between antipsychotics plus raloxifene versus antipsychotics plus placebo at 16 weeks according to strata of demographic and clinical characteristics. We found no evidence that the effect of raloxifene versus placebo on total PANSS scores differed according to participants' age, marital status, education, type of occupation, plasma FSH, or plasma estradiol. However, we found that raloxifene did worse (ie, less improvement than placebo) among subjects who had higher rates of hospitalizations per year and among those who had higher baseline PANSS total score (LR test *P* values ≤ .001). Specifically, among subjects with a high rate of hospitalizations (> 0.63 per year), raloxifene plus antipsychotics did worse than antipsychotics plus placebo by about 10 PANSS total points

Figure 2. Effect of Raloxifene Versus Placebo on PANSS, CGI-S, and BACS (N = 200)



[a]Lower score equals improvement.
[b]Higher score equals improvement.
[c]Estimated effect of raloxifene versus placebo at week 16 (95% confidence interval in parentheses) derived from a mixed model for repeated measures.
Abbreviations: BACS = Brief Assessment of Cognition in Schizophrenia, CGI-S = Clinical Global Impression Scale-Severity, PANSS = Positive and Negative Syndrome Scale.

Table 2. Baseline and Week 16 Assessments of Psychiatric and Cognitive Symptoms

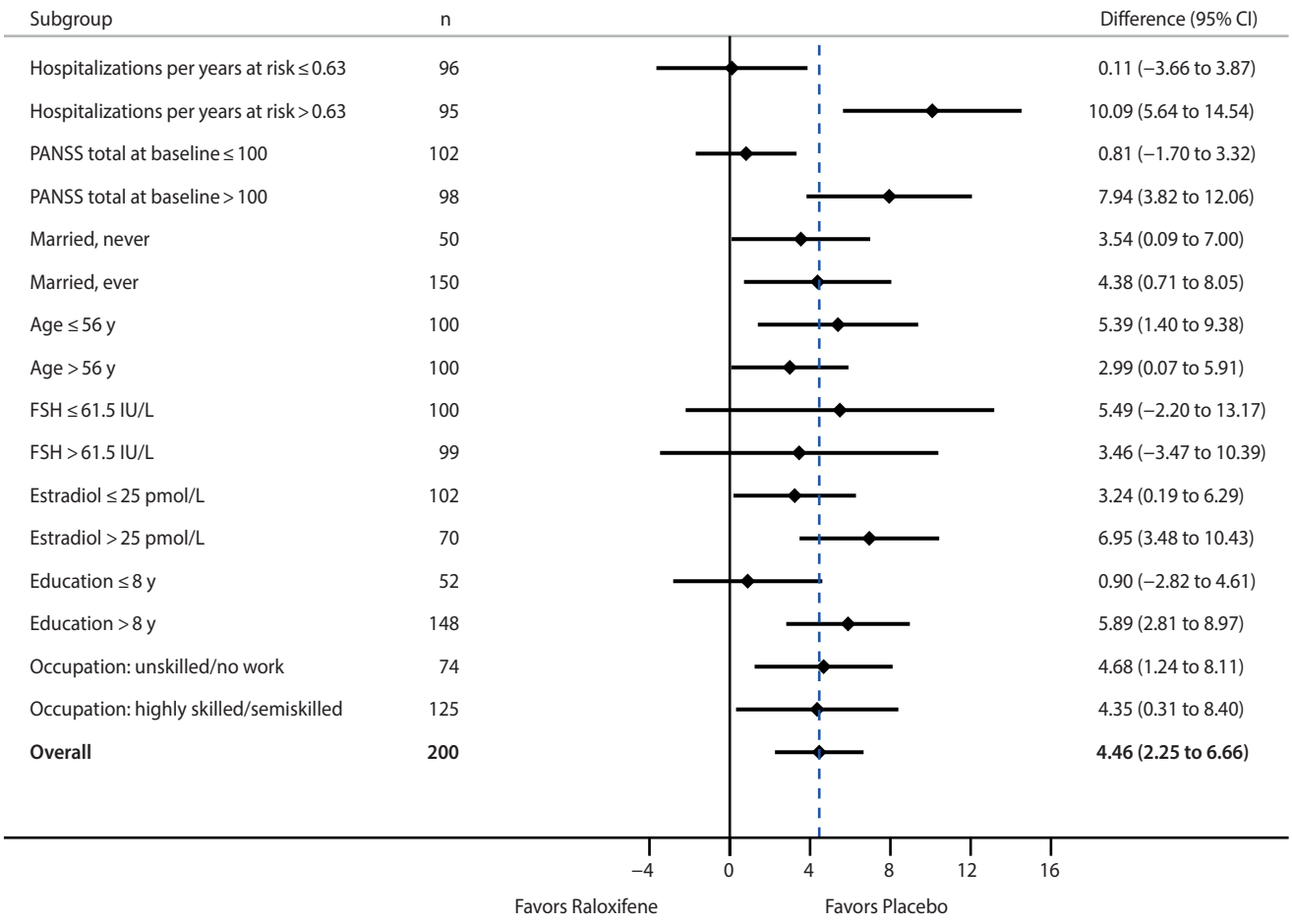
	Baseline				Week 16					
	Placebo		Raloxifene		Placebo		Raloxifene		Raloxifene – Placebo[a]	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Difference[b]	*P*
Observed cases analysis (all available data at 16 wk)	n = 100		n = 100		n = 79		n = 86			
PANSS total	101.2	(18.1)	101.7	(18.5)	81.3	(17.5)	86.1	(19.0)	3.75	.094
Positive symptoms	23.4	(3.9)	23.6	(4.3)	18.0	(4.6)	18.7	(4.9)	0.53	.430
Negative symptoms	26.5	(6.3)	27.0	(5.9)	21.7	(5.1)	23.7	(6.0)	1.58	.011
General symptoms	51.2	(10.8)	51.1	(11.4)	41.6	(9.7)	43.7	(10.3)	1.69	.154
CGI-S	4.9	(0.8)	4.9	(0.8)	3.9	(0.9)	4.1	(1.0)	0.14	.301
BACS (*z* scores)										
Total verbal memory	−2.3	(1.3)	−2.4	(1.3)	−2.2	(1.3)	−2.3	(1.3)	−0.13	.399
Digit sequencing	−2.2	(1.6)	−2.4	(1.6)	−2.2	(1.5)	−2.5	(1.7)	−0.22	.183
Token motor task	−1.8	(1.3)	−2.0	(1.5)	−1.5	(1.4)	−1.8	(1.6)	−0.08	.633
Total fluency	−2.3	(1.0)	−2.4	(1.0)	−2.2	(1.0)	−2.3	(1.0)	−0.08	.397
Symbol coding	−3.9	(1.4)	−4.1	(1.5)	−3.6	(1.7)	−3.8	(1.7)	−0.13	.496
Tower of London	−2.1	(1.8)	−2.4	(1.8)	−2.1	(1.7)	−2.4	(1.7)	−0.05	.729
BACS composite	−4.1	(1.7)	−4.4	(2.0)	−3.9	(1.8)	−4.2	(2.1)	−0.17	.332
Intention-to-treat (last value carried forward)	n = 100		n = 100		n = 100		n = 100			
PANSS total	101.2	(18.1)	101.7	(18.5)	81.8	(16.6)	85.5	(18.3)	3.36	.091
Positive symptoms	23.4	(3.9)	23.6	(4.3)	18.1	(4.4)	18.7	(4.7)	0.52	.377
Negative symptoms	26.5	(6.3)	27.0	(5.9)	21.8	(4.8)	23.4	(5.8)	1.35	.012
General symptoms	51.2	(10.8)	51.1	(11.4)	41.9	(9.4)	43.3	(10.2)	1.50	.159
CGI-S	4.9	(0.8)	4.9	(0.8)	3.9	(0.9)	4.1	(1.0)	0.13	.257
BACS (*z* scores)										
Total verbal memory	−2.3	(1.3)	−2.4	(1.3)	−2.1	(1.3)	−2.3	(1.3)	−0.10	.435
Digit sequencing	−2.2	(1.6)	−2.4	(1.6)	−2.0	(1.5)	−2.4	(1.8)	−0.21	.142
Token motor task	−1.8	(1.3)	−2.0	(1.5)	−1.4	(1.3)	−1.8	(1.6)	−0.15	.332
Total fluency	−2.3	(1.0)	−2.4	(1.0)	−2.1	(1.0)	−2.3	(1.0)	−0.11	.215
Symbol coding	−3.9	(1.4)	−4.1	(1.5)	−3.6	(1.6)	−3.8	(1.7)	−0.10	.545
Tower of London	−2.1	(1.8)	−2.4	(1.8)	−1.9	(1.8)	−2.2	(1.9)	−0.04	.758
BACS composite	−4.1	(1.7)	−4.4	(2.0)	−3.6	(1.8)	−4.1	(2.2)	−0.16	.273
Modified[c] intention-to-treat (last value carried forward)										
	n = 94		n = 95		n = 94		n = 95			
PANSS total	102.1	(18.1)	103.0	(18.0)	81.5	(16.9)	86.0	(18.5)	3.95	.056
Positive symptoms	23.6	(3.8)	23.9	(4.3)	18.0	(4.4)	18.7	(4.8)	0.63	.301
Negative symptoms	26.8	(6.3)	27.3	(5.8)	21.8	(4.9)	23.6	(5.8)	1.50	.008
General symptoms	51.7	(10.8)	51.9	(11.2)	41.8	(9.5)	43.7	(10.2)	1.83	.098
	n = 97		n = 99		n = 97		n = 99			
CGI-S	4.9	(0.8)	4.9	(0.8)	3.9	(0.9)	4.1	(1.0)	0.13	.275
BACS (*z* scores)	n = 85		n = 92		n = 85		n = 92			
Total verbal memory	−2.5	(1.3)	−2.5	(1.2)	−2.3	(1.3)	−2.3	(1.3)	−0.08	.559
Digit sequencing	−2.5	(1.5)	−2.6	(1.6)	−2.2	(1.5)	−2.5	(1.7)	−0.21	.184
Token motor task	−1.9	(1.3)	−2.1	(1.5)	−1.5	(1.4)	−1.8	(1.6)	−0.15	.361
Total fluency	−2.4	(1.0)	−2.5	(0.9)	−2.2	(1.0)	−2.3	(1.0)	−0.11	.239
Symbol coding	−4.0	(1.5)	−4.2	(1.5)	−3.6	(1.7)	−3.8	(1.7)	−0.12	.521
Tower of London	−2.4	(1.6)	−2.6	(1.7)	−2.1	(1.7)	−2.3	(1.8)	−0.07	.636
BACS composite	−4.3	(1.7)	−4.5	(1.9)	−3.8	(1.8)	−4.2	(2.2)	−0.19	.264

[a]Raloxifene versus placebo difference at week 16, adjusted for the respective baseline scores (analysis of covariance).
[b]PANSS and CGI-S: higher scores = more symptoms/less improvement; BACS: lower scores = reduced performance.
[c]Analysis sample includes only those with at least 1 follow-up measure.
Abbreviations: BACS = Brief Assessment of Cognition in Schizophrenia, CGI-S = Clinical Global Impression Scale-Severity, PANSS=Positive and Negative Syndrome Scale.

(95% CI, 5.64 to 14.54), while among those with a lower rate of hospitalizations (≤ 0.63) per year, the raloxifene plus antipsychotics versus antipsychotics plus placebo difference was close to zero. Similarly, among subjects with baseline total PANSS score > 100, raloxifene plus antipsychotics did worse than antipsychotics plus placebo by about 8 PANSS total points (95% CI, 3.82 to 12.06), while among those with baseline total PANSS score ≤ 100, the raloxifene versus placebo difference was close to zero.

Forest plots for PANSS subscales, CGI-S, and BACS composite score are included in Supplementary eFigures 1–5. Most of the statistically significant interactions between the effect of raloxifene and rate of hospitalization and baseline PANSS were also observed in the PANSS subscales and CGI-S. For BACS, although there was no difference between raloxifene and placebo in the overall population, we also found an interaction between the effect of raloxifene and the number of hospitalizations per year at risk (LR test *P* value = .025). Raloxifene did significantly worse than placebo in the high hospitalizations group (−0.63, 95% CI, −0.87 to −0.39) but slightly better in the low hospitalizations group (not statistically significant: 0.21; 95% CI, −0.16 to 0.59).

Figure 3. Difference in PANSS Total Score Between Raloxifene and Placebo at Week 16 by Population Subgroups[a]



[a]Differences are calculated using mixed models for repeated measures. A positive difference in this score indicates that patients treated with placebo improved more than those treated with raloxifene. There was no evidence of benefit from raloxifene in any subgroup. Dashed line represents the overall effect.
Abbreviations: FSH = follicle-stimulating hormone, PANSS = Positive and Negative Syndrome Scale.

Adverse Effects

One serious event occurred in the placebo group (chronic obstructive pulmonary disease), and 1 occurred in the raloxifene group (pneumonia). The overall frequency of adverse events was 42.0% in the placebo group and 48.0% in the raloxifene group ($P = 0.3953$). Changes in baseline and week 16 Simpson-Angus Scale scores for the placebo group (mean = −2.94, SD = 4.44) and raloxifene group (mean difference = −2.03, SD = 4.10) were not statistically significant ($P = 0.1765$).

DISCUSSION

To our knowledge, this is the first large randomized, double-blind, placebo-controlled, parallel group trial testing whether the estrogen agonist raloxifene produced symptomatic improvement in severely ill decompensated schizophrenia patients. Results unequivocally show no benefits for raloxifene in either symptoms or cognition in these patients. Specifically, patients receiving raloxifene showed worse outcome than patients receiving placebo on some of the parameters analyzed. These findings suggest that raloxifene had a possible deleterious effect. While this finding might be due to chance, it is also possible that the addition of raloxifene impedes the effectiveness of antipsychotics. The mechanism by which this might happen is not clear. We checked and found no known drug-drug interaction between raloxifene and several different antipsychotics.

Given that raloxifene could be prescribed off-label to postmenopausal women with schizophrenia, the present findings suggest that this should be done with caution in individuals with history of multiple hospitalizations, who are severely decompensated and have high baseline symptoms, or deferred until patients become relatively remitted.

Our finding in severely ill decompensated schizophrenia patients differs from randomized double-blind placebo-controlled trials with well-stabilized schizophrenia patients.[34–36] One possible reason for this discrepancy might include the fact that the patients in those studies were less severely ill: mean total PANSS scores at baseline

ranged from 63 to 83, whereas the mean total PANSS score in this current study was 101 (range, 68–157), indicating that perhaps raloxifene may be efficacious for patients with less severe symptoms, such as stable outpatients, even though efficacy was not found for those tested here. Our observed decrease in PANSS scores of about 18 points produced by antipsychotic treatment is consistent with a meta-analysis of individual patient data and with what is seen with antipsychotics in several registration studies for patients with high baseline PANSS scores[39] (Table 2). It is clearly possible that the large response to antipsychotics in our patients, who were severely ill, decompensated schizophrenia patients, obscured a beneficial effect of add-on raloxifene over placebo, as observed by Kulkarni et al[35,36] and Usall et al,[34] who evaluated stable outpatients. It is possible that individual differences in response to antipsychotic drugs in the current study could have increased the standard deviation of the improvement in PANSS scores.

We interpreted our observation of improvement in the raloxifene group being less than that of the placebo group to a statistical error in decompensated schizophrenia patients. By chance alone, one would expect no benefit or worsening in a small proportion of studies, but most would be within the 95% confidence interval. We should not rule out the possibility that the difference is real. There are examples involving drugs for physical illnesses in which a treatment prevents a cancer but makes the cancer more lethal for those in whom the cancer exists.[46] We have to consider that raloxifene could produce a benefit in stable outpatients and cause worsening in acutely exacerbated patients, one or the other, or neither. We performed a median split analysis based on many variables including the rate of rehospitalization and the baseline total PANSS scores. The negative effect of raloxifene occurred in patients who had frequent readmissions and were in an acute highly symptomatic exacerbation. Since patients with a high rate of hospitalization also had high baseline PANSS scores and high baseline negative symptoms scores, it is difficult to disentangle these variables due to problems of collinearity. Our sample differed from that of Usall et al,[34] whose inclusion criteria required at least 1 negative symptom rated at 4 or higher, whereas, our study did not select for the presence of negative symptoms. The mean baseline negative symptoms scale score in our sample was relatively high at 26.5–27, so we were not limited by a floor effect.

Three recently published papers that tested the effect of raloxifene on cognition in schizophrenia reported on stable patients with much lower PANSS scores at baseline. Specifically, Huerta-Ramos et al[37] studied 33 participants and found that raloxifene was better than placebo in the learning curve in the Spanish Complutense Verbal Learning Test and the Phonetic Fluency Test (r, $P = .041$ and $P = .011$ respectively, uncorrected for multiple comparisons). The BACS administered in the current study also included items assessing these cognitive domains but did not reveal differences between raloxifene and placebo. In contrast, Weickert et al[38] found that add-on raloxifene improved attention/processing speed and memory. Their sample included both males and females with baseline total PANSS scores of 60,[38] who were therefore much less ill than the patients participating in this present study, which might account for this discrepancy. Since the previous studies focused on stabilized participants, the specific population that did worse (PANSS > 100) here might have been excluded or underrepresented in the prior studies, making comparisons difficult.

Since our patients were not effectively stabilized at baseline, as demonstrated by large improvement produced by the concomitant antipsychotics, their acute symptoms may have interfered with the cognitive assessment. The more stable patients with fewer hospitalizations per year did trend toward improvement on the composite BACS changes, a trend not inconsistent with the positive cognitive effect observed in previous studies.[37,38] Weickert et al have reviewed estrogen-based therapies for cognitive remediation and found support from both animal and human studies.[47,48]

Our sample was drawn from a poorly educated, predominantly rural, largely non–technologically advanced society—a population unfamiliar with mental tests of cognition. It is likely that some of our patients had extremely low scores for this reason. Usall and colleagues recently reported beneficial effects of raloxifene, which were correlated with a genetic variant in the *SSR1* gene.[49,50] We cannot rule out genetic differences between our population and that of Usall and colleagues.

At the time our study was designed, our rationale was to replicate the improvement in symptoms reported in 2 previous studies (1 study did not report cognitive measures, and the other found that raloxifene did not benefit cognition) in a large multisite RCT. Therefore, this current study was not designed to assess the effect of raloxifene on cognition, which was included as a secondary outcome measure. Future studies on raloxifene focusing on cognition should follow the guidelines developed by a US Food and Drug Administration/National Institute of Mental Health consensus conference[51] for study of cognition in schizophrenia.

While we attribute our finding of greater symptom improvement on placebo to chance variation, we cannot rule out that it might have a slightly negative effect in those patients with severe symptoms at baseline and/or a high frequency of relapses per year.

The estrogen protective hypothesis is based fundamentally on the difference in the natural course of schizophrenia of women and men and is supported by a wide variety of studies. It provides an important clue in the development of a better preventative or therapeutic intervention. The failure of 1 trial of a given estrogenic compound in decompensated schizophrenia patients has negligible implications toward the role of estrogen in a wider context.

In summary, these data do not support the use of raloxifene in schizophrenia in postmenopausal women to reduce symptoms in severely ill, decompensated schizophrenia patients. This study was not designed to identify changes in cognition, so it cannot be readily compared to studies on stabilized schizophrenia patients.

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REFERENCES

1. Seeman MV. The role of estrogen in schizophrenia. *J Psychiatry Neurosci*. 1996;21(2):123–127.
2. Häfner H, an der Heiden W. Epidemiology of schizophrenia. *Can J Psychiatry*. 1997;42(2):139–151.
3. van der Werf M, Hanssen M, Köhler S, et al; RISE Investigators. Systematic review and collaborative recalculation of 133,693 incident cases of schizophrenia. *Psychol Med*. 2014;44(1):9–16.
4. Häfner H. Gender differences in schizophrenia. *Psychoneuroendocrinology*. 2003;28(suppl 2):17–54.
5. Melkersson KI, Hulting AL, Rane AJ. Dose requirement and prolactin elevation of antipsychotics in male and female patients with schizophrenia or related psychoses. *Br J Clin Pharmacol*. 2001;51(4):317–324.
6. Seeman MV. Gender differences in the prescribing of antipsychotic drugs. *Am J Psychiatry*. 2004;161(8):1324–1333.
7. Seeman MV. Interaction of sex, age, and neuroleptic dose. *Compr Psychiatry*. 1983;24(2):125–128.
8. Szymanski S, Lieberman JA, Alvir JM, et al. Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. *Am J Psychiatry*. 1995;152(5):698–703.
9. Goff DC, Henderson DC, Amico E. Cigarette smoking in schizophrenia: relationship to psychopathology and medication side effects. *Am J Psychiatry*. 1992;149(9):1189–1194.
10. Jeste DV, Lindamer LA, Evans J, et al. Relationship of ethnicity and gender to schizophrenia and pharmacology of neuroleptics. *Psychopharmacol Bull*. 1996;32(2):243–251.
11. Magharious W, Goff DC, Amico E. Relationship of gender and menstrual status to symptoms and medication side effects in patients with schizophrenia. *Psychiatry Res*. 1998;77(3):159–166.
12. Pinals DA, Malhotra AK, Missar CD, et al. Lack of gender differences in neuroleptic response in patients with schizophrenia. *Schizophr Res*. 1996;22(3):215–222.
13. Angermeyer MC, Kühn L, Goldstein JM. Gender and the course of schizophrenia: differences in treated outcomes. *Schizophr Bull*. 1990;16(2):293–307.
14. Goldstein JM. Gender differences in the course of schizophrenia. *Am J Psychiatry*. 1988;145(6):684–689.
15. Harrison G, Croudace T, Mason P, et al. Predicting the long-term outcome of schizophrenia. *Psychol Med*. 1996;26(4):697–705.
16. Mortensen PB, Juel K. Mortality and causes of death in first admitted schizophrenic patients. *Br J Psychiatry*. 1993;163:183–189.
17. Torgalsbøen A-K. Full recovery from schizophrenia: the prognostic role of premorbid adjustment, symptoms at first admission, precipitating events and gender. *Psychiatry Res*. 1999;88(2):143–152.
18. Usall J, Araya S, Ochoa S, et al; Assessment Research Group in Schizophrenia (NEDES). Gender differences in a sample of schizophrenic outpatients. *Compr Psychiatry*. 2001;42(4):301–305.
19. an der Heiden W, Krumm B, Müller S, et al. The Mannheim long-term study of schizophrenia. Initial results of follow-up of the illness over 14 years after initial inpatient treatment [in German]. *Nervenarzt*. 1995;66(11):820–827.
20. an der Heiden W, et al. Eine prospektive Studie zum Langzeitverlauf schizophrener Psychosen: Ergebnisse der 14-Jahres-Katamnese. *ZMP*. 1996;5:66–75.
21. Opjordsmoen S. Long-term clinical outcome of schizophrenia with special reference to gender differences. *Acta Psychiatr Scand*. 1991;83(4):307–313.
22. Weiser M, Reichenberg A, Rabinowitz J, et al. Gender differences in premorbid cognitive performance in a national cohort of schizophrenic patients. *Schizophr Res*. 2000;45(3):185–190.
23. Häfner H, Behrens S, De Vry J, et al. An animal model for the effects of estradiol on dopamine-mediated behavior: implications for sex differences in schizophrenia. *Psychiatry Res*. 1991;38(2):125–134.
24. Moses EL, Drevets WC, Smith G, et al. Effects of estradiol and progesterone administration on human serotonin 2A receptor binding: a PET study. *Biol Psychiatry*. 2000;48(8):854–860.
25. Perlman WR, Webster MJ, Kleinman JE, et al. Reduced glucocorticoid and estrogen receptor alpha messenger ribonucleic acid levels in the amygdala of patients with major mental illness. *Biol Psychiatry*. 2004;56(11):844–852.
26. Weickert CS, Miranda-Angulo AL, Wong J, et al. Variants in the estrogen receptor alpha gene and its mRNA contribute to risk for schizophrenia. *Hum Mol Genet*. 2008;17(15):2293–2309.
27. González-Burgos I, Rivera-Cervantes MC, Velázquez-Zamora DA, et al. Selective estrogen receptor modulators regulate dendritic spine plasticity in the hippocampus of male rats. *Neural Plast*. 2012;2012:309494.
28. Glausier JR, Lewis DA. Dendritic spine pathology in schizophrenia. *Neuroscience*. 2013;251:90–107.
29. van der Leeuw C, Habets P, Gronenschild E, et al; for G.R.O.U.P. Testing the estrogen hypothesis of schizophrenia: associations between cumulative estrogen exposure and cerebral structural measures. *Schizophr Res*. 2013;150(1):114–120.
30. Gillies GE, McArthur S. Estrogen actions in the brain and the basis for differential action in men and women: a case for sex-specific medicines. *Pharmacol Rev*. 2010;62(2):155–198.
31. Chua WL, de Izquierdo SA, Kulkarni J, et al. Estrogen for schizophrenia. *Cochrane Database Syst Rev*. 2005;(4):CD004719.
32. Begemann MJ, Dekker CF, van Lunenburg M, et al. Estrogen augmentation in schizophrenia: a quantitative review of current evidence. *Schizophr Res*. 2012;141(2–3):179–184.
33. 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):334–341.
34. 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):1552–1557.
35. 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):1142–1147.
36. Kulkarni J, Gavrilidis E, Gwini SM, et al. Effect of Adjunctive Raloxifene Therapy on Severity of Refractory Schizophrenia in Women: A Randomized Clinical Trial. *JAMA Psychiatry*. 2016;73(9):947–954.
37. 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):223–231.
38. Weickert TW, Weinberg D, Lenroot R, et al. Adjunctive raloxifene treatment improves attention and memory in men and women with schizophrenia. *Mol Psychiatry*. 2015;20(6):685–694.
39. Furukawa TA, Levine SZ, Tanaka S, et al. Initial severity of schizophrenia and efficacy of antipsychotics: participant-level meta-analysis of 6 placebo-controlled studies. *JAMA Psychiatry*. 2015;72(1):14–21.
40. Kreyenbuhl J, Buchanan RW, Dickerson FB, et al; Schizophrenia Patient Outcomes Research Team (PORT). The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. *Schizophr Bull*. 2010;36(1):94–103.
41. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
42. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Revised Edition. Washington, DC: US Department of Health, Education, and Welfare; 1976.
43. Keefe RS, Goldberg TE, Harvey PD, et al. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res*. 2004;68(2–3):283–297.
44. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand suppl*. 1970;212:11–19.
45. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU side effect rating scale: a new comprehensive rating scale for psychotropic drugs and a crosssectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand suppl*. 1987;334:1–100.
46. Ulrich CM, Potter JD. Folate and cancer—timing is everything. *JAMA*. 2007;297(21):2408–2409.
47. Weickert TW, Allen KM, Weickert CS. Potential role of oestrogen modulation in the treatment of neurocognitive deficits in schizophrenia. *CNS Drugs*. 2016;30(2):125–133.
48. Weickert CS, Weickert TW. Hormone modulation improves cognition in schizophrenia. *Neuropsychopharmacology*. 2016;41(1):384–385.
49. Usall J, Huerta-Ramos E, Labad J, et al; RALOPSYCAT Group. Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a 24-week double-blind, randomized, parallel, placebo-controlled trial. *Schizophr Bull*. 2016;42(2):309–317.
50. Labad J, Martorell L, Huerta-Ramos E, et al; RALOPSYCAT Group. Pharmacogenetic study of the effects of raloxifene on negative symptoms of postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2016;26(10):1683–1689.
51. Buchanan RW, Keefe RS, Umbricht D, et al. The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later? *Schizophr Bull*. 2011;37(6):1209–1217.

Supplementary material follows this article.

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Supplementary Material

Article Title: Raloxifene Plus Antipsychotics Versus Placebo Plus Antipsychotics in Severely Ill Decompensated Postmenopausal Females Women With Schizophrenia or Schizoaffective Disorder: A Randomized Controlled Trial

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List of Supplementary Material for the article

1. eFigure 1 — Difference in PANSS Positive Symptoms Score Between Raloxifene and Placebo at Week 16 by Population Subgroups
2. eFigure 2 — Difference in PANSS Negative Symptoms Score Between Raloxifene and Placebo at Week 16 by Population Subgroups
3. eFigure 3 — Difference in PANSS General Symptoms Score between Raloxifene and Placebo at Week 16 by Population Subgroups
4. eFigure 4 — Difference in CGI-S Score Between Raloxifene and Placebo at Week 16 by Population Subgroups
5. eFigure 5 — Difference in BACS Composite Z-Score Between Raloxifene and Placebo at Week 16 by Population Subgroups

Disclaimer

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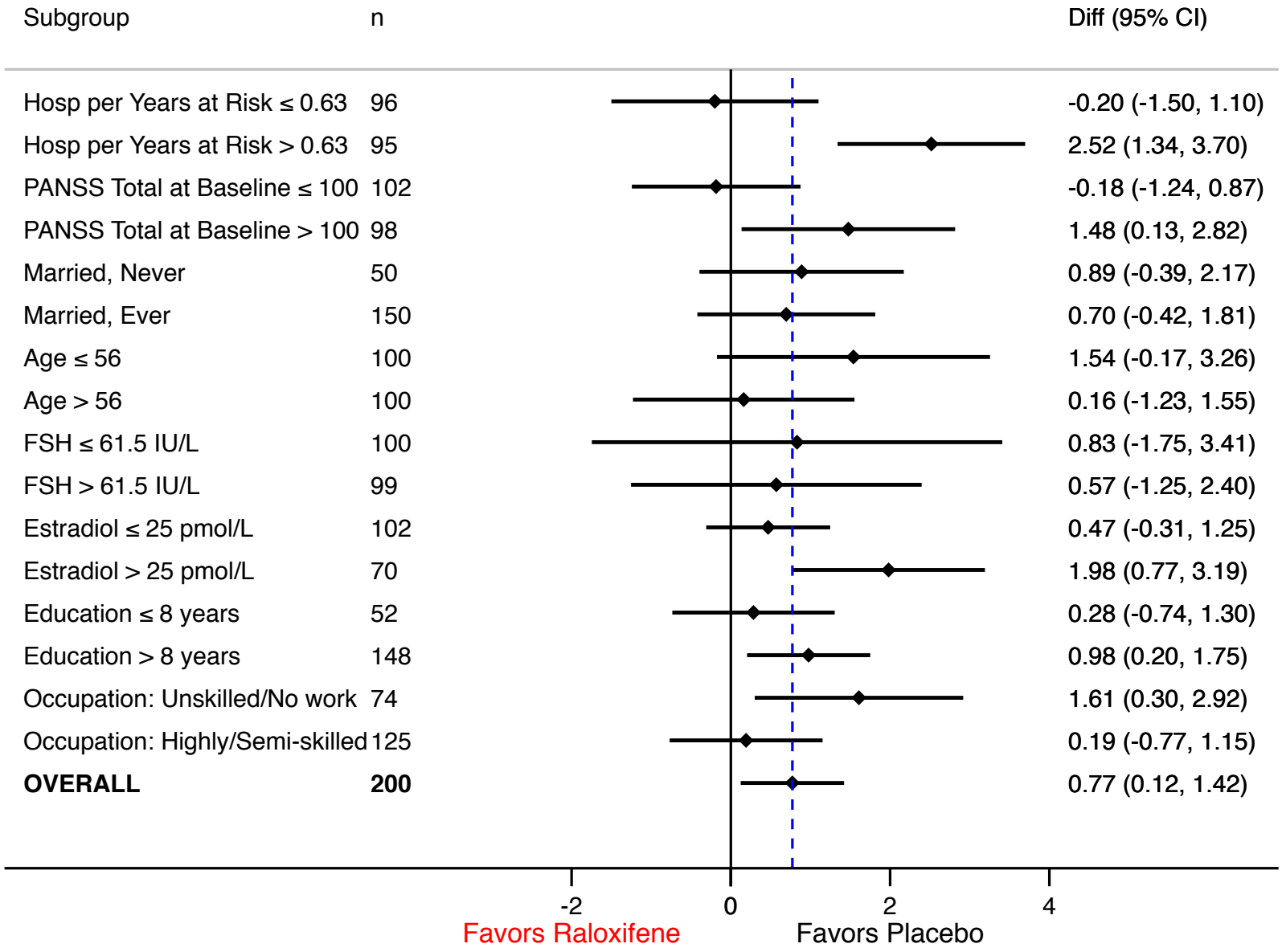
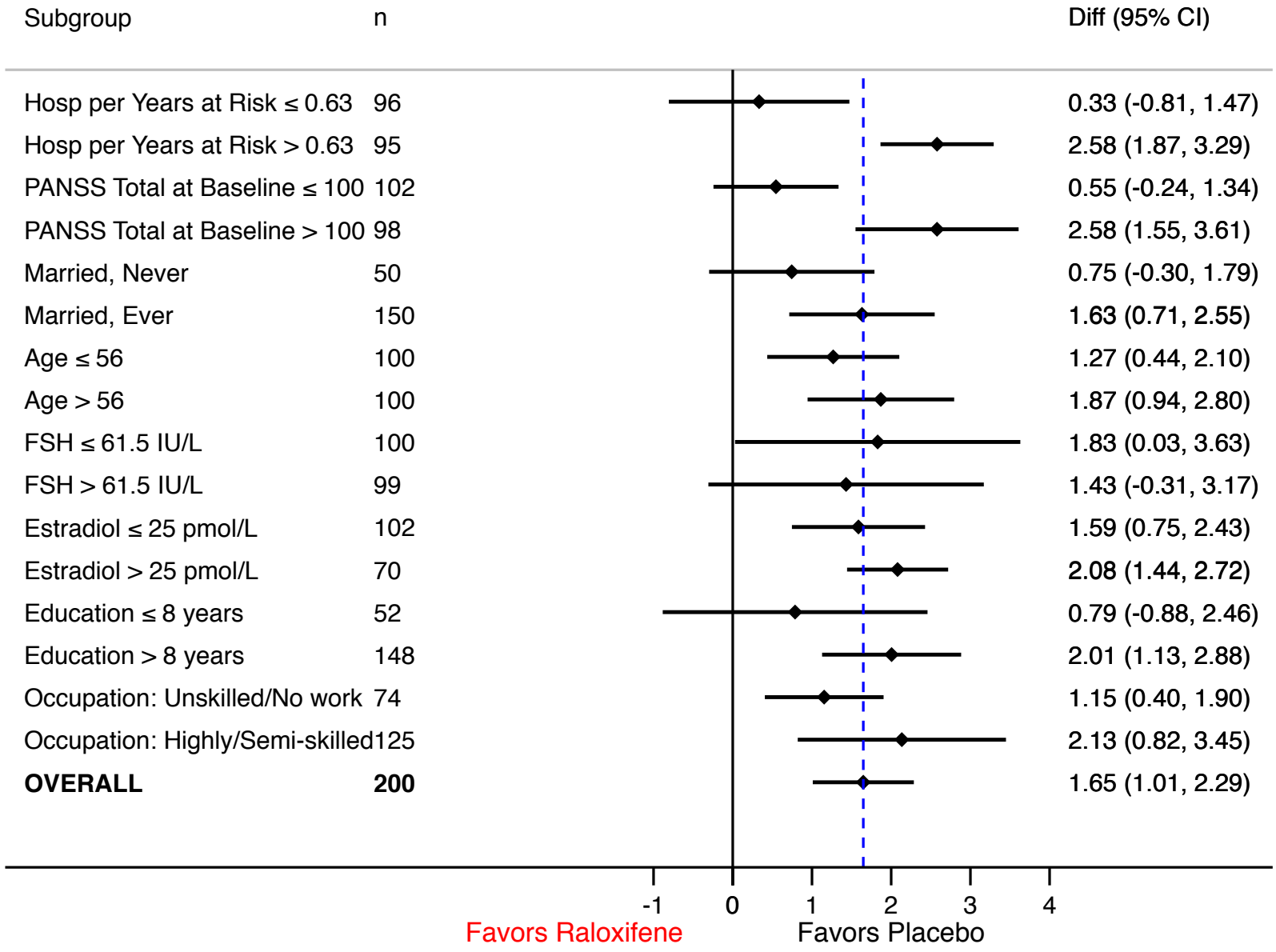
Supplementary eFigure 1. Difference in PANSS Positive Symptoms Score between Raloxifene and Placebo at Week 16 by Population Subgroups[a]



[a] Differences are calculated using mixed models for repeated measures. A positive difference in this score means placebo improved more than Raloxifene. There was no evidence of benefit from Raloxifene in any subgroup. Blue, dashed line represents the overall effect.

Abbreviations: FSH = follicle-stimulating hormone; Hosp = hospitalizations

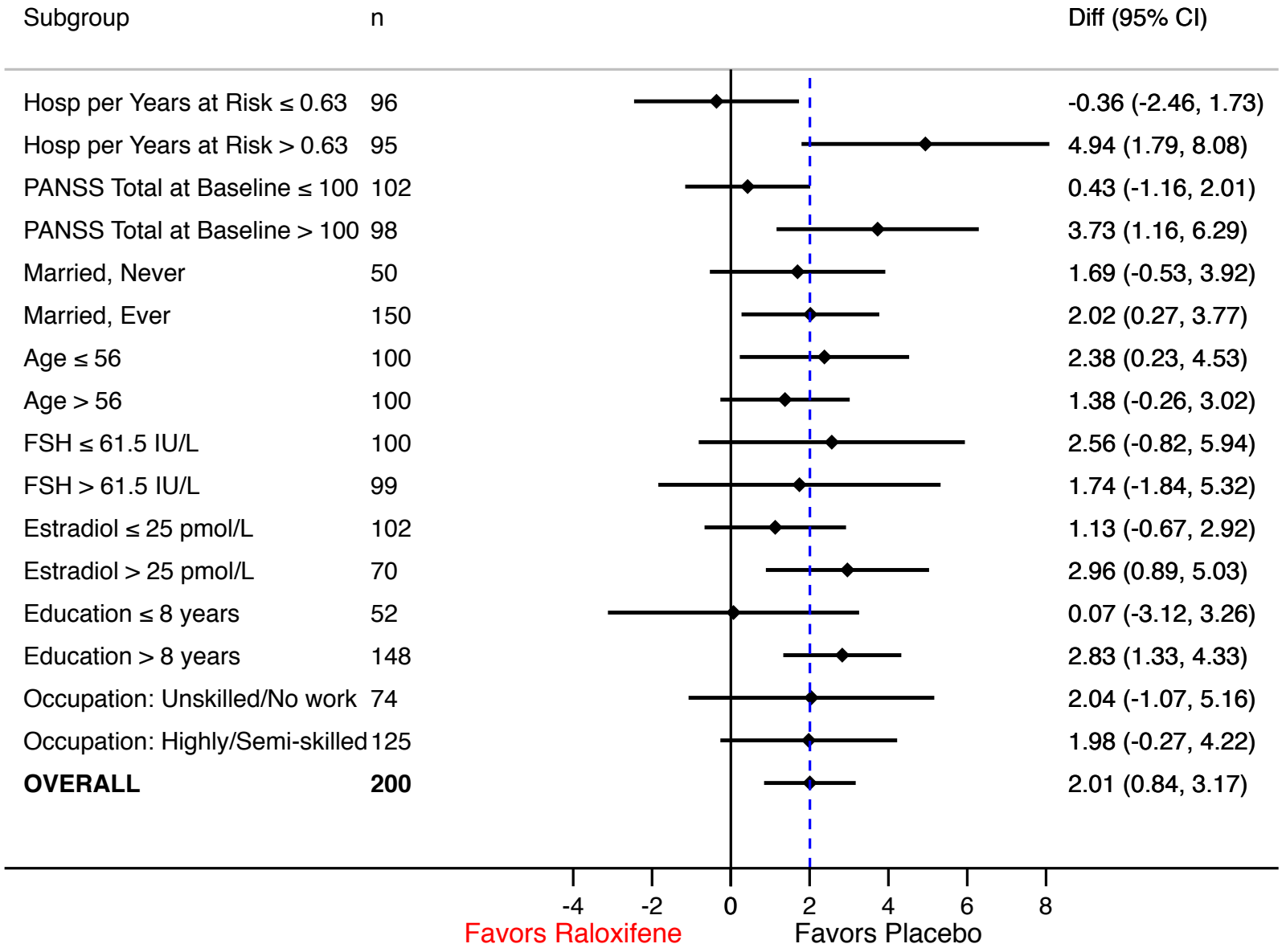
Supplementary eFigure 2. Difference in PANSS Negative Symptoms Score between Raloxifene and Placebo at Week 16 by Population Subgroups[a]



[a] Differences are calculated using mixed models for repeated measures. A positive difference in this score means placebo improved more than Raloxifene. There was no evidence of benefit from Raloxifene in any subgroup. Blue, dashed line represents the overall effect.

Abbreviations: FSH = follicle-stimulating hormone; Hosp = hospitalizations

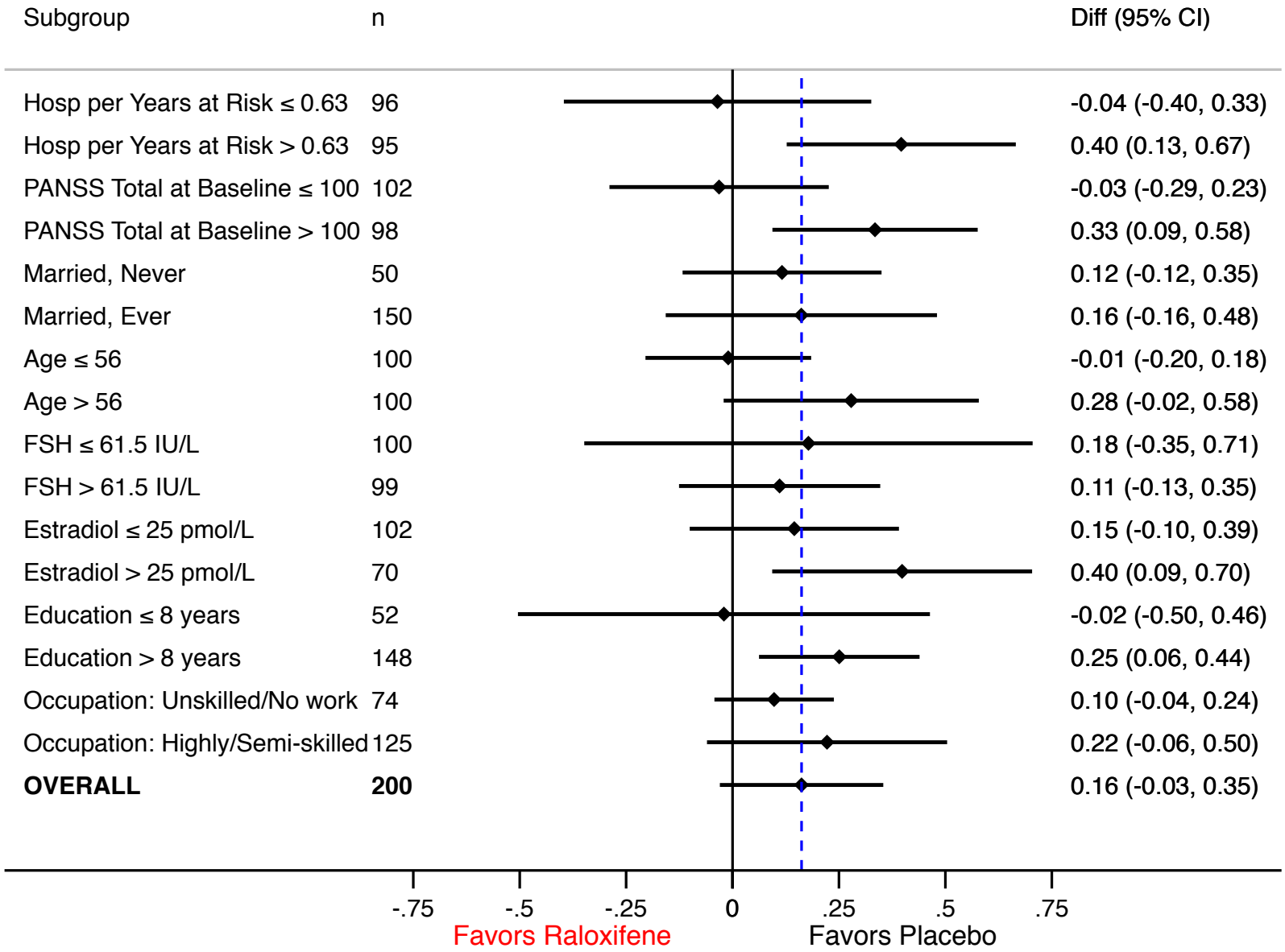
Supplementary eFigure 3. Difference in PANSS General Symptoms Score between Raloxifene and Placebo at Week 16 by Population Subgroups[a]



[a] Differences are calculated using mixed models for repeated measures. A positive difference in this score means placebo improved more than Raloxifene. There was no evidence of benefit from Raloxifene in any subgroup. Blue, dashed line represents the overall effect.

Abbreviations: FSH = follicle-stimulating hormone; Hosp = hospitalizations

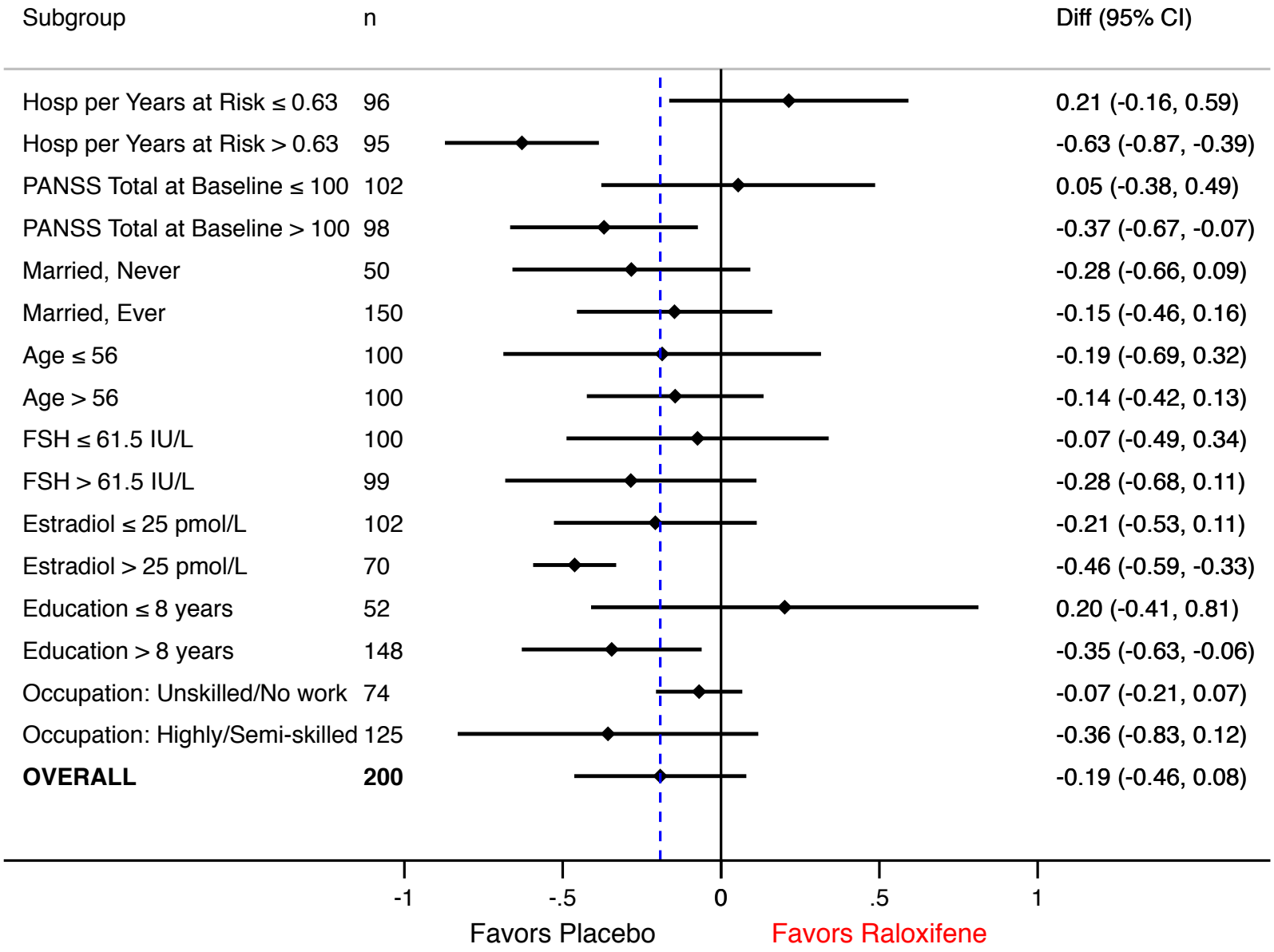
Supplementary eFigure 4. Difference in CGI-S Score between Raloxifene and Placebo at Week 16 by Population Subgroups[a]



[a] Differences are calculated using mixed models for repeated measures. A positive difference in this score means placebo improved more than Raloxifene. There was no evidence of benefit from Raloxifene in any subgroup. Blue, dashed line represents the overall effect.

Abbreviations: FSH = follicle-stimulating hormone; Hosp = hospitalizations

Supplementary eFigure 5. Difference in BACS Composite Z-Score between Raloxifene and Placebo at Week 16 by Population Subgroups[a]



[a] Differences are calculated using mixed models for repeated measures. A negative difference in this score means placebo improved more than Raloxifene. There was no evidence of benefit from Raloxifene in any subgroup. Blue, dashed line represents the overall effect.

Abbreviations: FSH = follicle-stimulating hormone; Hosp = hospitalizations