BRIEF REPORT

No Gender Differences in Placebo Responses of Patients with Major Depressive Disorder

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Background: *This study was designed to compare placebo responses in men and women.*

Methods: *Data for 501 women and 375 men with major depressive disorder treated with placebo from seven investigational randomized double-blind trials comparing fluoxetine with placebo were analyzed. Changes in major depressive disorder symptoms with placebo administration were measured as changes in total Hamilton Depression Rating Scale scores and adverse (nocebo) effects were measured by comparing treatment-emergent signs and symptoms.*

Results: *Both women and men with major depressive disorder showed significant symptomatic improvement following placebo administration, similar in magnitude and time course of response. Women on placebo reported slightly more nocebo effects than men.*

Conclusions: *The finding that women and men with major depressive disorder demonstrated a similar therapeutic outcome after placebo administration suggests that gender is not a predictor of placebo response.* Biol Psychiatry 2001;49:158–160 © *2001 Society of Biological Psychiatry*

Key Words: Placebo response, nocebo response, gender, major depressive disorder

Introduction

During the course of any disease, the improvement or deterioration of an individual patient's symptoms may be totally or partly independent of any drug effect. There is considerable evidence that whenever a supposedly inert treatment or inert preparation is used in an experimental treatment situation, 30–40% of those treated exhibit some benefit from such "placebo" (from Latin "I shall please") treatment (Beecher 1955). Placebo-controlled trials have also shown that a placebo can have harmful side effects or frankly toxic effects (Benson 1997), a phenomenon called the "nocebo" (from Latin " I shall harm") effect.

The question whether women and men respond differently to placebo administration has received hardly any attention. Rickels (1965) observed that women reported side effects on drug and placebo, whereas men reported side effects on active drug only. Wilcox et al (1992), who analyzed the placebo response relative to gender found women to be overall less responsive to placebo than men. Because gender specific placebo effects would have implications for pharmacological research, we decided to examine anew whether men and women differ in their responses to placebo administration.

Methods and Materials

Subjects

The fluoxetine clinical trial U.S. data base at Eli Lilly was used. All patients met criteria for nonpsychotic major depressive disorder (MDD), using the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 1980). After a complete description of the randomized double-blind nature of the fluoxetine treatment study, written informed consent was obtained from study participants. The placebo consisted of lactose, a sugar without pharmacologic potency. Trials lasted 5 weeks (2 trials) or 6 weeks (5 trials) including a 1-week placebo lead-in period. Patients, whose Hamilton Rating Scale ($HAMD_{21}$) total scores (Hamilton 1967) improved by more than 20% or fell below 20 during a placebo lead-in period, were not randomized.

We hypothesized that women would report greater and earlier improvement and more adverse events from placebo treatment than men.

Clinical Ratings

The therapeutic efficacy of the placebo response was measured as change in $HAMD_{21}$ scores determined by the treating psychiatrist. Nocebo or adverse events were defined as newly reported symptoms not present at the time of the entry into the study, recorded on the clinical report form of treatment-emergent signs and symptoms (TESS). Treatment-emergent signs and symptoms were categorized by their overall incidence, the number of patients with at least one or more symptoms, and by the number of patients with select symptoms related to an individual body system. Severity of depression was defined as a baseline $HAMD_{21}$ total score of 25 or more (severe) or less than 25 (mild

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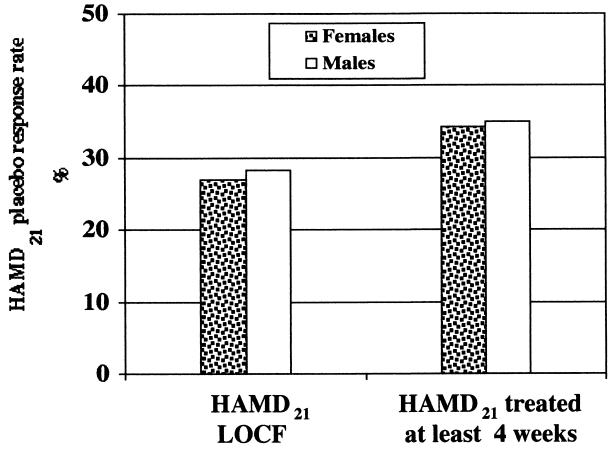

Figure 1. Placebo response rates, defined as a reduction greater than or equal to 50% in Hamilton Depression Rating Scale ($HAMD_{21}$) total scores, presented as percentage of responders for all enrolled patients with major depressive disorder treated with placebo who had at least one postbaseline measurement (LOCF) and for patients who were treated at least 4 weeks. Male and female patients had similar response rates ($p = .757$ and $p = .867$, respectively).

to moderate). Assessments were conducted at approximately 1-week intervals.

Data Analysis

Frequencies were compared using the Fisher exact test. To compare percentages among more than two groups, the Pearson χ^2 test was used. Analysis of response (the number of responders, who achieved at least a 50% decrease in total $HAMD_{21}$, or who achieved remission—end point $HAMD_{21} \leq 7$—refers to last observation carried forward (LOCF) data or from baseline to end point data for all subjects treated at least 4 weeks. Mean changes in baseline $HAMD_{21}$ scores, in specific depressive or physical symptoms for men and women or in TESS, were compared using analysis of variance with gender, trial, and gender by trial interaction in the model. Repeated measures analyses were performed using PROC MIXED in SAS with gender, trial, gender by trial, week, and gender by week and age in the model assuming an unstructured covariance matrix.

Results

There were 501 female and 375 male subjects in the placebo-treated sample, mean age: 50.1 years (SD = 17.6), with ages ranging from 12.0 to 90.5 years. Sixty-two percent of the placebo response group completed the study. Similar proportions of women (30.7%) and men (26.3%) in the placebo group qualified for a severe depression ($p = .174$). Female (mean age 49.7 ± 17.5 [SD] years) and male patients (50.7 ± 17.7 years) were similar in age [$F(1,861) = 0.17$, $p = .683$).

Figure 1 illustrates that the percentage of women who reported a therapeutic response from placebo were close to the proportion of men ($p = .757$ and $p = .867$, respectively). Remission analyses showed the same conclusion (LOCF men vs. women: 16.0% vs. 13.2%, $p = .278$; 4-week men vs. women: 20.8% vs. 17.5%, $p = .310$). Table 1 shows the significant reductions in mean $HAMD_{21}$ scores from baseline to end point in men and women taking placebo ($p < .001$) but no differences in mean symptomatic improvement between women and men [$F(1,840) = 0.07$, $p = .785$). Neither baseline severity as measured by the $HAMD_{21}$ total scores nor age showed gender differences in placebo response. The time course of the placebo response was similar in men and women ($p = .459$).

Table 1. Mean Changes in 21-Item Hamilton Depression Rating Scale Scores from Baseline to End Point for Placebo-Treated Men and Women with Major Depressive Disorder

		Baseline		End point		Within gender	Men/women	
Subjects	*n*	Mean	SD	Mean	SD	(*p*)	*F*	*p*
Women	492	25.2	5.2	18.1	8.9	.001	0.07	.785
Men	362	24.4	5.2	17.3	8.6	.001		

n, number of patients with both a baseline and a postbaseline measurement.

Nocebo Effects

More women than men reported ≥1 symptom (38.5% vs. 30.1%, $p < .01$; Table 2). Women reported a higher incidence of pain in general, chest pain, infections, accidental injuries, nausea, increased appetite, and nervousness. Men were more likely to report somnolence, tremor,

Table 2. Treatment-Emergent Signs and Symptoms (TESS) in Placebo-Treated Women and Men with Major Depressive Disorder That Showed Statistically Significant Differences

	Women ($n = 501$; %)	Men ($n = 375$; %)	*p*
Any adverse event			
≥TESS	71.7	65.6	.065
Body as a whole: symptoms			
≥1 TESS	38.5	30.1	.01
Pain	5.6	2.7	.043
Chest pain	3.4	1.1	.026
Infection	4.6	1.3	.006
Accidental injury	3.8	0.8	.004
Digestive system			
Nausea	10.8	5.9	.011
Increased appetite	2.0	0.3	.029
Nervous system			
Nervousness	10.6	5.1	.004
Somnolence[a]	4.0	7.2	.048
Tremor[a]	2.2	5.1	.024
Respiratory system			
Asthma[a]	0	1.1	.033

[a]Higher percentage in men.

and asthma. Depression severity did not affect the number of reported adverse effects (37% not severely depressed vs. 33% severely depressed patients reported one or more adverse events; $p = .373$).

Discussion

Our study suggests that men with major depressive disorder obtain as much symptomatic relief from placebo administration as women with major depressive disorder. Confirming previous observations of randomized controlled trials of patients with major depressive disorder, our study found about 30% of depressed patients to be placebo responders (Bialik et al 1995; Quitkin 1999). Both the magnitude and the time course of the placebo response were similar in women and in men. Furthermore, the depressive symptom profile of the placebo reaction was comparable in both genders.

Interestingly, Wilcox et al (1992) found women less responsive to placebo, but only when response rates were categorized using various reductions in depressive symptoms. Bialik et al (1995) analyzed placebo response rates by depression subtypes; they found higher placebo response rates in women with a first episode of depression when compared to men. Analysis of the nocebo effect, i.e., adverse reactions experienced from taking a placebo, indicated that women were more likely to react negatively to placebo administration than men. This finding confirms Rickels' observations (Rickels 1965). Previously identified predictors of a greater nocebo response are higher anxiety levels in patients with anxiety disorders (Uhlenhuth et al 1998) and a more competitive behavior pattern in healthy volunteers (Drici et al 1995).

In conclusion, our finding that men and women who participate in randomized controlled clinical trials of major depressive disorder show similar placebo response rates and patterns suggests that gender is not a significant variable influencing drug/placebo comparisons. Our observation that women tend to experience more adverse effects from placebo administration merits further study.

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