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Brief report

# Different gender response to serotonergic and noradrenergic antidepressants. A comparative study of the efficacy of citalopram and reboxetine

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**Abstract**

*Background:* It is well established that depressive disorders are more prevalent in women; however gender differences in the pharmacological response to antidepressants are not a consistent finding in all reports. It is considered that this discrepancy can be explained by the fact that in most clinical trials drug use for comparative purposes is not completely different. In this study gender differences in antidepressant response with citalopram (CTP), a selective serotonin reuptake inhibitor and reboxetine (RBX), a selective noradrenaline reuptake inhibitor were evaluated in a group of young men and premenopausal women.
*Method:* Eighty-six depressed patients 18 to 40 years old participated in an 8-week double-blind clinical trial. Subjects were divided in four groups according to sex and treatment assignation: females treated with CTP ($n=25$) or RBX ($n=23$), and males treated with CTP ($n=19$) or RBX ($n=19$). Response was determined using HDRS and BDI.
*Results:* ANOVA analysis considering change in HDRS scores from baseline to last evaluation found a significant interaction between gender and type of treatment. Females treated with CTP showed a significantly greater response than females treated with RBX, while in men no differences were observed for both drugs.
*Limitations:* Replication using larger sample size and longer treatment periods is required.
*Conclusions:* These results support previous findings which show that premenopausal women respond better than men to serotonergic antidepressants. They also support that a plausible interaction between gonadal hormones and serotonin may explain gender differences in antidepressant response.


*Keywords:* Gender; Antidepressant response; Depression; Citalopram; Reboxetine; Hormones

## 1. Introduction

Greater prevalence of major depressive disorder (MDD) in women is a consistent finding in most epidemiological studies (Kessler et al., 1994; Kessler, 2003; Kuehner, 2003). It is postulated that the increased tendency for women to report symptoms and seek treatment may augment the magnitude of these gender differences; however the increased prevalence of MDD in women versus men is observed both in clinical and community-based epidemiologic studies suggesting then that differences in help-seeking behavior do not account for the differences in prevalence (Kessler et al., 1981). Additionally, the

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assumption that the pattern of antidepressant response among men and women is similar has been questioned, and there is now sufficient although not complete evidence to consider that they present a different antidepressant treatment outcome. Korstein et al. (2000) found that while men respond better to tricyclic antidepressants (TCA) than to selective serotonin reuptake inhibitors (SSRI) women tend to do the opposite, observing this difference primarily in premenopausal women. At least, two additional reports have confirmed this finding (Sagud et al., 2002; Baca et al., 2004). Recently Thase et al. (2005) provided further evidence that age, gender and hormone replacement therapy moderates response to antidepressant medication. On the other hand however, several studies have failed in detecting such differences with several types of antidepressants (Hildebrandt et al., 2003; Parker et al., 2003; Wohlfarth et al., 2004). Nonetheless, current data suggest that there is sufficient biological and pharmacokinetic evidence which may predict gender differences in treatment response to antidepressants (Yonkers and Brawman-Mintzer, 2002).

To further assess if men and women respond differently to antidepressants, it is necessary to compare drugs with distinct types of effects on neurotransmitter systems. This becomes even more relevant when there is substantial evidence that estrogen has a role in regulating various aspects of neural transmission, particularly in the serotonergic system (Rubinow et al., 1998). Considering this, we conducted a clinical study to evaluate gender antidepressant response by comparing the efficacy of two completely different pharmacological types of antidepressants: citalopram (CTP) and reboxetine (RBX). Most previous studies have compared both TCA and new types of antidepressants including SSRI and others such as venlafaxine which has both noradrenergic and serotoninergic effects and thus are not specifically noradrenergic. RBX is a unique selective noradrenaline reuptake inhibitor (SNRI) with proved efficacy for the treatment of MDD and dysthymia (Schatzberg, 2000). CTP a well known SSRI, is considered as one of the most selective antidepressant for serotonin (Keller, 2000). We hypothesized that premenopausal women would respond better to CTP than to RBX, while in men no differences would be detected.

## 2. Subjects and methods

### 2.1. Subjects

Patients were recruited from the outpatient clinic of the National Institute of Psychiatry "Ramón de la Fuente" in Mexico City from March 2001 to September 2003. Individuals between 18 and 40 years, meeting the Diagnostic and Statistical Manual (DSM-IV) (APA, 1994) criteria for MDD after two independent clinical interviews, and scoring at least 18 in the 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) were asked to participate in the study. Patients were excluded if psychotic symptoms were present or a history of past manic, hypomanic or mixed episodes was confirmed. Also subjects with uncontrolled medical illnesses, evidence of drug abuse or severe personality disorders were not included. In the case of women individuals with irregular menstrual cycles, pregnancy, breastfeeding, current hormonal treatments and biological or surgical menopause were also excluded. All of those who agreed to participate signed a written informed consent form and the study was approved by the local Institutional Ethical Committee.

### 2.2. Assessments and methods

A complete clinical and psychiatric history was obtained in all participants at baseline, as well as basic laboratory studies and an electrocardiogram. Drug-naïve or drug-free subjects for any antidepressant for at least two weeks prior the beginning of the study were randomly assigned to an 8-week double-blind comparative trial with RBX or CTP. Drugs were administered orally at bedtime using identical capsules containing 4 mg of RBX or 20 mg of CTP as starting doses. Patients experiencing insomnia were allowed to take clonazepam (0.5 to 2.0 mg/night) only during the first 2 weeks of the study. No other psychotropic was permitted thereafter. All patients were evaluated weekly from weeks 1 through 4 and then at weeks 6 and 8. At each visit treatment response was determined with the HDRS, and the Beck Depression Inventory (BDI; Beck et al., 1961). Side effects were registered using a specific questionnaire designed for that purpose. In patients who did not respond by the end of week 4, dosification was increased up to 8 and 40 mg of RBX or CTP respectively during the following weeks. Medication compliance was determined by a pill-counting method. Response was defined as a 50% decrease in the total HDRS score, and remission as a final HDRS total score =8 (Frank et al., 1991).

### 2.3. Statistical analysis

Comparisons were done only with patients having at least five evaluations (basal and 4 weeks of treatment). In patients who had a minimum of 5 evaluations but did not complete the 8 weeks of follow-up, last observation carried forward (LOCF) procedure was used. Clinical and demographic characteristics between genders as well as side effects were compared using Chi Square test for categorical variables and analysis of variance (ANOVA) for continuous variables. Treatment by sex