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Sex Differences in Response to Citalopram: A STAR*D Report

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Abstract

Objective—Controversy exists as to whether women with depression respond better to selective serotonin reuptake inhibitors (SSRIs) than men. The purpose of this report was to determine whether men and women differ in their responses to treatment with the SSRI citalopram using a large sample of real world patients from primary and psychiatric specialty care settings.

Method—As part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 2876 participants were treated with citalopram for up to 12-14 weeks. Baseline demographic and clinical characteristics and outcomes were gathered and compared between men and women.

Results—At baseline, women were younger, had more severe depressive symptoms and were more likely to have: early onset; previous suicide attempt(s); a family history of depression, alcohol abuse or drug abuse; atypical symptom features; and one or more of several concurrent psychiatric disorders. Despite greater baseline severity and more Axis I comorbidities, women were more likely to reach remission and response with citalopram than men.

Conclusions—Women have a better response to the SSRI citalopram than men, which may be due to sex-specific biological differences particularly in serotonergic systems.

Keywords

antidepressants; gender differences; estradiol; women's health; depression

Introduction

Mood disorders are the leading cause of disability among women 15 to 44 years of age (Murray et al, 1990) and twice as many women as men (12% vs. 6%) suffer from major depression annually (Kessler et al, 1994). Controversy remains as to whether treatment response differs

between the sexes. Early studies found that women were slower to respond to tricyclic antidepressants (TCAs) (Prange, 1969; Glassman, 1977) and were less likely to achieve response (Raskin, 1974; Glassman et al, 1977). In a pivotal study of sex differences in treatment response in chronic depression, Kornstein et al. (2000) found that women responded best to the selective serotonin reuptake inhibitor (SSRI) while men responded best to the TCA; however, direct comparison of men vs. women on the SSRI was not reported. Women were more likely to drop out due to adverse events with the TCA than the SSRI, while men showed no between-medication differences with regard to dropping out due to adverse events.

Baca et al. (2004) used the same design as Kornstein et al. (2000) to study nonmelancholic major depression and found that men and women responded equally well to sertraline (SSRI), but men were more likely than women to drop out. Martényi et al. (2001) compared outcomes in a small sample (n=101) of depressed patients and found women were more likely to respond to fluoxetine (SSRI) than maprotiline (a noradrenergic agent), but direct comparison of men vs. women was not given. Khan et al. (2005) found that women with depression had a better response to the SSRIs than men with depression, but found no sex difference in remission rates with SSRIs.

Unfortunately, the overall sample size was small (N=130), and the study grouped multiple SSRIs together, with 59 men and 71 women in the pooled SSRI analyses.

Other studies have found no sex differences in response with SSRIs. Quitkin et al. (2002) examined records from 840 depression research clinic outpatients taking fluoxetine (a larger sample size than any prior published study) and found no significant sex differences in response rate or speed of response. The Danish University Antidepressant Group (Hildebrandt et al, 2003) conducted a pooled analysis of 292 inpatients with predominantly melancholic depression treated with five weeks of clomipramine (TCA), citalopram, paroxetine (SSRIs) or moclobemide (MAOI). They found no sex differences in treatment response, drop-out rates or side effects.

Thiels et al. (2005) lends further support for the lack of sex differences in response to SSRIs. Unlike the previous industry-sponsored pharmaceutical trials with typical exclusions for suicidality and general medical conditions (GMCs), this study enrolled prospective observational patients with depression (N=5452) seen in routine clinical practice in Germany (1660 participating physicians, of whom 516 were psychiatrists). After six months of treatment with sertraline, no significant sex differences were found in treatment response (with response defined as a $\geq 50\%$ reduction in a 12-item rating scale designed for the study), time to response, or treatment-emergent adverse events. Sertraline doses were slightly but significantly lower in women than in men (45.5 vs. 46.5 mg/day) and patients did not necessarily meet major depression.

Consequently, previous studies of gender differences in response to SSRI treatment have been small in scope, based on industry-sponsored clinical trials data with multiple exclusions, and were not conducted with real world patients. The study by Thiels et al. (2005) was the exception, although major depression was not a requirement for inclusion.

The current analysis was designed to determine whether there are sex differences in response to antidepressant treatment in major depression to the SSRI citalopram. Findings of such sex differences would have implications for choice of treatment in men and women, as well as for the prediction of likelihood of response to this class of antidepressants. We used data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Fava et al, 2003; Rush et al, 2004), the largest study of major depression ever conducted in the US and the largest to address sex differences in prospective depression treatment using a representative sample of treatment-seeking patients.

Methods

Study Overview and Organization

The rationale, design, and methods of STAR*D have been detailed elsewhere (Fava et al, 2003; Rush et al, 2004). Briefly, STAR*D aimed to define prospectively which of several treatments are most effective for outpatients with nonpsychotic major depressive disorder (MDD) who have an unsatisfactory clinical outcome to an initial and, if necessary, subsequent treatment(s). Treatment was provided at 18 primary and 23 psychiatric care public or private sector settings.

Study Population

To enhance generalizability, STAR*D enrolled only self-declared treatment-seeking outpatients 18-75 years of age, identified by their clinicians as having nonpsychotic MDD requiring treatment. Advertising for symptomatic volunteers was proscribed. Broadly inclusive entry criteria were used (Fava et al, 2003; Rush et al, 2004). Patients were eligible if they met DSM-IV criteria for single or recurrent nonpsychotic MDD (established by treating clinician and confirmed by a DSM-IV checklist), scored ≥ 14 (moderate severity) on the Clinical Research Coordinator (CRC)-rated 17-item Hamilton Rating Scale for Depression (HRSD₁₇) (Hamilton, 1960), and were not treatment resistant to an adequate antidepressant treatment trial during the current MDD episode (Trivedi et al, 2006). Exclusion criteria are detailed elsewhere (Fava et al, 2003; Rush et al, 2004).

All risks, benefits, and adverse events associated with STAR*D participation were explained to participants, who provided written informed consent prior to study entry. The STAR*D protocol was developed in accordance with the principles of the Declaration of Helsinki, and was approved by the Institutional Review Boards at the national and data coordinating centers, and the respective regional centers and clinical sites. The study sample consists of all participants enrolled in STAR*D who completed one return visit and had a baseline Research Outcome Assessor (ROA) call to obtain the primary outcome measure, HRSD₁₇. (Trivedi et al, 2006) Of the 3110, who met the HRSD₁₇ inclusion criteria, 2876 returned for at least 1 return visit and are the sample for this analysis.

Baseline Measures

At baseline, trained CRCs based at each site collected standard demographic information, self-reported psychiatric history, and current general medical comorbidities as evaluated by the Cumulative Illness Rating Scale (Linn et al, 1968) which was completed using a manual to guide scoring (Miller and Towers, 1991). CRCs administered the initial HRSD₁₇ and assessed depressive symptoms using the 16-item Quick Inventory of Depressive Symptomatology – Clinician-rated (QIDS-C₁₆). The participant completed the 16-item Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR₁₆) (Rush et al, 2003; Trivedi et al, 2004) for assessment of depressive symptoms.

Participants also completed the Psychiatric Diagnostic Screening Questionnaire (PDSQ) (Zimmerman and Mattia, 1999; 2001) to estimate the presence of 11 potential concurrent DSM-IV psychiatric disorders. Based on prior reports (Rush et al, 2005), we defined the presence of concomitant Axis I disorders using thresholds with a 90% specificity in relation to the “gold standard” diagnosis rendered by a structured interview.

Research Outcomes Assessors (ROAs) masked to treatment and not located at any clinical site collected the HRSD₁₇ and the 30-item Inventory of Depressive Symptomatology – Clinician-rated (IDS-C₃₀) (Rush et al, 1986; 1996; Trivedi et al, 2004) by telephone interview within 72 hours of study entry for assessment of depressive symptoms. Responses to items on these

measures were used to estimate the presence of atypical (Novick et al, 2004), melancholic (Khan et al, 2006), and anxious (Fava et al, 2004) symptom features.

A telephone-based Interactive Voice Response system (Mundt et al, 1997; Kobak et al, 1999) collected health perceptions via the 12-Item Short Form Health Survey (SF-12) (Ware and Sherbourne, 1992), and quality of life via the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott et al, 1993) and the Work and Social Adjustment Scale (WSAS) (Mundt et al, 2002).

Course of Treatment Measures

An integral part of our measurement-based care intervention (Trivedi et al, 2006; 2007) was the collection of clinically relevant information at each clinic visit to inform treatment decision-making. Depressive symptom severity was obtained at each clinic visit with the QIDS-SR₁₆ and the QIDS-C₁₆. Side effects were assessed using the Frequency, Intensity, and Burden of Side Effects Rating scale (FIBSER) (Wisniewski et al, 2006), which uses three 7-point subscales to evaluate frequency, intensity and global burden measures, respectively.

Intervention

Treatment consisted of a 12-14 week trial of citalopram (STAR*D Level 1) with the aim of reaching symptom remission, defined as a QIDS-C₁₆ score ≤ 5 or HRSD₁₇ ≤ 7 . The protocol (Rush et al, 2004) required a fully adequate dose of citalopram for a sufficient time to maximize the likelihood of achieving remission and ensure that participants who did not remit were truly resistant to the medication.

Dose adjustments were guided by recommendations in a treatment manual (www.star-d.org). Individualized starting doses and dose adjustments were used to minimize side effects, maximize safety, and optimize the chances of therapeutic benefit for each participant. Citalopram was to begin at 20 mg/day and be raised to 40 mg/day by weeks 2-4, and to 60 mg/day (final dose) by weeks 4-6. Dose adjustments were guided by symptom changes based on the QIDS-C₁₆, side-effect burden based on the FIBSER, and on how long a participant had received a particular dose.

The protocol recommended treatment visits at weeks 0 (baseline), 2, 4, 6, 9, and 12 (with an optional week 14 visit if needed). After an optimal trial (based on dose and duration), participants who reached remission (QIDS-C₁₆ ≤ 5) or response (response defined as an improvement $\geq 50\%$ over the baseline QIDS-C₁₆ score without remission) could enter a 12-month naturalistic follow-up, but all who did not reach remission were encouraged to enter the subsequent randomized trial (Level 2 of STAR*D). Participants could discontinue citalopram before 12 weeks if 1) intolerable side effects required a medication change, 2) an optimal dose increase was not possible due to side effects or participant choice, or 3) significant symptoms (QIDS-C₁₆ score ≥ 9) were present after nine weeks at maximally tolerated doses. Participants could opt to move to the next treatment level if they had intolerable side effects or if their QIDS-C₁₆ score was >5 after an adequate trial in terms of dose and duration. Intensive efforts were made to provide consistent high-quality care, including the use of a treatment manual, initial didactic instruction, ongoing support and guidance by the CRC, the use of the QIDS-C₁₆ and the FIBSER at each visit, and a centralized treatment monitoring and feedback system (www.star-d.org) (Trivedi et al, 2006; Wisniewski et al, 2004).

Safety Assessments

Side effects were monitored clinically. Serious adverse events (SAEs) were monitored using a multi-tiered approach (Wisniewski et al, 2004) that involved the CRCs, study clinicians, the

interactive voice response system, the clinical manager, safety officers, regional center directors, and the NIMH Data Safety and Monitoring Board.

Concomitant Medications

Concomitant treatments for current medical illnesses, associated symptoms of depression (e.g., sleep and agitation), and citalopram side effects were permitted at study entry and during the treatments, based on clinical judgment.

Main outcome measures

The primary outcome measure was the HRSD₁₇ collected by ROAs using telephone-based structured interviews at entry and exit from citalopram treatment. The secondary outcomes included the QIDS-SR₁₆ and FIBSER collected at baseline and at each treatment visit.

Statistical Analysis

Remission was defined as an exit HRSD₁₇ score ≤ 7 (or last observed QIDS-SR₁₆ score ≤ 5). As defined by the original proposal, participants for whom the exit HRSD₁₇ score was missing were designated as not reaching remission. Response was defined as a reduction of $\geq 50\%$ from the baseline QIDS-SR₁₆, without remission, at the last assessment. Intolerance was defined *a priori* as either leaving treatment before four weeks or leaving at or after four weeks with intolerance as the identified reason. The alpha level was set at 0.05 (two-sided). No adjustments were made for multiple comparisons, so results must be interpreted accordingly.

Summary statistics are presented as means and standard deviations for continuous variables, and percentages for discrete variables. Student's t-tests and Mann-Whitney U tests were used to compare continuous baseline clinical and demographic features, treatment features, and side effect and serious adverse event rates between male and female participants. Chi-square tests compared discrete characteristics between male and female participants.

Logistic regression models were used to compare remission and response rates, after adjusting for regional center and other factors shown to differ between men and women at baseline. Kaplan-Meier curves were used to present the cumulative probability of first remission and cumulative probability of first response, both measured using the QIDS-SR₁₆. Log-rank statistics were used to test whether there was a statistically significant difference in the cumulative proportions.

Results

Baseline Characteristics

Of the 2876 participants included in this analysis, 37.9% were treated in primary care. Overall, the sample had suffered from depression for a mean of 15.5 years, had multiple episodes of depression (mean 5.5, median 3) and had a long current episode (mean length 24.6 months, median 8 months). Mean entry HRSD₁₇ scores revealed moderate depression (HRSD₁₇ = 21.8) (Table 1).

At baseline, women were less likely to be married or seen in specialty care than men, and more likely to be Hispanic or African-American, widowed or have public insurance. Women were almost three years younger (Table 2). Women were significantly more depressed at baseline by the IDS-C₃₀ and the QIDS-SR₁₆, but not by the HRSD₁₇. CIRS scores showed no sex differences in the total general medical burden (Table 2). Although the mean number of episodes differed between men and women the median (3) did not (Table 2).

Women were more likely to have a family history of depression, alcohol abuse or drug abuse. Women were more likely to have attempted suicide (20.8% vs. 12.9%), but they were not viewed to show greater suicide risk at entry. Women were more likely to have onset of their first major depressive episode before age 18 (41.5% vs. 31.5%) and have atypical symptom features (21.2% vs. 14.7%), but were slightly less likely to have melancholic features (22.1% vs. 25.9%) (Table 2c).

Women were more likely to have an anxiety disorder (26.5% vs. 18.6%), panic disorder (14.1% vs. 11.3%), social phobia (33.0% vs. 28.4%), somatoform disorder (3.2% vs. 1.0%), hypochondriasis (5.0% vs. 3.4%) or bulimia (16.6% vs. 6.8%), and less likely to have comorbid alcohol abuse (8.7% vs. 18.0%) or drug abuse (5.7% vs. 10.3%) (Table 2).

Remission and Response by Sex

Based on the HRSD₁₇ (ROA) data (primary outcome), women were significantly more likely to achieve remission with citalopram than men (29.4% vs. 24.1%). The QIDS-SR₁₆ data (secondary outcome) also showed women more likely to remit, but not to a significant degree. Women were more likely to respond to citalopram by the QIDS-SR₁₆ (48.5% vs. 44.0%). Mean exit QIDS-SR₁₆ scores were similar between sexes, although women entered the study with higher QIDS-SR₁₆ ratings. Consequently, both the change in QIDS-SR₁₆ and the percent change from baseline QIDS-SR₁₆ were significantly greater in women (Table 3).

Since men and women differed on a number of baseline variables, adjusted analyses were performed for remission and response rates. Adjustments included regional center and baseline demographic and clinical features that differed significantly between men and women at baseline (e.g., age, race, marital status, family history, suicide attempts, depression subtype, number of episodes, and baseline QIDS-SR₁₆). After adjustment, women remained significantly more likely to achieve remission by the HRSD₁₇ (OR: 1.33), but remission results by the QIDS-SR₁₆ were still not significant (Table 3). No significant difference was found between men and women regarding time to remission (Figure 1) or time to response (Figure 2).

Treatment Course

There were no significant sex differences in the maximum dose of citalopram, although a greater proportion of men (46.2% vs. 42.1%) received 50 mg or more per day of citalopram. Similar proportions of men and women completed eight weeks or more of treatment (~72%). Overall, women did have significantly more weeks in treatment (10.2 vs. 9.8), but there was no sex difference in the time from reaching final dose to study exit (Table 4). There were also no sex differences in overall serious adverse events or psychiatric serious adverse events. Side effects showed no significant sex differences by frequency, intensity or burden; nor was there a sex difference in the number who exited due to intolerance (Table 5).

Discussion

The current report details the first large-scale study to use patients with depression from both primary and specialty care clinics to study sex differences in response to antidepressant treatment with an SSRI, citalopram. This finding was observed on the HRSD₁₇, our a priori specified primary outcome using independent blind research outcome assessors to rate depression symptoms, and persisted after adjustment for baseline differences. The QIDS-SR₁₆ findings were similar but were not significant before or after adjustment. Our findings indicate that women have a better response than men to antidepressant treatment with citalopram. Unlike some other studies, we did not observe a sex difference in frequency, intensity or burden of side effects. This suggests that side effect burden was not a reason for

the lower response rate in men. Maximum citalopram dose and dose of citalopram at exit did not significantly differ by sex, which suggests that inadequate dose of citalopram was not an explanation for sex differences in remission. Further, the lower remission rate in men was not due to a difference in time on medication, since 71.7% of men and 72.0% of women had at least eight weeks of treatment with citalopram. The elimination of these potential explanations for the sex differences found in this study increases the likelihood that the explanation is a differential biological response to citalopram in women.

This study has several significant strengths not possessed by previous studies, including a large sample size, the use of well standardized independent raters (ROAs) to judge endpoints for remission, the inclusion of only outpatients who met criteria for unipolar major depression, the inclusion of patients with concurrent Axis I and III disorders or suicidality (not requiring inpatient treatment), and the examination of both response and remission. The only prior study addressing depression that used a general patient population observed no sex differences in response to sertraline (Thiels et al, 2005). In that study, measurements of depressive symptoms were taken relatively infrequently (baseline, 2 weeks, 1, 3 and 6 months), the study used a depression rating scale unique to the study, raters were not standardized and there was no documentation that participants had major depression. The clinical diagnosis of depressive episode by ICD-10 was made for only 64% of men and 66% of women. Unlike the STAR*D study, in the Thiels et al study women were significantly older than men and had an older age of onset (onset age of 48.2 years in women and 47.1 years in men). Additional differences between the Thiels et al study depressed population and the STAR*D population include the average episode length of three months vs. eight months in STAR*D and only 30% recurrent vs 75% recurrent in the STAR*D population. The Thiels et al study did not use algorithm-based treatment guidelines and thus final mean doses of sertraline were extremely low and sub therapeutic on most patients (average dose =45.5 mg for men and 46.5 mg for women). Despite the low dose of sertraline, the response rate based on the Clinical Global Impression scale was quite high in the Thiels et al study, with 85.5% of participants judged to be responders after one month of treatment. In contrast, the low overall response (46.9%) and remission rates (HRSD₁₇: 27.5%, QIDS-SR₁₆: 32.9%) in our sample, the high prevalence of recurrent depression (75%) and the median current episode length of eight months suggest that our participants were more depressed and treatment resistant than those in the Thiels et al study. Thus, the finding of a sex difference in response to citalopram, with a 33% greater likelihood of remission in women than men, has meaning for everyday clinical practice for treatment of major depression.

Although our study sample included a subset of the originally enrolled STAR*D sample (2876 of 4041), the baseline sex differences found were generally similar to those found in our report on the first 1500 participants enrolled (Marcus et al, 2005) and in our follow-up report on the remaining 2541 participants (Marcus et al, in press). Of note are the similar findings in women of greater baseline severity of depression by both clinician rating and self rating, younger age of MDD onset, and greater likelihood of past suicide attempt(s). This suggests that the subsample of participants who continued in treatment were representative of the original participants who enrolled seeking treatment for depression, and thus were representative of treatment-seeking patients with depression seen in typical clinical practice.

Our findings are opposite to those of older studies with TCAs, particularly imipramine, which frequently found a better response in men to these predominantly noradrenergic reuptake inhibitors. The sex differences in response to citalopram, an antidepressant that acts predominantly on serotonergic systems, may be related to differences in the biology of men and women, particularly with respect to the role of estrogen on serotonergic systems. Since our study did not address mechanisms by which men and women may differ in responsiveness to citalopram, we can only summarize possible differences that may account for this differential

response. Studies in non-human primates (reviewed in Bethea et al, 2002) have confirmed that estrogen 1) increases tryptophan hydroxylase, the rate-limiting step in serotonin synthesis 2) decreases 5HT_{1a} autoreceptor binding, which would serve to increase serotonin levels at the synapse and 3) modulates the serotonin transporter, which leads to increased transporter expression in the hypothalamus (Bethea et al, 2002). Furthermore, it is possible that organizational effects of estrogen on the brains of females occurring in utero and post-natally may contribute to changes in serotonin receptors to make women differentially sensitive to SSRIs. Finally the whole context of childhood and adolescent development differs between men and women, so additional cognitive and psychological factors may also contribute to the differential responsiveness to SSRIs in women.

Study limitations include the use of a single agent only (citalopram), the lack of a placebo control, and open-label treatment. Thus it is unclear if the greater responsiveness in women can be entirely ascribed to citalopram. However, a report by Casper et al. (2001) found no sex differences in depressed patients regarding response to placebo, which suggests that our finding of sex differences for citalopram might be specific to the drug or the drug class. Other limitations include the failure to measure medication adherence as well as the failure to measure concomitant non-depressive psychotherapy (e.g., couples therapy, group therapy, psychodynamic psychotherapy), although psychotherapies with documented efficacy for depression were excluded. Furthermore, psychotherapies that were permitted were those ongoing at the time of referral to the study, so it is unlikely that psychotherapy per se could explain the outcomes in the study. While differential attrition could influence the results, we did not observe sex differences in attrition (Warden et al, 2007). The study also included a number of patients with psychiatric diagnoses in addition to major depression, which may have influence outcome, particularly comorbid anxiety disorders which were more frequent in women. However, individuals with comorbid anxiety disorders demonstrated a poorer response to citalopram than those without anxiety disorders (Fava et al, 2008). Furthermore, the increased frequency of anxiety disorders was controlled for in the adjusted analysis.

In conclusion, this large multi-site study of outpatients with nonpsychotic MDD in both primary and specialty care found that women were more likely to achieve remission than men in response to citalopram. These differences occurred despite a greater baseline severity of depression in women and no sex differences in side effect frequency, intensity or burden. Sex differences in response to citalopram could not be accounted for by differences in dose of citalopram or number of treatment visits. Differences in time in treatment were not clinically important either. Such findings suggest that the greater response to SSRIs in women may be due to sex-specific biological differences.

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Number of Participants							
Male	1036	982	831	647	430	243	86
Female	1828	1702	1425	1145	796	478	189
Total	2864	2684	2256	1792	1226	721	275

Log-Rank Statistic=0.02: p=0.8926

Figure 1. Time to Remission by Sex

After adjustment for baseline differences there was no significant difference in time to remission between men and women.

Number of Participants							
Male	1023	963	754	528	332	153	57
Female	1788	1674	1246	885	550	282	100
Total	2811	2637	2000	1413	882	435	157

Log-Rank Statistic=2.81: p=0.0935

Figure 2. Time to Response by Sex

After adjustment for baseline differences, women were found to respond slightly faster to citalopram at $p=.09$.

Table 1

Baseline Characteristics, N=2876

Baseline Characteristics		%
Setting		
Primary Care		37.9
Specialty Care		62.1
Race		
White		75.8
Black or African American		17.6
Other		6.6
Ethnicity-Hispanic		13.0
Sex-Female		63.7
Marital Status		
Never Married		28.7
Married		41.7
Divorced		26.5
Widowed		3.1
Employment Status		
Unemployed		38.2
Employed		56.2
Retired		5.6
Family History of Depression		55.6
Baseline Characteristics	Mean (SD)	Median (observed Range)
Age	40.8(13.0)	40(18-75)
Education (Years of Schooling)	13.4(3.2)	13(0-27)
Income (\$/month)	2358(3030)	1600(0-50000)
General Medical Comorbidities		
Categories endorsed	3.1(2.3)	3(0-11)
Total Score	4.4(3.7)	4(0-22)
Severity Index	1.2(0.6)	1.2(0-4)
Age at onset of 1 st MDE episode	25.3(14.4)	21(2-74)
Number of MDE episodes	5.5(9.2)	3(1-99)
Length of current MDE episode (Months)	24.6(51.7)	8(0-670)
Length of illness (Years)	15.5(13.2)	12(0.5-64)
HRSD ₁₇ (ROA)	21.8(5.2)	21(14-40)
IDS-C ₃₀ (ROA)	38.6(9.6)	38(12-70)
QIDS-SR ₁₆	16.2(4.0)	16(3-27)

Baseline Characteristics	%
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MDE: Major Depressive Episode, HRSD₁₇: 17-item Hamilton Rating Scale for Depression, ROA: Research Outcomes Assessor, IDS-C₃₀: 30-item Inventory of Depressive Symptomatology – Clinician-rated, QIDS-SR₁₆: 16-item Quick Inventory of Depressive Symptomatology – Self-Rated

Table 2
Baseline Demographic Characteristics by with Sex

Demographic Characteristics	Sex		p-value
	Male N=1043 (36.3%)	Female N=1833 (63.7%)	
	%	%	
Setting			<.0001
Primary Care	31.3	41.7	
Specialty Care	68.7	58.3	
Race			0.0219
White	78.7	74.1	
African American	15.3	18.9	
Others	6.0	7.0	
Ethnicity-Hispanic			<.0001
No	91.5	84.5	
Yes	8.5	15.5	
Marital status			<.0001
Never Married	29.5	28.2	
Married	44.6	40.1	
Divorced	24.6	27.6	
Widowed	1.3	4.1	
Employment status			0.0006
Unemployed	36.8	39.1	
Employed	55.4	56.6	
Retired	7.8	4.3	
Insurance Status			<.0001
Private insurance	49.6	51.9	
Public insurance	9.5	17.0	
No insurance	40.9	31.1	
Family Hx. of Depression	49.8	58.8	<.0001
Family Hx. of Alcohol Abuse	38.5	43.1	0.0181
Family Hx. of Drug Abuse	21.6	25.9	0.0099
Family Hx. of suicide ^a	2.8	4.0	0.0986
Attempted Suicide	12.9	20.8	<.0001
Present Suicide Risk	2.9	3.2	0.6611
Age at onset			<.0001
<18 years	31.5	41.5	
≥18 years	68.5	58.5	
Anxious Features	50.8	54.6	0.0533
Atypical Features	14.7	21.2	<.0001
Melancholic Features	25.9	22.1	0.0215

Demographic Characteristics	Sex		p-value
	Male N=1043 (36.3%)	Female N=1833 (63.7%)	
	%	%	
Chronic Depression ^b	25.4	25.2	0.8668
Recurrent Depression	75.0	76.1	0.5223
Psychiatric Comorbidity			
Anxiety Disorder	18.6	26.5	<.0001
OCD	15.5	13.6	0.1738
Panic	11.3	14.1	0.0384
Social Phobia	28.4	33.0	0.0098
PTSD	19.8	21.0	0.4420
Agoraphobia	11.0	12.2	0.3453
Alcohol Abuse	18.0	8.7	<.0001
Drug Abuse	10.3	5.7	<.0001
Somatoform	1.0	3.2	0.0004
Hypochondriasis	3.4	5.0	0.0432
Bulimia	6.8	16.6	<.0001
	Mean(SD)	Mean(SD)	
Age (years)	42.6(12.7)	39.8(13.1)	<.0001
Years of Schooling	13.7(3.0)	13.3(3.4)	0.0012
Income (\$/month)	2486(3411)	2285(2790)	0.9760
CIRS			
Categories endorsed	3.1(2.3)	3.1(2.3)	0.9195
Total Score	4.6(4.0)	4.3(3.6)	0.0585
Severity Index	1.2(0.6)	1.2(0.6)	0.1571
Symptom Severity			
HRSD ₁₇	21.6(5.1)	21.9(5.2)	0.0667
IDS-C ₃₀	37.5(9.2)	39.2(9.7)	<.0001
QIDS-SR ₁₆	15.6(3.9)	16.5(4.0)	<.0001
	Median(IQR)	Median(IQR)	
Number of episodes	3(6-1)	3(5-1)	0.0030
Length of current Episode (months)	8(24-3)	8(24-3)	0.9124
Length of illness(years)	12(26-4)	12(23-4)	0.3614

^aDefined by self-report.

^b≥2 years in the index episode.

CIRS: Cumulative Illness Rating Scale, HRSD₁₇: 17-item Hamilton Rating Scale for Depression, IDS-C₃₀: 30-item Inventory of Depressive Symptomatology – Clinician-rated, QIDS-SR₁₆: 16-item Quick Inventory of Depressive Symptomatology – Self-Rated, IQR: Inter-Quartile Range

Table 3

Outcomes by Sex

Outcome	Sex			Total N=2876	Unadjusted		Adjusted ¹
	Men N=1043 (36.3%)	Women N=1833 (63.7%)	%		Odds Ratio	p-value	
HRSD ₁₇ Remission	24.1	29.4	27.5		1.31	0.0021	1.33
QIDS-SR ₁₆ Remission	31.3	33.7	32.9		1.12	0.1842	1.15
QIDS-SR ₁₆ Response	44.0	48.5	46.9		1.20	0.0202	1.13
							0.2140
							0.0103
							0.1788

Outcome	Sex			Total N=2876	Unadjusted		Adjusted ¹
	Men N=1043 (36.3%)	Women N=1833 (63.7%)	%		Odds Ratio	p-value	
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QIDS-SR ₁₆ Response	44.0	48.5	46.9		1.20	0.0202	1.13
							0.2140
							0.0103
							0.1788

¹ adjusted for Regional center, clinical setting, race, Hispanic, marital status, employment status, insurance status, family history of depression, attempted suicide, age at onset class, anxiety disorder, panic, social phobia, alcohol abuse, drug abuse, age, schooling, number of episodes and base QIDS-SR₁₆.

HRSD₁₇: 17-item Hamilton Rating Scale for Depression, QIDS-SR₁₆: 16-item Quick Inventory of Depressive Symptomatology – Self-Rated

Table 4
Treatment Characteristics in Relation to Symptomatic Outcome by Sex

Dose and treatment	Sex						p-value
	Men N=1043 (36.3%)			Women N=1833 (63.7%)			
	Total N=2876						
	n	%	n	%	N	%	
Maximum dose of Citalopram (mg/day)							
< 20	16	1.5	47	2.6	61	2.2	
20-39	245	23.6	449	24.5	694	24.2	
40-49	299	28.7	563	30.8	862	30.1	
≥ 50	480	46.2	770	42.1	1250	43.5	
Dose of citalopram at study exit (mg/day)							
< 20	30	2.9	75	4.1	105	3.7	
20-39	273	26.3	511	27.9	784	27.3	
40-49	301	28.9	556	30.4	857	29.9	
≥ 50	436	41.9	687	37.6	1123	39.1	
Time in treatment (weeks)							
<4	100	9.6	223	12.2	323	11.2	
≥4 but <8	145	18.7	290	15.8	485	16.9	
≥8	748	71.7	1320	72.0	2068	71.9	
	Mean	SD	Mean	SD	Mean	SD	
Number of visits	4.8	1.4	4.8	1.6	4.8	1.5	
Time to first treatment visit (weeks)	2.3	1.1	2.4	1.1	2.3	1.1	
Time in treatment (weeks)	9.8	3.9	10.2	4.3	10.0	4.2	
Time from final dose to study exit (weeks)	5.1	4.1	5.1	3.9	5.1	4.0	

Table 5

Adverse Events, side effects by Sex

Side effects, adverse events	Sex						p-value
	Male N=1043(36.3%)			Women N=1833(63.7%)			
	n	%	n	%	n	%	
Maximum SE Frequency							
None	153	14.7	295	16.2	448	15.7	0.1770
10%-25% of the time	276	26.5	532	29.2	808	28.2	
50%-75% of the time	343	33.0	571	31.4	914	32.0	
90%-100% of the time	268	25.8	423	23.2	691	24.1	
Maximum SE Intensity							
None	151	14.5	291	16.0	442	15.5	0.1184
Trivial	273	26.3	520	28.6	793	27.7	
Moderate	432	41.5	741	40.7	1173	41.0	
Severe	184	17.7	269	14.7	453	15.8	
Maximum SE Burden							
No impairment	190	18.3	393	21.6	583	20.4	0.0668
Minimal-mild impairment	429	41.2	745	40.9	1174	41.0	
Moderate-marked impairment	320	30.8	544	29.9	864	30.2	
Severe impairment-unable to function	101	9.7	139	7.6	240	8.4	
Serious Adverse Events							
Death, non-suicide	50		66	3.6	116	4.0	0.1179
	2		1		3		
Hospitalization for GMCs	25		33		58		
Medical illness without hospitalization	1		3		4		
Psychiatric hospitalization(substance abuse)	5		3		8		
Psychiatric hospitalization(suicidal ideation)	12		24		36		
Psychiatric hospitalization (worsening depression)	3		3		6		
Psychiatric hospitalization(other)	0		2		2		
Suicidal ideation (without hospitalization)	4		2		6		
Any Psychiatric Serious Adverse Events	23	2.2	34	1.9	57	2.0	
						0.5170	

Side effects, adverse events	Sex				Total N=2876	p-value
	Male N=1043(36.3%)		Women N=1833(63.7%)			
	n	%	n	%		
Intolerance	191	18.3	299	16.3	17.0	0.1701

SE: Side Effect, GMCs: General Medical Conditions