Do Depressed Patients With Diabetes Experience More Side Effects When Treated With Citalopram Than Their Counterparts Without Diabetes? A STAR*D Study

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Objective: Diabetes mellitus (DM) is often comorbid with major depressive disorder, yet the impact and types of side effects experienced by patients with DM receiving antidepressant treatment have not been examined. This study examined antidepressant treatment side effects in depressed patients with and without DM to determine whether side effects differed between groups.

Method: From July 2001 through April 2004, the Sequenced Treatment Alternatives to Relieve Depression study enrolled 2,876 outpatients with *DSM-IV* major depressive disorder from primary and psychiatric care settings. The current study compared participants with and without DM regarding frequency, intensity, and burden of side effects—using the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)—and types of side effects experienced when treated with citalopram (12–14 weeks, 20–60 mg/d).

Results: There was no statistically significant difference in the maximum rating of side effects during treatment between participants with and without DM. At the last clinic visit, participants with DM reported fewer and less intense side effects and less impairment from side effects than those without DM (after adjustment for confounding effects of age, race, Hispanic ethnicity, employment status, family history of depression, anxious depression, atypical depression, age at first major depressive episode, and length of illness). However, those with DM had more side effect symptoms consistent with the diagnosis of DM (eg, blurred vision and tremors).

Conclusions: Participants with DM reported experiencing side effects at lower rates than those without DM. After statistical adjustment, the groups did not differ significantly regarding types of side effects experienced.

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Major depressive disorder (MDD) is a serious mental health problem that affects approximately 16 million individuals in the United States.[1] Current estimates show that the majority of these individuals receive little or no treatment.[2] Major depressive disorder is associated with high morbidity and mortality,[3] profound mental and physical impairment, and losses in work productivity, which can result in high indirect and direct societal costs.[2]

Major depressive disorder often occurs concurrently with serious medical comorbidities, such as cancer and diabetes mellitus (DM). Previous studies reported that individuals with DM are twice as likely to have MDD as are individuals without DM.[4–6] The presence of major depressive disorder in patients with diabetes is a significant public health burden and is associated with hyperglycemia, increased diabetic complications and mortality,[7] increased costs, and poorer adherence to a healthy diet and regular exercise.[8] In addition, patients with diabetes and comorbid depression appear to experience more physical symptoms associated with diabetes than their nondepressed counterparts.[9] Because MDD can be a risk factor for nonadherence with medical treatment,[10] the appropriate treatment of MDD when it occurs concurrently with DM takes on increased importance since improvement in mood may improve glycemic control.

Selective serotonin reuptake inhibitors (SSRIs) are the most common antidepressants prescribed for the treatment of MDD. These drugs have revolutionized MDD treatment with advantages that include a better safety profile, benign side effects, a reduction in the likelihood of fatal cardiac events, ease of dose titration,[11] and lower discontinuation rates.[12] Tricyclic antidepressants and SSRIs have similar therapeutic effects; however, SSRIs have been reported to have a longer time to

CLINICAL POINTS

- Participants with diabetes mellitus reported experiencing side effects from citalopram treatment at lower frequencies compared to those without diabetes mellitus.
- Participants with and without diabetes mellitus differed, but not significantly, in the types of side effects reported.

response (4–6 weeks) before changes in depression severity are observed.[13]

The safety and efficacy of the SSRI citalopram have been reported in a large number of controlled clinical trials over the past 10 years.[11] These studies have shown that citalopram is a reliable, effective antidepressant that can be used safely in many patient populations (eg, the elderly).[14] Citalopram has also been shown to be effective in preventing the relapse and recurrence of MDD.[15] The most common side effects associated with citalopram treatment are sleep disturbances, gastrointestinal disturbances (eg, nausea and vomiting), excessive sweating, headache, sexual dysfunction, and tremors. Citalopram was also included in the US Food and Drug Administration's black box warning for suicidality in pediatric use of antidepressants.[16]

Side effects often occur during treatment with antidepressants. Side effects can have a detrimental impact on patient adherence to treatment and can cause increased attrition in controlled studies.[17,18] Further, clinicians need to understand and anticipate the impact of adverse events reported by depressed patients. When treating depression, clinicians must engage in a delicate balancing act, as they must not only anticipate and manage side effects but also determine the optimal dose of antidepressants required to effect sustained MDD remission.

Given that individuals with MDD are twice as likely to have comorbid DM,[4–6] it would be useful to know whether side effects from citalopram treatment differ in depressed patients with and without DM. Such information would help clinicians to adapt existing treatment modalities to individual patient needs and to better educate patients about what to expect during treatment, thus increasing the probability of patient adherence to the MDD treatment regimen.

To date, only 5 controlled studies on the effect of antidepressant medication[19–21] and/or psychotherapeutic treatments[22,23] on depression in patients with DM have been reported in the scientific literature. These studies focused on the treatment of MDD in patients with DM and on improving glycemic control. Since then, 1 open-label study has demonstrated not only improved depression outcomes with antidepressant treatment, but also improved glycemic control during both acute and maintenance treatment phases.[24] The frequency and type of side effects from antidepressant treatment were not discussed in these reports.

In this current study, we report on the results of a secondary analysis of data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, in which we sought to determine whether side effects from citalopram treatment differ in depressed patients with and without DM. The STAR*D study is the largest antidepressant medication trial conducted in the United States to date. The study used a measurement-based care approach and an automated feedback system to ensure adequate and safe antidepressant treatment delivery suitable for both clinical research and routine practice.[25] The implementation of measurement-based care ensured that antidepressant medication treatment was optimal regarding dose and duration, yet flexible enough to ensure safety given the wide range of comorbid general medical and psychiatric disorders allowed in the trial.

The STAR*D study offered a unique opportunity to examine the differences in side effects reported by patients with nonpsychotic MDD with and without DM who were treated with citalopram. To our knowledge, this is the first study to examine the frequency, intensity, and burden of side effects along with a characterization of the types of side effects experienced by depressed outpatients with and without DM who were being treated for nonpsychotic MDD in both primary and psychiatric care settings.

METHOD

Study Population

Description of STAR*D. Study participants were identified from 4,041 participants enrolled in the STAR*D study from July 2001 through April 2004. The STAR*D study was a multisite, prospective series of clinical trials designed to examine the effectiveness of various pharmacotherapeutic and/or psychotherapeutic antidepressant treatment options in outpatients with unipolar, nonpsychotic MDD who did not respond to initial and subsequent treatments at either primary or psychiatric care clinic settings. The methodology of STAR*D has been described in greater detail elsewhere.[26,27]

Broad inclusion and minimal exclusion criteria were used to recruit a representative sample for the STAR*D study from primary and psychiatric care clinics across the United States. A diagnosis of MDD was confirmed by a review of *DSM-IV* checklist criteria at study baseline and a score ≥ 14 on the 17-item Hamilton Depression Rating

Scale (HDRS-17)[28,29] gathered by the clinical research coordinators at study entry.

Participant safety and study data management processes were monitored by the STAR*D National Coordinating Center (University of Texas Southwestern Medical Center, Dallas), Data Coordinating Center (Epidemiology Data Center, University of Pittsburgh, Pennsylvania), and the Data Safety Monitoring Board at the National Institute of Mental Health (NIMH, Bethesda, Maryland). An internal reporting system was developed to monitor all serious adverse events (SAEs). The Data Safety Monitoring Board at the NIMH monitored the resolution of all SAEs.

All eligible, consented participants were enrolled in the first level of antidepressant treatment (STAR*D level 1) and received citalopram (20–60 mg/d) for up to 14 weeks, with evaluations conducted in up to 6 postbaseline clinic visits (weeks 2, 4, 6, 9, and 12 and a potential week 14 visit). This report is based on the experiences related to citalopram observed among participants during this initial phase of the STAR*D trial. An evaluable sample of the enrolled participants (N = 2,876) was used in this report. The development of this sample is described in detail elsewhere.[25]

Measurement-based care. A systematic approach to treatment, or measurement-based care, was implemented in order to standardize care across all STAR*D clinics (both primary and psychiatric care).[25] The STAR*D participants were routinely evaluated at every clinic visit for ratings of depressive symptom severity and side effect frequency, intensity, and burden. The measurement-based care system used the following: (1) guided medication dose adjustments and treatment duration, (2) documented clinician adherence to treatment recommendations, and (3) prompt feedback to clinicians to enhance appropriate treatment decisions. This system ensured adequate and safe antidepressant treatment delivery suitable for both clinical research and routine practice.[30]

Clinical Assessments

The clinical research coordinators collected sociodemographic, medical, and psychiatric history data (both personal and familial) at study entry. Data on prescribed nonstudy medications were collected at study entry using the non-STAR*D medication log. The primary outcome measure of depression severity was the HDRS-17 administered at baseline by independent, blinded research outcome assessors who also obtained the 30-item Inventory of Depressive Symptomatology-Clinician Rating (IDS-C-30)[31,32] by telephone interview within 72 hours of study entry. Responses to individual items on the HDRS-17 or the IDS-C-30 were used to determine the presence of anxious features,[33] atypical features,[34] and melancholic features.[35]

The HDRS-17 and the IDS-C-30 were also administered by the research outcome assessor at the completion of citalopram treatment (within 12–14 weeks postentry). The 16-item Quick Inventory of Depressive Symptomatology-Clinician Rating (QIDS-C-16)[36,37] was obtained by the clinical research coordinators at study entry and at all successive clinic visits to measure treatment response and inform clinical decision making. Participants also completed the 16-item QIDS–Self-Rated (QIDS-SR-16)[37] at each clinic visit to measure outcomes.

The clinical research coordinators completed the 14-item Cumulative Illness Rating Scale (CIRS)[38,39] to assess the comorbidity and severity of general medical conditions. Each of the 14 general medical condition categories of the CIRS was assessed using a 5-point scale (0–4; 0 = no impairment and 4 = extremely severe/immediate treatment required). The CIRS total score was calculated by adding the scores for 12 of the 14 categories, excluding the endocrine category (which was used in the definition of DM in this report) and the psychiatric illness category.

A telephone-based interactive voice response system was used to collect self-report data on participant life enjoyment and satisfaction using the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire,[40] on physical and mental function using the 12-item Short-Form Health Survey,[41] and on work productivity using the 6-item Work and Social Adjustment Scale[42] and the 5-item Work, Productivity, and Activity Impairment scale.[43] These data were collected at study entry, at week 6, and at the completion of citalopram treatment.

Side Effects

The frequency, intensity, and burden of the side effects of citalopram treatment were documented using the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER).[44] Study participants completed this measure at each postbaseline clinic visit. The FIBSER is composed of three 7-point subscales that measure the frequency, intensity, and burden of side effects, respectively. For this report, the maximum-reported ratings of side effects during citalopram treatment and the side effects level reported at the last clinic visit were used.

The Patient-Rated Inventory of Side Effects (PRISE)[26] was also completed by participants at each postbaseline clinic visit. This instrument was used to categorize any common side effects experienced in 8 organ systems. Within each organ system, specific side effects and the severity (eg, tolerable, distressing) of the worst side effect were reported. For this report, the side effects reported by participants at the last clinic visit were used.

Diabetes Classification

The DM status of participants was classified on the basis of information available in the CIRS and medication logs. An individual was considered to have DM if 1 or both of the following criteria were met: (1) diabetes had been reported on the CIRS and (2) the participant reported

use of oral hypoglycemic medication and/or insulin at baseline (recorded in the medication log).

No distinction was made between the types of DM. A medical chart review was conducted at 1 clinical site to evaluate the accuracy of participant self-report data (STAR*D research data) and medical evaluation data (medical chart review).

Statistical Analysis

Descriptive statistics, including means and standard deviations, were calculated for continuous variables, and percentages were calculated for categorical variables. Statistical differences in the discrete baseline characteristics between participants with and without DM were determined using the χ^2 statistic and the Fisher exact test. Statistical differences in the continuous baseline characteristics between participants with and without DM were determined using the Student *t* test or the Wilcoxon test.

Because of the ordinal outcomes, multinomial logistic regression was used to test the significance of the maximum frequency, intensity, and burden of side effect ratings reported in level 1 treatment with citalopram and reported at the last clinic visit, as well as type of side effect reported, adjusted for characteristics that were significantly different between participants with and without DM. For each characteristic, 2 adjusted analyses were performed—1 without and another with the CIRS summary score. This analysis was done to address the multiorgan system impact of DM. Survival analyses (ie, Kaplan-Meier curves and the log-rank test) were used to examine the differences between participants with and without DM regarding time to first occurrence of the following side effect features: frequency ≥ 50% of the time, intensity of at least moderate level, and burden of at least moderate impairment. Statistical significance for all tests was set at $P < .05$ (2 sided). No adjustments were made for multiple comparisons; so, the reader must interpret accordingly.

RESULTS

The sociodemographic and clinical characteristics of participants with and without DM are shown in Table 1. A total of 235 participants were classified as having DM. Compared to those without DM, significantly larger proportions of participants with DM were black (27% vs 17%, $P = .0003$), Hispanic (20% vs 12%, $P = .0004$), unemployed (52% vs 37%, $P < .0001$), or married (49% vs 41%, $P < .0001$). In addition, participants with DM were, on average, older (mean ± SD = 50.4 ± 10.4 vs 39.9 ± 12.9 years, $P < .0001$) and reported fewer years of education (12.4 ± 3.8 vs 13.5 ± 3.2 years, $P < .0001$). They also reported significantly more general medical comorbidities, excluding DM (6.6 ± 3.8 vs 3.8 ± 3.3, $P < .0001$). Participants with DM were also more likely to be treated in primary care settings (56% vs 36%, $P < .0001$); were, on average, older at the onset of their first MDD episode (31.4 ± 16.5 vs 24.8 ± 14.0 years, $P < .0001$); and reported a longer current MDD episode (31.1 ± 65.5 vs 23.9 ± 50.3 months, $P = .0049$) than those without DM. Depression severity, as measured using the HDRS-17, IDS-C-30, QIDS-C-16, and QIDS-SR-16, did not differ significantly between patients with and without DM. However, participants with DM reported a higher prevalence of atypical (24% vs 18%, $P = .0402$) and anxious features (64% vs 52%, $P = .0007$).

Citalopram treatment characteristics did not substantially differ between the 2 groups (Table 2). Upon entry into level 1, STAR*D participants with DM were seen for a mean ± SD of 4.8 ± 1.5 visits and those without DM for 4.9 ± 1.5 visits ($P = .2031$). Patients with DM had approximately the same number of weeks in treatment with citalopram as did participants without DM (10.5 ± 4.0 vs 10.0 ± 4.2, $P = .0546$). Participants with and without DM did not differ in maximum citalopram dosage (mg/d) (45.4 ± 15.8 vs 43.6 ± 16.2, $P = .0994$) or time to first citalopram treatment visit (weeks) (2.5 ± 1.5 vs 2.3 ± 1.1, $P = .0566$). Comparisons of citalopram treatment response between the 2 participant groups will be reported in a forthcoming article.

The frequency, intensity, and burden of side effects by DM status are presented in Table 3. In general, those with DM reported fewer side effects (frequency) and reported experiencing side effects at lower intensities and at lower levels of impairment. However, the differences were greater between participants with and without DM at the last clinic visit than at the point of the maximum-reported measurement, and these differences were statistically significant after adjustment for potential confounders. The odds for lower levels of side effect frequency, intensity, and burden were greater in those with DM compared to those without DM at the last clinic visit and were significant after adjustment for confounding factors. Compared to participants without DM, those with DM were 1.35 times more likely to report side effects at a lower rate, 1.34 times more likely to report side effects at a lower intensity, and 1.45 times more likely to report that they either had no impairment or minimal-to-mild impairment from side effects due to depression treatment.

Figure 1 shows Kaplan-Meier curves for the times to first report of side effects that occurred ≥ 50% of the time for participants with and without DM. Participants with DM reported experiencing a later onset of side effects that occurred ≥ 50% of the time ($\chi^2_1 = 8.07$, $P = .0045$). Figures 2 ($\chi^2_1 = 3.59$, $P = .0581$) and 3 ($\chi^2_1 = 1.85$, $P = .1743$) show Kaplan-Meier curves for the times to first report of side effects of at least moderate intensity and side effects resulting in at least moderate impairment,

Table 1. Baseline Characteristics by Diabetes Status

Characteristic	Diabetic (n = 235)	Nondiabetic (n = 2,641)	*P* Value[a]
Gender, n (%)			.1271
Male	96 (41)	947 (36)	
Female	139 (59)	1,694 (64)	
Race, n (%)			**.0003**
White	162 (69)	2,018 (76)	
Black	63 (27)	443 (17)	
Other[b]	10 (4)	180 (7)	
Hispanic, n (%)			**.0004**
No	187 (80)	2,316 (88)	
Yes	48 (20)	325 (12)	
Employment, n (%)			**< .0001**
Employed	88 (37)	1,525 (58)	
Unemployed	122 (52)	976 (37)	
Retired	25 (11)	136 (5)	
Marital status, n (%)			**< .0001**
Never married	40 (17)	783 (30)	
Married	115 (49)	1,084 (41)	
Divorced/separated	64 (27)	698 (26)	
Widowed	16 (7)	73 (3)	
Setting, n (%)			**< .0001**
Primary	131 (56)	960 (36)	
Specialty	104 (44)	1,681 (64)	
Insurance, n (%)[c]			**< .0001**
Private	109 (47)	1,316 (51)	
Public	55 (24)	342 (13)	
None	65 (28)	903 (35)	
Family history of depression, n (%)[d]			**< .0001**
No	137 (58)	1,131 (43)	
Yes	98 (42)	1,487 (57)	
Family history of suicide, n (%)[e]			.6009
No	228 (97)	2,514 (96)	
Yes	7 (3)	95 (4)	
Anxious features, n (%)			**.0007**
No	85 (36)	1,261 (48)	
Yes	150 (64)	1,380 (52)	
Atypical features, n (%)[f]			**.0402**
No	179 (76)	2,155 (82)	
Yes	56 (24)	485 (18)	
Melancholic features, n (%)[f]			.2493
No	187 (80)	2,013 (76)	
Yes	48 (20)	627 (24)	
Psychiatric comorbidities, n (%)[g]			.4870
0	76 (33)	904 (35)	
1	71 (31)	678 (26)	
2	31 (13)	435 (17)	
3	22 (10)	236 (9)	
4+	29 (13)	335 (13)	
Age, mean (SD), y	50.4 (10.4)	39.9 (12.9)	**< .0001**
Education, mean (SD), y	12.4 (3.8)	13.5 (3.2)	**< .0001**
Household income, mean (SD) (monthly US $)	1,991 (2,610)	2,388 (3,061)	.0036
General medical comorbidities, mean (SD)			
CIRS total score (excluding diabetes)	6.6 (3.8)	3.8 (3.3)	**< .0001**
Clinical characteristics, mean (SD)			
Age at first MDE, y	31.4 (16.5)	24.8 (14.0)	**< .0001**
Length of episode, mo	31.1 (65.5)	23.9 (50.3)	**.0049**
Length of illness, y	19.0 (15.4)	15.2 (12.9)	**.0016**
No. of MDEs	6.2 (10.6)	5.4 (9.1)	.8368
Depression severity at baseline, mean (SD)			
HDRS-17 total score	22.0 (5.2)	21.8 (5.2)	.4567
IDS-C-30 total score	38.9 (10.3)	38.5 (9.5)	.4942
QIDS-C-16 total score	16.8 (3.2)	16.9 (3.2)	.5460
QIDS-SR-16 total score	16.2 (4.2)	16.2 (4.0)	.9202

[a]Bolded values indicate statistical significance.
[b]Other = multiracial, Native American, Alaskan/Pacific Islander, and Asian American.
[c]Data missing for 86 patients.
[d]Data missing for 23 patients.
[e]Data missing for 32 patients.
[f]Data missing for 1 patient.
[g]Data missing for 59 patients.
Abbreviations: CIRS = Cumulative Illness Rating Scale, HDRS-17 = 17-item Hamilton Depression Rating Scale, IDS-C-30 = 30-item Inventory for Depressive Symptomatology-Clinician Rating, MDE = major depressive episode, QIDS-C-16 = 16-item Quick Inventory for Depressive Symptomatology-Clinician Rating, QIDS-SR-16 = 16-item Quick Inventory for Depressive Symptomatology–Self-Rated.

Table 2. Treatment Characteristics in Relation to Symptomatic Outcome by Diabetes Status

Dose and Treatment	Diabetic (n = 235)	Nondiabetic (n = 2,641)	Total (N = 2,876)	*P* Value
Maximum dose of citalopram, n (%)[a]				.4742
< 20 mg/d	3 (1.3)	60 (2.3)	63 (2.2)	
20–39 mg/d	50 (21.5)	644 (24.4)	694 (24.2)	
40–49 mg/d	70 (30.0)	792 (30.1)	862 (30.1)	
≥ 50 mg/d	110 (47.2)	1,140 (43.2)	1,250 (43.5)	
Dose of citalopram at study exit, n (%)[a]				.6125
< 20 mg/d	7 (3.0)	98 (3.7)	105 (3.7)	
20–39 mg/d	58 (24.9)	726 (27.6)	784 (27.3)	
40–49 mg/d	68 (29.2)	789 (29.9)	857 (29.9)	
≥ 50 mg/d	100 (42.9)	1,023 (38.8)	1,123 (39.1)	
Time in treatment, n (%)				.1789
< 4 wk	18 (7.7)	305 (11.5)	323 (11.2)	
≥ 4 but < 8 wk	39 (16.6)	446 (16.9)	485 (16.9)	
≥ 8 wk	178 (75.7)	1,890 (71.6)	2,068 (71.9)	
No. of visits, mean (SD)	4.9 (1.5)	4.8 (1.5)	4.8 (1.5)	.2031
Time to first treatment visit, mean (SD), wk	2.5 (1.5)	2.3 (1.1)	2.3 (1.1)	.0566
Time in treatment, mean (SD), wk	10.5 (4.0)	10.0 (4.2)	10.0 (4.2)	.0546
Time from final dose to study exit, mean (SD), wk	5.4 (5.4)	5.1 (3.8)	5.1 (4.0)	.7138

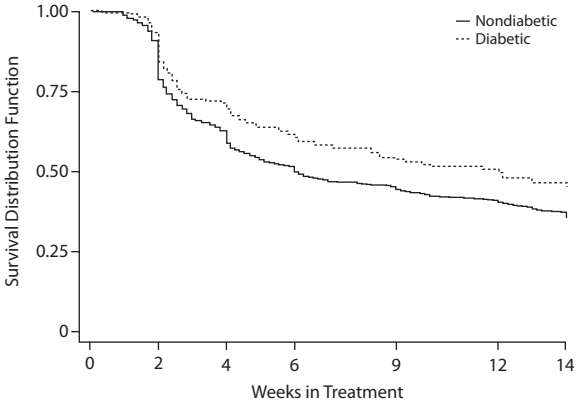
[a]Data missing for 7 patients.

Table 3. Frequency, Intensity, and Burden of Side Effects by Diabetes Status (maximum reported during treatment and at last clinic visit) Using the Frequency, Intensity, and Burden of Side Effects Rating Scale

			Maximum Reported During Treatment					
Side Effect Measure, %	Diabetic (n = 235)	Nondiabetic (n = 2,641)	OR Unadjusted	*P* Value[a]	OR Adjusted[b]	*P* Value[a]	OR Adjusted[c]	*P* Value[a]
Side effect frequency			1.29	**.034**	1.19	.162	1.19	.183
None	22	15						
10%–25% of the time	29	28						
50%–75% of the time	24	33						
90%–100% of the time	25	24						
Side effect intensity			1.20	.144	1.16	.274	1.14	.312
None	21	15						
Trivial	26	28						
Moderate	36	41						
Severe	17	16						
Side effect burden			1.16	.245	1.21	.145	1.19	.186
No impairment	24	20						
Minimal-mild impairment	40	41						
Moderate-marked impairment	26	31						
Severe impairment–unable to function	9	8						
			Reported at Last Clinic Visit in Level 1 (citalopram) Treatment					
Side effect frequency			1.43	**.006**	1.37	**.020**	1.35	**.029**
None	53	42						
10%–25% of the time	23	30						
50%–75% of the time	11	16						
90%–100% of the time	13	12						
Side effect intensity			1.41	**.008**	1.37	**.021**	1.34	**.034**
None	53	42						
Trivial	21	28						
Moderate	14	20						
Severe	11	9						
Side effect burden			1.46	**.004**	1.47	**.007**	1.45	**.009**
No impairment	58	48						
Minimal-mild impairment	26	32						
Moderate-marked impairment	11	15						
Severe impairment–unable to function	5	5						

[a]Bolded values indicate statistical significance.
[b]Adjusted using age, race, Hispanic ethnicity, employment status, family history of depression, presence of anxious depression, atypical depression, age at first major depressive episode, and length of illness (adjusted CIRS score was not included).
[c]Adjusted using age, race, Hispanic ethnicity, CIRS total score (without endocrine and psychiatric illness categories), employment status, family history of depression, presence of anxious depression, atypical depression, age at first major depressive episode, and length of illness.
Abbreviations: CIRS = Cumulative Illness Rating Scale, OR = odds ratio.

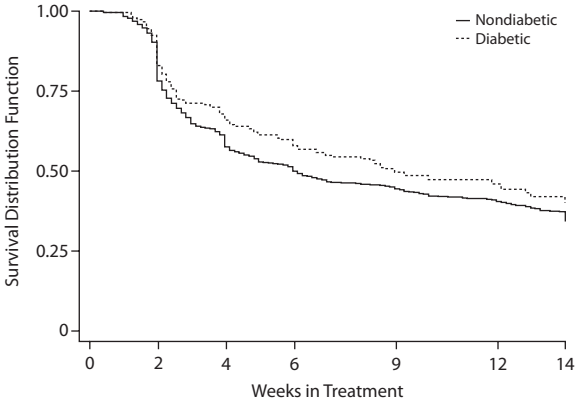
Figure 1. Time to Side Effects Occurring ≥ 50% of the Time by Diabetes Status[a]



	Weeks in Treatment						
N at Risk	0	2	4	6	9	12	14
Diabetic	232	213	158	130	103	66	24
Nondiabetic	2,629	2,373	1,550	1,183	923	595	226
Total	2,861	2,586	1,708	1,313	1,026	661	250

[a]Log-rank statistic = 8.07, $P = .0045$.

Figure 2. Time to Side Effects of at Least Moderate Intensity by Diabetes Status[a]



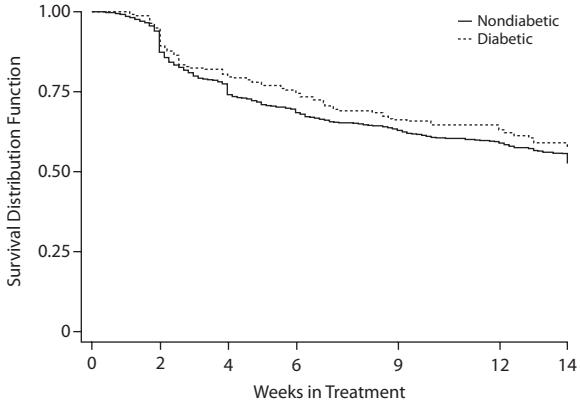
	Weeks in Treatment						
N at Risk	0	2	4	6	9	12	14
Diabetic	232	211	150	124	94	60	20
Nondiabetic	2,629	2,350	1,514	1,177	920	598	225
Total	2,861	2,561	1,664	1,301	1,014	643	245

[a]Log-rank statistic = 3.59, $P = .0581$.

respectively, for participants with and without DM. Neither showed a statistically significant difference between groups.

The types of side effects reported at the last clinic visit (grouped by organ system) are shown in Table 4. Larger proportions of participants with DM reported gastrointestinal disturbances (67% vs 56%), heart symptoms (40% vs 30%), skin symptoms (52% vs 43%), eye and ear problems (49% vs 30%), and genital/urinary symptoms (37% vs 26%). However, the differences in the proportion of individuals with DM reporting these types of side effects was not statistically significant after adjustment for confounders (including the CIRS score).

Figure 3. Time to Side Effects of at Least Moderate Impairment by Diabetes Status[a]



	Weeks in Treatment						
N at Risk	0	2	4	6	9	12	14
Diabetic	232	218	180	124	122	86	33
Nondiabetic	2,629	2,443	1,900	1,581	1,276	829	316
Total	2,861	2,661	2,080	1,736	1,398	915	349

[a]Log-rank statistic = 1.85, $P = .1743$.

DISCUSSION

To our knowledge, the current study is the first to examine side effects in outpatients with and without DM who were receiving treatment for MDD. This was the first study to assess the frequency, intensity, and burden of side effects due to citalopram treatment (FIBSER) and to characterize the symptoms experienced while receiving depression treatment (PRISE). We found that, overall, participants with DM reported experiencing side effects due to citalopram at lower frequencies and later than those without DM at the last clinic visit in level 1 (after adjustment for confounders). The STAR*D participants with DM also reported lower rates of side effects of at least moderate intensity and lower rates of side effects resulting in at least moderate impairment than those without DM. However, there were no significant differences in any of the treatment characteristics (eg, citalopram dose and number of clinic visits) between the 2 participant groups. Also, participants with DM reported experiencing a greater proportion of side effects in 7 of 8 organ systems (eg, gastrointestinal and skin). However, this difference was not statistically significant after adjustment for potential confounders.

There have been 6 studies (5 controlled[19–23] and 1 open label[24]) that focused on the treatment of MDD in patients with DM. Four of these studies have shown consistently that patients with DM and MDD respond favorably to antidepressant pharmacotherapeutic/psychotherapeutic

Table 4. Reported Side Effects (categorized by organ systems) by Diabetes Status at the Last Clinic Visit While Taking Citalopram

Reported Side Effects (presence), %	Diabetic (n = 235)	Nondiabetic (n = 2,641)	OR	*P* Value[a]	OR[b]	*P* Value[a]	OR[c]	*P* Value
Gastrointestinal	67	56	1.58	**.0015**	1.16	.3448	1.03	.8468
Diarrhea	25	21		.0849				
Constipation	19	13		**.0084**				
Dry mouth	37	35		.5338				
Nausea/vomiting	15	16		.7266				
Heart	40	30	1.52	**.0027**	1.16	.3330	1.01	.9839
Palpitations	11	10		.5970				
Dizziness	24	20		**.0871**				
Chest pain	15	9		**.0032**				
Skin	52	43	1.48	**.0044**	1.24	.1453	1.12	.4274
Rash	6	7		.3484				
Increased perspiration	20	17		.2496				
Itching	23	19		.0872				
Dry skin	29	22		.0222				
Nervous system	57	55	1.11	.4547	0.98	.9088	0.87	.3518
Headache	41	41		.8771				
Tremors	17	12		**.0378**				
Poor coordination	12	11		.8075				
Dizziness	18	19		.7980				
Eyes/ears	49	30	2.17	< **.0001**	1.35	**.0435**	1.22	.1880
Blurred vision	34	18		< **.0001**				
Ringing in the ears	25	17		**.0073**				
Genital/urinary	37	26	1.68	**.0003**	1.25	.1437	1.13	.4484
Difficulty urinating	8	4		**.0039**				
Painful urination	2	2		.7268				
Frequent urination	27	19		**.0045**				
Menstruation irregularity	6	5		.2914				
Sleep	55	58	0.89	.3839	0.82	.1739	0.76	.0692
Difficulty sleeping	42	44		.5815				
Sleeping too much	18	19		.6262				
Sexual dysfunction	47	42	1.22	.1485	1.22	.1876	1.16	.3380
Loss of sexual desire	34	31		.3022				
Trouble achieving orgasm	18	20		.4287				
Trouble with erections	15	8		< **.0001**				

[a]Bolded values indicate statistical significance.
[b]Adjusted using age, race, Hispanic ethnicity, employment status, family history of depression, presence of anxious depression, atypical depression, age at first major depressive episode, and length of illness (adjusted CIRS score was not included).
[c]Adjusted using age, race, Hispanic ethnicity, CIRS total score (without endocrine and psychiatric illness categories), employment status, family history of depression, presence of anxious depression, atypical depression, age at first major depressive episode, and length of illness.
Abbreviations: CIRS = Cumulative Illness Rating Scale, OR = odds ratio.

treatment during the acute phase of treatment.[19,20,22,23] However, none of the pharmacotherapeutic studies reported on the frequency, intensity, and burden in addition to types of side effects. Reports of side effects were limited to short descriptions of the most prevalent types of side effects (eg, gastrointestinal) experienced by patients.

Our findings are different from those previously reported in the literature. In a survey of patients with DM within a large health maintenance organization (HMO), Ludman et al[9] found that patients with MDD reported a greater number of physical DM symptoms after controlling for DM complications, DM treatment intensity, and glycemic control. Also, in a survey of 367 patients with DM from 2 primary clinics in an HMO, Ciechanowski et al[45] showed that depressive symptoms had an adverse effect on adherence to diet and medication regimen. A possible explanation for our observations is that patients with DM were less adherent to their antidepressant medication regimens and thus experienced less side effects. Depression in patients with DM is associated with poor adherence to DM medication regimens, poor glycemic control, and an increased risk of microvascular and macrovascular complications. It is possible that the lack of adherence to medication in depressed patients with DM is not limited to diabetic medication. Unfortunately, patient adherence to antidepressant treatment was not assessed in the present study.

The lack of any significant differences in any of the citalopram treatment characteristics observed between participants with and without DM could be explained by the implementation of the STAR*D measurement-based care treatment model and is further supported by the finding that there were fewer differences in the maximum FIBSER scores between participants with and without DM after adjustment for confounding factors. Through measurement-based care, clinician adherence to protocol-specific treatment was monitored on the basis of measured symptoms and side effect burden, as well as dose and duration of antidepressant at each clinic visit during the acute-phase treatment of major depression.[25]

In this study, participants with DM reported several side effects that could raise some concerns. It should be noted that 2 side effect measures were utilized in STAR*D: the FIBSER and the PRISE. These 2 assessments differed in that the FIBSER assessed the frequency, intensity, and burden of side effects due to citalopram treatment and the PRISE characterized symptoms experienced by STAR*D participants that may or may not have been due to citalopram treatment. On the PRISE, participants with DM reported side effects related to gastrointestinal disturbance symptoms (constipation), chest pains, dermatologic problems, tremors, eye and ear problems (blurred vision and ringing in the ears), genitourinary disturbances (difficult/frequent urination), and erectile dysfunction more frequently than those without DM. These side effects may or may not have been due to citalopram.

Since side effect data were not gathered at baseline, we do not know if these side effects were present in higher frequency among participants with DM at study entry. We can speculate that more of the participants with DM reported these side effects (eg, gastrointestinal disturbance, erectile dysfunction), as they are consistent with the health effects of DM.

Study limitations include the lack of a clinical diagnosis of DM, the lack of side effects/symptom data at baseline, the lack of a validated measure of compliance, and the lack of a placebo group. The criteria for the classification of DM were based upon participant self-report on the CIRS and on the use of oral hypoglycemic medication and/or insulin (recorded in the medication log). However, an agreement study conducted at 1 STAR*D clinical site[46] suggested that the accuracy of the DM classification was congruent with medical records. It was not possible to determine if there were any differences between the side effects experienced prior to initiation of citalopram and those experienced after initiation because side effects/symptoms data were not assessed at baseline.

Study strengths include the ability to generalize the results to representative patient samples due to the study's large sample size, broad inclusion criteria, and outpatient sample recruited from both primary care and psychiatric care settings. An additional strength is the use of a side effect measure that assesses the frequency, intensity, and burden of side effects (FIBSER) in addition to an assessment of the type of side effects (PRISE).

In summary, this study shows that after adjustment for confounders, a smaller proportion of STAR*D participants with DM reported experiencing side effects from citalopram treatment compared to those without DM. Participants with and without DM differed, but not significantly, in the types of side effects reported. Many of the side effects reported were consistent with the diagnosis of DM. There was an overlap between the symptoms of DM and the side effects that can result from citalopram treatment in participants with DM (eg, gastrointestinal disturbances and sexual dysfunction). This information may help treating clinicians to better educate patients and to develop an individualized disease management plan to minimize the side effects from MDD treatment in patients with DM, which may increase the probability of patient adherence to treatment of depression.

Drug name: citalopram (Celexa and others).

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