Family History of Depression and Therapeutic Outcome: Findings From STAR*D

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Objective: It is unclear whether a positive family history of depression affects the clinical presentation or effectiveness of treatment for major depressive disorder (MDD). We aimed to determine whether depressed patients with a positive family history of depression differed from those without in terms of baseline sociodemographic and clinical characteristics, including concurrent comorbid conditions and treatment outcome with citalopram in a large, multicenter effectiveness trial.

Method: Clinical outcome and sociodemographic information were collected on 2876 participants with DSM-IV MDD enrolled from July 2001 through April 2004 in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Participants with and without a family history of depression, as determined by self-report at initial assessment, were compared.

Results: Over half (55.6%) (1585/2853) of the evaluable sample reported a positive family history of depression. A positive family history of depression was associated with an earlier age at onset of MDD, a longer length of illness, and more comorbid generalized anxiety disorder and prior suicide attempts. These participants had a slightly faster onset of remission, and slightly greater side effect burden, but they did not differ overall in response or remission rates.

Conclusions: A family history of depression was associated with several clinical characteristics, although its usefulness as a predictor of treatment outcome is questionable. The slightly faster remission with an SSRI despite the slightly greater side effect burden indicates the effectiveness of using an SSRI in treating depressed patients both with and without a family history of depression.

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Depression is the fourth leading cause of disability worldwide, with a lifetime prevalence estimated to be between 15% and 20%, according to the World Health Organization.[1] Studies have shown that family history of depression is an important factor for predicting the likelihood of an individual having depression, as well as the severity and outcome of a depressed individual's illness.[2–4] Depressed individuals who have a family history of depression are more likely to show an earlier age at onset, increased depression severity, longer depressive episodes,[5,6] more Axis I comorbidities (e.g., anxiety, substance abuse),[7] and incomplete recovery[8] than those without a family history of depression.

Having a family history of depression may affect response to antidepressant treatment. Winokur[9] suggested that depressed patients with a family history of depression respond more favorably to antidepressant treatment than

those without. Antidepressant response in family members could help guide antidepressant selection for other first-degree relatives with depression. Regarding pharmacotherapy, Franchini et al.[10] studied 45 individuals with unipolar or bipolar depression who responded to fluvoxamine and also had a first-degree relative diagnosed with unipolar or bipolar depression who had been treated with fluvoxamine. A favorable response to fluovoxamine was found for 67% (N = 30) of the 45 proband and relative pairs. In a family case study, O'Reilly et al.[11] found that 4 depressed individuals in the same family showed no improvement with tricyclic or selective serotonin reuptake inhibitor (SSRI) antidepressants, but all 4 showed response, and, in some cases, remission with the monoamine oxidase inhibitor tranylcypromine. In a study of 116 patients with unipolar or bipolar depression, Abou-Saleh and Coppen[12] found that patients with a family history of depression had a better response to prophylactic lithium than those without. In a sample of 98 patients with bipolar disorder, Engstrom et al.[13] found that those with a family history of unipolar depression (N = 20) showed a more favorable response to treatment with lithium than those with a family history of bipolar disorder. However, Mendlewicz et al.[14] noted that patients with bipolar disorder who had a family history of bipolar disorder were more likely to respond to lithium treatment than those without such a family history.

Not all research supports an association between family history of depression and response to treatment. In a retrospective analysis of 72 patients with depression, Morishita and Arita[15] found no association between having a family history of depression and having a response to fluvoxamine. Further, having a family history of major depressive disorder (MDD) or mania has been associated with a poorer prognosis and less response to treatment.[16]

The purpose of this study was to compare a large population of depressed patients with and without a family history of depression to determine whether the 2 groups differ regarding sociodemographic and clinical characteristics, comorbidities, treatment characteristics, and response to the SSRI citalopram.

METHOD

Study Overview and Organization

This study was conducted as part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. STAR*D was a series of randomized controlled trials designed to assess the efficacy of antidepressant treatment algorithms. Treatment was provided in a stepwise fashion in which a participant who did not achieve remission with the initial treatment (citalopram) could be randomized to subsequent treatment(s). The rationale, method, and design of the STAR*D study have been detailed elsewhere.[17–19]

Investigators and clinical research coordinators at each of 14 regional centers across the United States oversaw protocol implementation at 2 to 4 clinical sites that provide primary (18 sites) or psychiatric (23 sites) care to patients in both the public and private sectors. A central pool of research outcome assessors conducted telephone interviews to obtain primary outcomes.

Participants

From July 2001 through April 2004, STAR*D enrolled outpatients who were 18 to 75 years of age and had a diagnosis of nonpsychotic MDD. The clinically established diagnosis was verified using a checklist based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[20] To enhance generalizability of findings, the study enrolled only patients seeking medical care in routine medical or psychiatric outpatient treatment (as opposed to recruitment through advertisements). All risks, benefits, and adverse events associated with STAR*D participation were explained to participants, who provided written informed consent before entering the study. The protocol was approved by the institutional review boards at each clinical site and regional center, the study's data coordinating center, and the Data Safety and Monitoring Board of the National Institute of Mental Health (NIMH).

Broad inclusion criteria and minimal exclusion criteria that allowed a majority of Axis I and Axis II disorders were used to ensure a representative sample. A baseline 17-item Hamilton Rating Scale for Depression[21,22] ($HAM\text{-}D_{17}$) score ≥ 14 was required for enrollment. STAR*D enrolled patients for whom outpatient treatment with antidepressant psychotropic medication was deemed safe and appropriate by their clinician. Patients with a primary diagnosis of bipolar, psychotic (e.g., schizophrenia, schizoaffective), obsessive-compulsive, or eating (e.g., anorexia nervosa, bulimia) disorders were excluded from the study. Also excluded were those with general medical conditions contraindicating the use of protocol medications in the first 2 treatment steps, substance dependence requiring inpatient detoxification, or a clear history of nonresponse or intolerance (in the current major depressive episode) to any protocol antidepressant in the first 2 treatment steps.[18] Patients who were pregnant, breastfeeding, or intending to conceive within the 9 months subsequent to study entry were excluded.

Diagnostic and Outcome Measures

Baseline measures were collected by clinical research coordinators at each clinical site and by telephone (in English or Spanish) via interviews with research outcome assessors and an automated interactive voice response system.[18,19,23,24] Clinical research coordinators collected personal and family histories and sociodemographic information as well as depressive symptom severity using

the HAM-D_{17} and the 16-item Quick Inventory of Depressive Symptomatology-Clinician rating (QIDS-C_{16}).[25–27] The clinical research coordinator collected the self-report Psychiatric Diagnostic Screening Questionnaire[25,28–30] (PDSQ) at baseline to determine the presence/absence of 11 potential concurrent Axis I (psychiatric) disorders.

The clinical research coordinators also completed the 14-item Cumulative Illness Rating Scale (CIRS)[31,32] to gauge the severity/morbidity of general medical conditions relevant to different physiologic systems. The severity of each of the 14 illness categories was scored 0 (no problem) to 4 (extremely severe/immediate treatment required/end organ failure/severe impairment in function). The CIRS generated 3 scores: the number of general medical condition categories endorsed (0–13, excluding the psychiatric illness category), the severity index (average severity of the categories endorsed), and the total severity (number of categories endorsed multiplied by the severity index).

The research outcome assessors collected the HAM-D_{17} score (primary research outcome) and the 30-item Inventory of Depressive Symptomatology-Clinician rating (IDS-C_{30})[25,33] within 72 hours of study entry to measure depressive symptom severity. The presence of anxious symptom features was determined by using the anxiety/somatization factor of the HAM-D_{17},[34] while the presence of atypical and melancholic symptom features was determined by using the IDS-C_{30}. Research outcome assessors also collected the 5-item Income and Public Assistance Questionnaire.

The interactive voice response collected function and quality-of-life measures within 72 hours of study entry. These included the 12-item Short-Form Health Survey (SF-12),[35] which measured perceived physical functioning and mental health functioning; the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[36]; the Work and Social Adjustment Scale (WSAS)[37]; and the 5-item Work Productivity and Activity Impairment Questionnaire.[38] The interactive voice response also collected the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR_{16})[25–27] at baseline and after each clinic visit for assessment of depressive symptom severity. STAR*D secondary outcomes were based on the QIDS-SR_{16}.

Measures of symptom severity and side effects were collected at each clinic visit to enable the participant and clinician to make informed decisions regarding treatment. Clinical research coordinators collected the QIDS-C_{16}, research outcome assessors collected the HAM-D_{17}, and the interactive voice response collected the QIDS-SR_{16} and the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER).[39]

Intervention and Measurement-Based Care

Citalopram was selected as a representative SSRI due to its limited discontinuation symptoms, demonstrated safety in elderly and medically fragile patients, once-a-day dosing, small number of dose adjustment steps, and a favorable drug-drug interaction profile.[17,18] The aim of treatment was to achieve symptom remission (defined as QIDS-C_{16} score ≤ 5). The protocol[17,18] required a fully adequate dose of citalopram for a sufficient time to ensure that the likelihood of achieving remission was maximized and that those who did not reach remission were truly resistant to the medication.

The treatment protocol was designed to provide an optimal dose of citalopram based on dosing recommendations in a treatment manual,[40] which allowed individualized starting doses and dose adjustments to minimize side effects, maximize safety, and optimize the chances of therapeutic benefit for each participant. Medication management was assisted by ratings of symptoms (QIDS-C_{16}) and side effects (FIBSER) obtained at each treatment visit.[18] Citalopram was started at 20 mg/day and then raised to 40 mg/day by week 4 and to 60 mg/day (final dose) by week 6 (day 42). Dose adjustments were based on symptom changes, side effect burden, and the length of time a participant had received a particular dose. However, appropriate flexibility was allowed that included initiation of citalopram at < 20 mg/day or a slower dose escalation to the optimal target dose of 60 mg/day so that participants with concomitant medical and psychiatric disorders could be safely included in the sample.

The protocol recommended treatment visits at weeks 2, 4, 6, 9, and 12 (with an optional week 14 visit, if needed). After an optimal trial (based on dose and duration), remitters and responders (response was defined as ≥ 50% reduction in baseline QIDS-C_{16} score at 12 weeks) could enter the 12-month naturalistic follow-up; however, those responders who did not achieve remission were encouraged to enter the subsequent randomized trial. Participants could discontinue citalopram before 12 weeks if intolerable side effects required a medication change, an optimal dose increase was not possible due to side effects or participant choice, or significant depression symptoms (QIDS-C_{16} score ≥ 9) were present after 9 weeks at maximally tolerated doses. Participants could opt to move to the next treatment level if they had intolerable side effects or if the QIDS-C_{16} score was > 5 after an adequate trial in terms of dose and duration.

Maximum efforts to provide comprehensive, high quality care were substantiated by use of a treatment manual (including the treatment protocol and procedures), initial didactic instruction, ongoing support and guidance by the clinical research coordinator, use of a structured evaluation of symptoms and side effects at each visit, and a centralized treatment monitoring and feedback system.[19,40] To enhance the quality and consistency of care, physicians used a clinical decision support system that relied on measurement of symptoms (QIDS-C_{16} and QIDS-SR_{16}), side effects (FIBSER), medication

adherence (self-report), and clinical judgment. A Web-based treatment monitoring system provided feedback to clinical research coordinators regarding each participant's fidelity to the treatment recommendations. The clinical research coordinators could then help guide physicians in vigorously dosing when inadequate symptom reduction had occurred despite acceptable side effects.[18]

Safety Assessments

Side effects were evaluated using the participant-completed FIBSER at each treatment visit, with ratings based on a 7-point scale in which higher scores indicated greater frequency, intensity, or burden.[39] Serious adverse events were monitored using a multitiered approach that involved the clinical research coordinators, study clinicians, the interactive voice response system, the clinical manager, safety officers, regional center directors,[41] and the NIMH Data Safety and Monitoring Board.

Concomitant Medications

Concomitant treatments for current general medical conditions (as part of ongoing clinical care), associated symptoms of depression (e.g., sleep, anxiety, agitation), and citalopram side effects (e.g., sexual dysfunction) were permitted on the basis of clinical judgment by the treating clinician. Stimulants, anticonvulsants, antipsychotics, alprazolam, nonprotocol antidepressants (except trazodone ≤ 200 mg at bedtime for insomnia), and depression-targeted psychotherapies were proscribed.

Definition of Family History of Depression

At baseline, participants were asked to indicate whether their first-degree relatives (e.g., parents, siblings, or children) had a history of unipolar depression. If they answered yes to any question, they were considered to have a positive family history of depression.

Statistical Analysis

Summary statistics are presented as means and standard deviations for continuous variables and as percentages for discrete variables. Student t tests and Mann-Whitney U tests were used to compare continuous baseline sociodemographic and clinical features and treatment features across family history groups. We used χ^2 tests to compare discrete sociodemographic (e.g., gender), treatment (e.g., side effect burden), and outcome (e.g., serious adverse events) characteristics across family history groups.

Logistic regression models were used to compare remission and response rates after we adjusted for the effect of baseline characteristics that were not equally distributed across those with and without a family history of depression. Clinic visit data were used to define times to first response (≥ 50% reduction in baseline QIDS-SR_{16}) and first remission (QIDS-SR_{16} ≤ 5) as the first observed point. Log-rank tests were used to compare the cumulative proportion of participants with remission or response between those with and without a family history of depression. Cox proportional hazards models were used to examine the time to response and remission after we adjusted for the effect of baseline characteristics that were not equally distributed across those with and without a family history of depression.

Remission was defined as an exit HAM-D_{17} score ≤ 7 (or last observed QIDS-SR_{16} score ≤ 5). When outcome HAM-D_{17} scores were missing, participants were assumed to not have achieved remission (as defined in the original proposal).[18] Response was defined as a reduction of ≥ 50% in baseline QIDS-SR_{16} at the last assessment. Intolerance was defined a priori as either leaving treatment before 4 weeks for any reason or leaving treatment at or after 4 weeks with intolerance as the identified reason. Statistical significance of analyses of depressive severity outcomes was adjusted for multiple testing by using a Bonferroni correction. To maintain an overall type I error rate of .05 and with 8 outcomes in the adjusted analyses, a 2-sided p value of .00625 was used to define statistical significance.

RESULTS

Sociodemographic and Clinical Characteristics

Table 1 summarizes the sociodemographic and clinical characteristics of the analyzable sample as a whole (N = 2876) and compares participants with and without a family history of depression with regard to these characteristics. Of the whole sample, 2853 participants had data available to assess a family history of depression and 1585 (55.6%) indicated a positive family history.

Most participants were female and the racial composition was representative of the U.S. population.[42] Most participants were employed, married, and seen in a specialty care clinic. Participants with a family history of depression had an earlier age at onset of MDD, fewer depressive episodes, and a longer length of illness; all of which were clinically meaningful differences. Moreover, participants with such a family history were more likely to have a family history of alcohol abuse, drug abuse, or suicide and were more likely to report prior suicide attempt(s). Although statistically significant differences were found between groups regarding sociodemographic variables, these differences were not clinically meaningful.

Table 2 summarizes the general medical comorbidities and psychiatric comorbidities in participants with and without a family history of depression. Those with and those without a family history reported similar numbers of general medical comorbidities. Regarding psychiatric concurrent comorbidities, having a family history of depression was associated with GAD. However, a negative family history of depression was found to be associated with posttraumatic stress disorder (PTSD).

Table 1. Baseline Demographic and Clinical Characteristics by Family History of Depression

Characteristic	Total (N = 2853), %	Family History of Depression: No (N = 1268 [44.4%]), %	Family History of Depression: Yes (N = 1585 [55.6%]), %	p Value
Setting				.2239
Primary care	38.0	39.2	37.0	
Specialty care	62.0	60.8	63.0	
Race				< .0001
White	75.9	71.1	79.8	
African American	17.5	22.3	13.6	
Other	6.6	6.6	6.6	
Ethnicity–Hispanic				.0028
No	87.0	84.9	88.6	
Yes	13.0	15.1	11.4	
Sex				< .0001
Male	36.1	40.8	32.4	
Female	63.9	59.2	67.6	
Marital status				.0301
Never married	28.7	26.1	30.8	
Married	41.7	43.0	40.5	
Divorced	26.5	27.3	26.0	
Widowed	3.1	3.6	2.7	
Employment status				.0020
Employed	56.2	53.7	58.1	
Unemployed	38.2	39.1	37.5	
Retired	5.6	7.2	4.4	
Insurance status				.0020
Private insurance	51.2	50.5	51.8	
Public insurance	14.2	16.8	12.2	
No insurance	34.6	32.7	36.0	
Family history of alcohol abuse	41.4	31.7	49.2	< .0001
Family history of drug abuse	24.3	16.4	30.6	< .0001
Family history of suicide	3.6	2.4	4.6	.0018
Attempted suicide	17.8	12.9	21.7	< .0001
Present suicide risk	3.1	2.4	3.5	.0913
Age at onset				< .0001
≤ 18 y	37.8	27.5	46.1	
> 18 y	62.2	72.5	53.9	
Anxious features	53.1	52.6	53.5	.6325
Atypical features	18.8	19.0	18.7	.8142
Melancholic features	23.4	24.2	22.8	.3733
Chronic depression	25.3	25.2	25.4	.9378
Recurrent depression	75.7	70.0	80.3	< .0001
	Mean (SD)	Mean (IQR)	Mean (IQR)	
Age, y	40.8 (13.0)	42.3 (13.2)	39.6 (12.8)	< .0001
Education, y	13.4 (3.2)	13.3 (3.4)	13.6 (3.1)	.0150
Income, $/mo	2362 (3040)	2294 (3183)	2415 (2920)	.0414
General medical comorbidities (CIRS)				
Categories endorsed	3.1 (2.3)	3.1 (2.3)	3.2 (2.3)	.1789
Total score	4.4 (3.7)	4.5 (3.8)	4.4 (3.7)	.2322
Severity index	1.2 (0.6)	1.3 (0.7)	1.2 (0.6)	.0057
SF-12				
Physical	48.7 (12.1)	47.4 (12.4)	49.7 (11.7)	< .0001
Mental	25.6 (8.1)	26.0 (8.1)	25.3 (8.2)	.0197
Quality of life				
Q-LES-Q	39.2 (14.3)	39.2 (14.3)	39.2 (14.4)	.9817
WSAS	24.9 (8.7)	25.0 (8.8)	24.8 (8.6)	.4773
Age at onset of first MDE, y	25.3 (14.4)	28.4 (15.0)	22.8 (13.4)	< .0001
No. of MDEs	5.5 (9.2)	5.5 (9.5)	5.4 (8.9)	< .0001
Length of current MDE episode, mo	24.6 (51.7)	24.1 (48.2)	24.8 (54.0)	.7867
Length of illness, y	15.5 (13.2)	13.9 (12.9)	16.8 (13.3)	< .0001
$HAM\text{-}D_{17}$[a]	21.8 (5.2)	21.7 (5.2)	21.8 (5.2)	.6605
$IDS\text{-}C_{30}$[a]	38.6 (9.6)	38.5 (9.6)	38.6 (9.6)	.8465
$QIDS\text{-}SR_{16}$	16.2 (4.0)	16.0 (4.0)	16.3 (4.0)	.0307

[a]Research outcome assessor.

Abbreviations: CIRS = Cumulative Illness Rating Scale, $HAM\text{-}D_{17}$ = 17-item Hamilton Rating Scale for Depression, $IDS\text{-}C_{30}$ = 30-item Inventory of Depressive Symptomatology, IQR = interquartile range, MDE = major depressive episode, $QIDS\text{-}SR_{16}$ = 16-item Quick Inventory of Depressive Symptomatology–Self-Rated, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SF-12 = 12-item Short Form Health Survey, WSAS = Work and Social Adjustment Scale.

Table 2. Presence of General Medical and Psychiatric Comorbidities by Family History of Depression

Feature	Family History of Depression: No (N = 1268 [44.4%]), %	Family History of Depression: Yes (N = 1585 [55.6%]), %	p Value
General medical comorbidities (CIRS items)			
Total score[a]	4.5 (3.8)	4.4 (3.7)	.2322
CIRS count			.4258
0	11.0	9.0	
1	15.6	15.1	
2	17.8	17.8	
3	14.7	15.0	
≥ 4	40.9	43.1	
Psychiatric comorbidities based on PDSQ			
GAD	21.3	25.4	.0108
OCD	15.5	13.3	.0838
Panic disorder	13.4	12.8	.6102
Social phobia	30.0	32.6	.1438
PTSD	23.6	18.2	.0004
Agoraphobia disorder	12.7	11.1	.1924
Alcohol abuse	11.0	12.9	.1221
Drug abuse	6.7	7.8	.2513
Somatoform disorder	2.6	2.2	.4859
Hypochondriasis	4.6	4.2	.5835
Bulimia	11.1	14.6	.0063
Axis I disorder count			.7109
0	35.1	34.5	
1	26.9	26.3	
2	16.0	17.0	
3	9.0	9.3	
≥ 4	13.0	12.9	

[a]Mean (SD).
Abbreviations: CIRS = Cumulative Illness Rating Scale, GAD = generalized anxiety disorder, OCD = obsessive-compulsive disorder, PDSQ = Psychiatric Diagnostic Screening Questionnaire, PTSD = posttraumatic stress disorder.

Response and Remission

There was no statistically significant difference between groups in terms of response or remission (Table 3). However, those with a family history of depression had a slightly faster time to response and remission, as shown in Figures 1 and 2, respectively. For those with a positive family history of depression who did reach remission or response, the mean (SD) times to remission and response were 11.6 (3.1) and 11.5 (3.3) weeks, respectively, compared to 11.7 (3.2) and 11.5 (3.4) weeks, respectively, for those without a positive family history. After adjusting for the effect of baseline characteristics that were not equally distributed across those with and without a family history of depression, we found no significant association with time to first remission (hazard ratio, 1.05; p = .4204) or time to first response (hazard ratio, 1.01; p = .8745).

Treatment Characteristics

No significant difference was found between participants with and without a family history of depression in terms of maximum dose of citalopram or dose of citalopram at study exit (Table 4). However, participants with a family history of depression were found to have a higher side-effect burden, but no difference was found regarding side-effect frequency or intensity (Table 5). There was no significant difference found between groups in terms of severe adverse events.

DISCUSSION

Participants with a family history of depression were more likely to have an earlier age at depression onset, longer length of illness, and prior suicide attempts and were more likely to have a family history of alcohol abuse, drug abuse, or suicide. There was no difference between participants with and without a family history of depression in terms of psychiatric comorbidities, except with the greater presence of GAD and PTSD in the former and latter, respectively. Although participants with a positive family history of depression showed a slightly faster rate of remission, both groups had similar treatment characteristics (i.e., citalopram dose, treatment length) and showed similar response and remission rates with citalopram.

This study found minimal clinically significant differences regarding sociodemographic characteristics between participants with and without a family history of depression, despite a few statistically significant differences. For example, 79.8% of those with a positive family history of depression were white versus 71.1% of those without such a history. This is consistent with the findings of Weissman et al.,[43] in which participants with and without a family history of MDD did not differ on sociodemographic variables.

Clinical features were similar between groups, including depression severity and number of depressive episodes. For example, the group with a family history of depression was found to have a mean of 5.4 depressive episodes and a mean score of 16.3 on the QIDS-SR_{16}, while the group without family history had a mean of 5.5 depressive episodes and a mean score of 16.0 on the QIDS-SR_{16}. These findings are consistent with the findings of Nierenberg et al.[44] and Weissman et al.[43] However, our study found that participants with a family history of depression were significantly younger at depression onset, which is consistent with other reports.[6,7] For example, patients with a positive family history of depression had an onset of their first episode approximately 6 years earlier than those without. This finding highlights the importance of close assessment and monitoring of children, adolescents, and young adults who have a family history of depression.

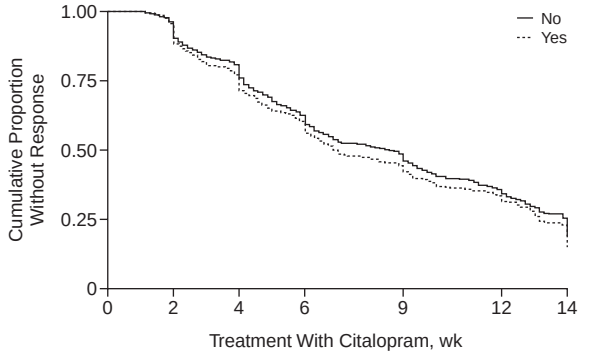
The greater likelihood of concurrent GAD and family history of alcohol abuse or drug abuse among patients with a positive family history of depression is consistent with previous literature. The Collaborative Family Study of Depression (Yale University and the National Institute of Mental Health) studied 335 probands with mood

Table 3. Remission and Response Status by Family History of Depression

Outcome	Total (N = 2853), %	Family History of Depression: No (N = 1268 [44.4%]), %	Family History of Depression: Yes (N = 1585 [55.6%]), %	p Value	Adjusted Results[a]: OR	Adjusted Results[a]: p Value
HAM-D_{17}, remission				.1134	1.00	.9851
No	72.4	73.9	71.2			
Yes	27.6	26.1	28.8			
QIDS-SR_{16}, remission				.0497	1.09	.3754
No	67.1	69.0	65.5			
Yes	32.9	31.0	34.5			
QIDS-SR_{16}, response				.0655	1.03	.7349
No	52.9	54.8	51.4			
Yes	47.1	45.2	48.6			
					Family History of Depression	
QIDS-SR_{16}	Mean (SD)	Mean (SD)	Mean (SD)		No, Mean (SE)	Yes, Mean (SE)
Exit score	9.1 (5.9)	9.3 (5.8)	9.0 (6.0)	.0772	9.4 (0.5)	9.3 (0.5)	.5928
Score change	–7.1 (5.9)	–6.7 (5.8)	–7.3 (6.0)	.0046	–6.7 (0.5)	–6.8 (0.5)	.5928
Percent change, %	–42.9 (35.2)	–41.1 (35.1)	–44.3 (35.2)	.0175	–40.3 (2.9)	–41.3 (2.9)	.4773

[a]Adjusted for the effect of baseline characteristics that were not equally distributed across those with and without a family history of depression.
Abbreviations: HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology–Self-Rated.

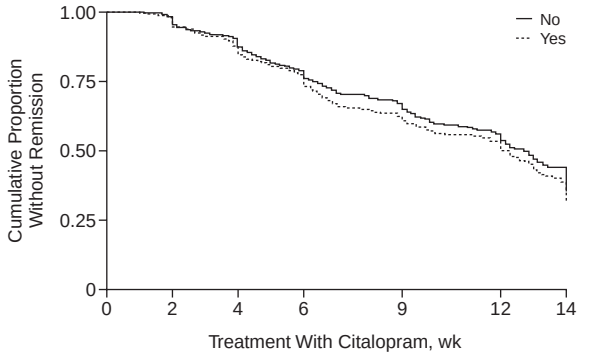
Figure 1. Time to Response by Family History of Depression[a]



No, N	1243	1168	908	641	418	206	77
Yes, N	1550	1452	1079	765	459	227	79
Total, N	2793	2620	1987	1406	877	433	156

[a]Log-rank statistic = 4.3; p = .0375.

Figure 2. Time to Remission by Family History of Depression[a]



No, N	1262	1190	1014	801	579	339	129
Yes, N	1584	1487	1231	981	640	374	143
Total, N	2846	2677	2245	1782	1219	713	272

[a]Log-rank statistic = 4.5; p = .0330.

disorders and 2003 relatives at risk and found that drug abuse and generalized anxiety were higher in the relatives of probands with major depression.[45] Also, it has been suggested that those with a family history of MDD have a 5-fold risk of developing alcohol dependence[43] and are at greater risk for substance abuse.[7]

The findings of this study add further evidence for the association between GAD and depression. In the National Comorbidity Survey, a majority of patients (67%) with GAD were also diagnosed with unipolar depression.[46] Current literature suggests that anxiety and depression share common neurotransmitter pathways.[47,48] For example, research has shown that variation in the serotonin promoter region is related to an increased risk for developing depression[49] and anxiety.[50] Wittchen et al.[51] showed that parental history of mental illness is a risk factor for the comorbidity of depression and anxiety; however, Leckman et al.[52] suggested that rates of anxiety disorders are higher in depressed patients who have a parental history of both mood and anxiety disorders. Currently, there is debate as to whether GAD and MDD are separate disorders given that they share many of the same genetic risk factors and are highly comorbid.[48,53]

Interestingly, PTSD was associated with a negative family history of depression. There is limited research to date regarding the association of family history of mood disorder and PTSD, with many studies finding results inconsistent with one another.[54] Ozer et al.[55] conducted a meta-analysis of 68 studies regarding PTSD. Of the 7 predictors of PTSD found, family history of psychopathology yielded one of the smallest effect sizes (r = .17). This suggests that family history of mood disorder may be

Table 4. Treatment Characteristics in Relation to Symptomatic Outcome by Family History of Depression

	Total (N = 2853)		Family History of Depression: No (N = 1268 [44.4%])		Family History of Depression: Yes (N = 1585 [55.6%])		
Characteristic	N	%	N	%	N	%	p Value
Maximum dose of citalopram, mg/d							.5338
< 20	62	2.2	28	2.2	34	2.2	
20–39	687	24.1	296	23.4	391	24.8	
40–49	858	30.2	373	29.4	485	30.7	
≥ 50	1239	43.5	571	45.0	668	42.3	
Dose of citalopram at study exit, mg/d							.5741
< 20	103	3.6	48	3.8	55	3.5	
20–39	776	27.3	341	26.9	435	27.6	
40–49	853	30.0	367	28.9	486	30.8	
≥ 50	1114	39.1	512	40.4	602	38.1	
Time in treatment, wk							.8146
< 4	321	11.2	139	11.0	182	11.5	
≥ 4 but < 8	479	16.8	209	16.5	270	17.0	
≥ 8	2053	72.0	920	72.5	1133	71.5	
	Mean	SD	Mean	SD	Mean	SD	
No. of visits	4.8	1.5	4.8	1.5	4.8	1.5	.7060
Time to first treatment visit, wk	2.3	1.1	2.4	1.2	2.3	1.0	.1741
Time in treatment, wk	10.0	4.2	10.2	4.2	9.9	4.1	.1787
Time from final dose to study exit, wk	5.1	4.0	5.1	3.9	5.1	4.1	.5481

Table 5. Side Effects and Serious Adverse Events by Family History of Depression

	Total (N = 2853)		Family History of Depression: No (N = 1268 [44.4%])		Family History of Depression: Yes (N = 1585 [55.6%])		
Variable	N	%	N	%	N	%	p Value
Maximum side-effect frequency							.0598
None	446	15.7	224	17.8	222	14.1	
10%–25% of the time	801	28.2	351	27.9	450	28.5	
50%–75% of the time	906	31.9	391	31.0	515	32.6	
90%–100% of the time	685	24.1	294	23.3	391	24.8	
Maximum side-effect intensity							.0664
None	440	15.5	219	17.4	221	14.0	
Trivial	786	27.7	334	26.5	452	28.6	
Moderate	1166	41.1	504	40.0	662	42.0	
Severe	446	15.7	203	16.1	243	15.4	
Maximum side-effect burden							.0145
No impairment	581	20.5	287	22.8	294	18.6	
Minimal-mild impairment	1166	41.1	482	38.2	684	43.4	
Moderate-marked impairment	855	30.1	383	30.4	472	29.9	
Severe impairment-unable to function	236	8.3	108	8.6	128	8.1	
Serious adverse events	116	4.1	58	4.6	58	3.7	.2189
Death, nonsuicide	3		2		1		
Hospitalization for GMCs	58		35		23		
Medical illness without hospitalization	4		3		1		
Psychiatric hospitalization							
Substance abuse	8		2		6		
Suicidal ideation	36		16		20		
Worsening depression	6		3		3		
Other	2		1		1		
Suicidal ideation (without hospitalization)	6		2		4		
Any psychiatric serious adverse events	57	2.0	23	1.8	34	2.2	.5298
Intolerance	485	17.0	220	17.4	265	16.7	.6557

Abbreviation: GMC = general medical comorbidity.

differently related to specific anxiety disorders.

More participants with a positive family history of depression had attempted suicide or had a family history of completed suicide. The reason for the high rate of attempted suicide in the positive family history of depression group is unclear. It may be possible that it was related to the presence of GAD. For instance, prior investigations[56,57] have found that the presence of anxiety increases the risk of suicide in depressed patients. Specifically, in the National Comorbidity Survey, GAD did differentiate between those who attempted suicide and those who made suicidal gestures (i.e., self-injury with no intent to die).[58] However, both groups in the current study were similar with regard to other anxiety spectrum disorders, including obsessive-compulsive disorder and panic disorder. Thus, the presence of GAD alone may not account for the higher percentage of patients with a positive family history of depression who attempted suicide.

The high presence of family history of suicide in participants with a positive family history of depression may be a possible factor for the increased risk of suicide attempt in this group. Runeson and Asberg[59] identified 8396 individuals who completed suicide in a Swedish national death register. They found that family history of suicide, independent of psychiatric disorders, was a significant risk factor for suicide. This finding was substantiated by Tremeau et al.,[60] who found a positive family history of suicide to be associated with many suicidal characteristics. Moreover, Qin et al.[61] found that familial suicidal history increases the risk of suicide (OR = 2.14) regardless of psychiatric admission, gender, or age. Lastly, as found in an earlier STAR*D report, genetic markers in genes GRIK2 and GRIA3 were related to suicidal ideation during treatment with citalopram, suggesting a heritable component in suicide risk.[62] Based on prior research and the findings of this study, further investigation is needed regarding the relationship between family history of suicide, family history of depression, and comorbid anxiety disorders as well as the effect of these 3 factors on

suicide risk. For instance, these 3 factors may have an additive effect in increasing the risk of suicide.

This study is the first to report a slightly greater speed of remission with citalopram in patients with a positive family history of depression compared to those without. The reason for and the clinical relevance of the faster speed of remission are unclear. It is possible that those with a family history of depression respond somewhat faster to pharmacotherapy due to their having similar biologically related mood disorders and medication response. Evidence for this can be found in the concordant antidepressant response rate between first degree relatives with mood disorders (e.g., parent and child), which has been suggested to be approximately 50%.[8] Further, in a study examining response to fluvoxamine, the concordance rate between first-degree relatives was found to be 67%, which indicated a relationship between a family history of mood disorder (either MDD or bipolar disorder) and response to antidepressant psychotropic treatment.[10] As newer techniques, like pharmacogenetics, can help to identify appropriate and effective antidepressants,[63,64] knowing the family history of mood disorder and family history of pharmacotherapy efficacy may help physicians in choosing an effective medication regimen. Consequently, participants with a family history of mood disorder showed greater adverse side effect burden, although frequency and intensity were similar between groups. The reason for this is unclear and further research is needed in this area.

The limitations of this study included not using a structured interview form to determine family history of depression, such as the Research Diagnostic Criteria-Family History version.[65] However, patients with depression have been found to be reliable informants of respective mood disorders in their family.[66] Kendler et al.[66] evaluated female twin pairs (N = 1176) in which 1 twin had MDD or GAD and found that the twin with MDD or GAD was more likely to report the same psychiatric disorder in a parent than the twin with no diagnosis. While this may result in an informant bias, the self-informant diagnostic method tends to be conservative, with a low false-positive relative to false-negative rate.[66] Another limitation was that family history of treatment-response information was not collected, and that information may be helpful in optimizing treatment efficacy. The strengths of this study included the recruitment of participants from both psychiatric and community primary care clinics to avoid an artificially inflated finding of participants with a family history of mood disorder. Sullivan et al.[67] noted that individuals with MDD recruited from a psychiatric clinic were more likely to have a family history of mood disorder than persons in a community sample. In our study, we found no difference in either speed of remission or side-effect burden between participants enrolled from primary care and those enrolled from a psychiatric care setting. Nonetheless, the current study's participant sample was derived from a clinical trial and not an epidemiologic study, and thus certain findings may not be generalizable.

Overall, our findings suggest that MDD patients with and without a family history of depression differ minimally in terms of sociodemographic or clinical features. Those with positive family history do remit slightly more rapidly despite increased side-effect burden. Future studies should examine treatment outcome with SSRIs while examining its relationship to family history. Determining the efficacy of these treatments for patients with a family history of depression may improve the future treatment of these patients.

Drug names: alprazolam (Xanax, Niravam, and others), citalopram (Celexa and others), fluvoxamine (Luvox and others), tranylcypromine (Parnate and others).

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