Are Depressed Outpatients With and Without a Family History of Substance Use Disorder Different? A Baseline Analysis of the STAR*D Cohort

Lori L. Davis, M.D.; Elizabeth C. Frazier, M.A.; Bradley N. Gaynes, M.D., M.P.H.; Madhukar H. Trivedi, M.D.; Stephen R. Wisniewski, Ph.D.; Maurizio Fava, M.D.; Jennifer Barkin, M.P.H.; T. Michael Kashner, Ph.D.; Richard C. Shelton, M.D., Ph.D.; Jonathan E. Alpert, M.D., Ph.D.; and A. John Rush, M.D.

Objective: This report compares the baseline demographic and clinical characteristics of outpatients with nonpsychotic major depressive disorder (MDD) and a family history of substance use disorder (SUD) versus those with MDD and no family history of SUD.

Method: Using data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, we grouped participants with MDD (DSM-IV criteria) according to presence or absence of family history of SUD based on participant report. Between-group comparisons were made of demographic and clinical characteristics, depressive symptoms, and psychiatric comorbidities. Patients were enrolled from July 2001 until August 2004.

Results: Of 4010 participants, 46% had a positive family history of SUD. Those with a positive family history were less likely to be Hispanic ($p = .0029$) and more likely to be female ($p = .0013$). They were less educated ($p = .0120$), less likely to be married ($p < .01$), and more likely to be divorced ($p < .01$). They also reported an earlier age at onset of MDD, greater length of illness, and more major depressive episodes (all $p < .001$). They had an increased likelihood of recurrent MDD, more prior suicide attempts, and more concurrent psychiatric comorbidities, including posttraumatic stress disorder, SUD, and generalized anxiety disorder (all $p < .0001$).

Conclusion: Depressed patients with a family history of SUD had a more severe previous course of depression, were more likely to have attempted suicide, and had a greater burden of psychiatric comorbid conditions than patients without such a family history. These findings represent important clinical features to be considered in the evaluation and treatment planning of patients with MDD.

(J Clin Psychiatry 2007;68:1931–1938)

Received May 29, 2006; accepted April 29, 2007. *From the Department of Veterans Affairs (VA) Medical Center, Tuscaloosa, Ala., and Department of Psychiatry, University of Alabama School of Medicine, Tuscaloosa and Birmingham (Dr. Davis); Department of Psychology, University of Alabama at Birmingham (Ms. Frazier); Department of Psychiatry, University of North Carolina at Chapel Hill (Dr. Gaynes); Department of Psychiatry, University of Texas (UT) Southwestern Medical Center at Dallas (Drs. Trivedi, Kashner, and Rush); University of Pittsburgh Epidemiology Data Center, Pittsburgh, Pa. (Dr. Wisniewski and Ms. Barkin); Depression Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Boston (Drs. Fava and Alpert); and Department of Psychiatry, Vanderbilt University, Nashville, Tenn. (Dr. Shelton).*

This project has been funded with Federal funds from the National Institute of Mental Health (NIMH), National Institutes of Health, under Contract N01MH90003 (ClinicalTrials.gov identifier NCT00021528) to UT Southwestern Medical Center at Dallas (Dr. Rush).

The content of this publication does not necessarily reflect the views or policies of the U.S. Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Acknowledgments are listed at the end of the article.

Financial disclosure appears at the end of the article.

Corresponding author and reprints: Lori L. Davis, M.D., VA Medical Center (151), 3701 Loop Rd. East, Tuscaloosa, AL 35404 (e-mail: lori.davis@va.gov).

Understanding the nature of familial co-occurrence of major depressive disorder (MDD) and substance use disorders (SUD; henceforth excluding nicotine and caffeine) remains an area of active research. Are these disorders independently transmitted in families or is there good evidence for genuine coaggregation due to genetic or behavioral predisposition? Additionally, do depressed patients with a family history of SUD have a different type of depression than those without a family history of SUD?

In the general population, individuals with MDD are significantly more likely to have a first-degree relative with alcohol abuse or dependence compared to individuals without MDD.[1] A recent study found that U.S. Navy recruits with depression were nearly 4 times more likely than those without depression to have a family history of alcohol abuse.[2] Conversely, first-degree relatives with alcohol abuse or dependence have been shown to be 2.6 times more likely to be related to a proband with MDD.[3] In a study that examined physical health in depressed and

nondepressed children (aged 6–17 years) of opiate addicts, 35% of male and 68% of female children of opiate addicts were diagnosed with MDD.[4] Furthermore, 35% of male and 65% of female children of opiate addicts were diagnosed with other mood disorders, including dysthymic disorder and depressive disorder not otherwise specified.

Some studies on the familial relationship between depression and SUD have yielded mixed results. The Collaborative Study on the Genetics of Alcoholism, which included data from 8296 relatives of alcoholic probands and 1654 controls, found that alcohol dependence, antisocial personality disorder, several anxiety disorders, MDD, and dysthymic disorder cluster in the families of alcohol-dependent individuals. However, after controlling for multiple factors, there was only a modest association of MDD in relatives of alcoholics (odds ratio = 1.35).[5] Additionally, a study of children of alcoholics failed to find significantly higher rates of depression in the child proband, although there was a significantly higher rate of overanxious disorder in the children.[6]

Winokur[7] described a distinction between a familial pure depressive disease (FPDD) and depression spectrum disease (DSD) in patients with unipolar depression. FPDD is characterized by the onset of depression typically after age 40 years, equivalent incidence rates of affective disorder across genders among first-degree relatives, minimal occurrence of familial alcoholism and antisocial personality disorder, fewer total familial psychiatric disorders, and a notable association between the age at onset of depression in depressed individuals and the age at onset of depression in their depressed relatives. Conversely, DSD is characterized by an earlier age at onset of depression, typically below age 40 years, increased incidence of familial affective disorder, significantly higher rates of affective disorder in female versus male first-degree relatives, greater familial occurrence of alcoholism and antisocial personality disorder, and an overall greater level of psychiatric illness. In other words, Winokur utilized the presence or absence of familial alcoholism and/or antisocial personality disorder as the criteria to differentiate FPDD families from DSD families. In support, Coryell and others[8] reported significantly higher familial rates of alcoholism in female versus male individuals diagnosed with depression. Therefore, the occurrence of familial alcoholism for women diagnosed with depression was indicative of DSD. More recently, Cadoret, Winokur, and colleagues[9] utilized an adoption study design to distinguish genetic from environmental factors in an examination of the etiology of DSD. Results indicate the presence of confounding environmental factors (fetal alcohol exposure, a disturbed adoptive parent, age at the time of adoption, and a family with an adopted sibling with a psychiatric problem) that most likely contribute to an increased risk of depression in women, but not men. Also, results indicate that a genetic factor appears to be present for alcoholism exerting itself in women as a gene-environment interaction leading to DSD.[9]

From a more recent large multicenter study, Winokur and Coryell[10] found that depressed individuals with a familial history of alcoholism (i.e., DSD) were significantly different at baseline than depressed individuals without a family history of alcoholism (i.e., FPDD). In contrast to those with FPDD, those with DSD reported more familial anxiety and somatization disorders, a greater lifetime prevalence of divorce, a greater lifetime prevalence of suicide attempts, a greater number of negative life events, and a longer time to recover from the baseline MDD episode. Also, in comparison to those with FPDD, those with DSD were more likely to develop alcoholism and drug abuse during the 5-year follow-up period. In summary, and for the purposes of the current analysis, major depressive disorder is a heterogeneous disorder with one possible basis for subtyping being the FPDD versus DSD distinction that is based on the presence (DSD) versus absence (FPDD) of a family history of alcoholism.

The objective of this report is to further evaluate the demographic and clinical differences between patients with MDD and a family history of SUD versus MDD patients without a family history of SUD. This study was conducted using data gathered for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which offered an opportunity to contribute to the current body of knowledge regarding the complex relationship between MDD and the presence or absence of a family history of SUD.

METHOD

Study Design

The STAR*D study was a multicenter randomized controlled study designed to prospectively define the effectiveness and acceptability of treatments for outpatients with nonpsychotic MDD who had an unsatisfactory clinical outcome from 1 or more previous antidepressant treatments. The rationale and methods of the STAR*D study are detailed elsewhere.[11,12]

Briefly, the STAR*D enrolled 4041 adult outpatients with a diagnosis of nonpsychotic MDD from primary or psychiatric care clinical sites in the public or private sector. Diagnosis of MDD was based on a general clinical interview by a physician that was confirmed by an independent interviewer using a checklist of DSM-IV diagnostic symptoms for MDD. Entry required an indication for antidepressant medication treatment and a score of 14 or higher on the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$).[13,14] Broad inclusion and minimal exclusion criteria were used to ensure recruitment of a sample representative of outpatients with nonpsychotic MDD

typically seen in clinical practice. Patients with suicidal ideation remained eligible for participation as long as there was no immediate need for inpatient treatment. Patients with active SUD were eligible as long as inpatient care or immediate detoxification was not necessary. Concomitant medications for general medical conditions were allowed if the medications did not contraindicate the use of any Level 1 or 2 treatment options. Patients receiving counseling or therapy (e.g., counseling to address marital discord or psychodynamic treatment of character issues) were eligible unless the psychotherapy was specifically targeted at their depression.

Patients were excluded if they had a lifetime history of schizophrenia, schizoaffective disorder, bipolar disorder, current psychotic depression, or a primary diagnosis of anorexia nervosa, bulimia nervosa, or obsessive-compulsive disorder. Patients with a history of nonresponse to an adequate trial or who clearly were unable to tolerate any potential Level 1 or 2 treatment options within the current MDD episode were also excluded. Patients who had severe, unstable concurrent psychiatric conditions likely to require hospitalization within the 6 months subsequent to study entry were excluded, as were patients who were breastfeeding, pregnant, or planning to conceive within the 6 to 9 months subsequent to study entry.

This study was approved and overseen by the National Institute of Mental Health Data Safety and Monitoring Board, as well as institutional review boards at the STAR*D National Coordinating Center (University of Texas Southwestern Medical Center), the Data Coordinating Center (University of Pittsburgh), and the 14 regional centers that supervised the protocol implementation of relevant clinical sites. Participants (enrolled from July 2001 until August 2004) provided written informed consent prior to study entry.

Assessment Procedure

After signing an informed consent, participants completed a baseline evaluation described elsewhere in detail.[12] Briefly, at baseline, Clinical Research Coordinators who were trained and certified in protocol implementation and data collection procedures gathered demographic and clinical information and administered the HAM-D_{17} and the 16-item Quick Inventory of Depressive Symptomatology–Clinician-Rated.[15] In addition, centralized Research Outcomes Assessors, blinded to treatment level, assessed the participant via telephone interview within 72 hours of the baseline clinic visit, administering the HAM-D_{17} and the 30-item Inventory of Depressive Symptomatology–Clinician-Rated (IDS-C_{30}).[16]

At baseline, participants completed the 16-item Quick Inventory of Depressive Symptomatology–Self-Report[15] to assess severity of depressive symptoms, and the Psychiatric Diagnostic Screening Questionnaire (PDSQ).[17] The PDSQ is a self-report, 126-item, "yes" or "no" survey to screen for 13 DSM-IV disorders. It has well-established psychometric properties when compared to structured clinician-administered interviews, such as the Structured Clinical Interview for DSM-IV. The PDSQ assesses the presence or absence of an alcohol or drug use disorder (abuse or dependence) with 6 questions for alcohol use and 6 questions for drug use, referencing the previous 6 months. The presence of all Axis I disorders was established using PDSQ responses set at a threshold requiring 90% specificity.[18]

Measures of the participants' functional status and functional impairment at work and in home management, social leisure activities, private leisure activities, and relationships were gathered by telephone within 72 hours of study entry via the Interactive Voice Response system.[19,20] These measures included the 12-item Short-Form Health Survey,[21] the 5-item Work and Social Adjustment Scale,[22] and the Quality of Life Enjoyment and Satisfaction Questionnaire.[23]

During a general psychiatric interview at baseline, clinicians assessed the participants' family history of SUD and checked "yes" or "no" for drug or alcohol abuse or dependence in any first-degree relative, listed as parent, sibling, or child. The clinician specifically asked if family members had ever been diagnosed or treated for alcohol or drug abuse or dependence and if so, whether the relative was a parent, sibling, and/or child. The study did not use a standardized instrument to assess family history of SUD. The exact number of relatives affected was not collected.

Statistical Analyses

Participants were grouped according to presence or absence of family history of SUD. Analyses compared the group positive for family history of SUD to the group negative for family history of SUD. A positive family history of SUD is defined as the presence of a current or lifetime history of any drug and/or alcohol use disorder (excluding nicotine or caffeine) in any first-degree relative (i.e., parent, sibling, or child). Proband participants who were determined by the clinician to have a positive history ("yes") of SUD in 1 or more first-degree relatives were categorized as family-history positive. Group percentages are presented for categorical variables, and means with standard deviations are presented for continuous measures. The assumptions for the test of each continuous variable were assessed. If the assumptions were not met, nonparametric methods were employed. Discrete sociodemographic and clinical characteristics were compared between the family-history positive and family-history negative groups using χ^2 analysis. For discrete characteristics that were statistically significant, Bonferroni post hoc comparisons were conducted. A t test was used to compare continuous sociodemographic and

clinical characteristics. Bivariate regression models (logistic for discrete variables and linear for continuous variables) were used to assess the association of family history of SUD with depressive severity, quality of life and functioning, presence of depressive symptoms (present if the relevant IDS-C_{30} item was scored > 1), and psychiatric comorbidities. Multivariable regression models were used to assess the association of family history of SUD with depressive severity, quality of life and functioning, and psychiatric comorbidities (independent of the effect of age at MDD onset, education, ethnicity, sex, history of suicide attempt, family history of mood disorder, and personal history of SUD). Multivariable logistic regression models were also used to assess the association of family history of SUD with depressive symptom severity, as measured by the IDS-C_{30} (independent of the effect of age at MDD onset, education, ethnicity, sex, history of suicide attempt, family history of mood disorder, severity of depression, and personal history of SUD).

The statistical significance for all tests was set at $p < .05$. The sample size for each comparison varies due to small amounts of missing data. No correction for multiple tests was made, so results must be interpreted accordingly.

RESULTS

The STAR*D study enrolled 4041 participants with nonpsychotic MDD. Of the 4010 participants who provided information on family history of drug or alcohol abuse or dependence, 46% (N = 1852) endorsed a positive family history of SUD. Overall, 23% (N = 920) reported a family history of alcohol use disorder only, 6% (N = 230) reported a family history of drug use disorder only, and 18% (N = 702) reported a family history of both alcohol and drug use disorders. Of those with a positive family history of an alcohol use disorder (with or without drug use disorder; N = 1622), 76% identified a parent, 42% identified a sibling, and 6% identified a child as the affected first-degree relative. Of the 932 with a family history of drug use disorder (with or without alcohol use disorder), 30% identified a parent, 63% identified a sibling, and 16% identified a child as the affected first-degree relative. As noted above, the total exceeds 100% since the proband participant could be assessed as having more than 1 affected relative for more than 1 SUD.

Table 1 shows baseline demographic and clinical characteristics of the STAR*D participants relative to family history of SUD. Participants with a positive family history were significantly less likely to be Hispanic (p = .0029) and more likely to be

Table 1. Baseline Demographic and Clinical Characteristics Associated With Family History of Substance Use Disorder (SUD)

Characteristic	Negative Family History of SUD	Positive Family History of SUD	p Value
Race, N (%)			.0680
White	1640 (76.0)	1393 (75.2)	
Black or African American	357 (16.5)	346 (18.7)	
Other	161 (7.5)	113 (6.1)	
Ethnicity-Hispanic, N (%)			.0029
Yes	304 (14.1)	203 (11.0)	
No	1853 (85.9)	1649 (89.0)	
Sex, N (%)			.0013
Male	853 (39.5)	641 (34.6)	
Female	1305 (60.5)	1211 (65.4)	
Employment status, N (%)			.1286
Employed	1251 (58.1)	1042 (56.3)	
Unemployed	766 (35.6)	710 (38.4)	
Retired	135 (6.3)	99 (5.3)	
Education, N (%)[a]			.0120
< High school	264 (12.3)	252 (13.6)	
High school to college graduate	1685 (78.3)	1470 (79.4)	
Beyond college graduate	203 (9.4)	129 (7.0)	
Age at onset of MDD, N (%)			< .0001
< 18 y	674 (31.5)	801 (43.7)	
≥ 18 y	1463 (68.5)	1030 (56.3)	
Recurrence of MDD, N (%)			< .0001
1 episode	608 (31.7)	372 (24.0)	
> 1 episode	1313 (68.3)	1181 (76.0)	
Attempted suicide, N (%)			< .0001
Yes	279 (12.9)	381 (20.6)	
No	1876 (87.1)	1470 (79.4)	
Treatment setting, N (%)			.8114
Primary care	838 (38.8)	726 (39.2)	
Specialty	1320 (61.2)	1126 (60.8)	
Marital status, N (%)[b]			.0044
Married	909 (42.2)	740 (40.0)	
Never married	670 (31.1)	525 (28.4)	
Divorced	506 (23.5)	526 (28.4)	
Widowed	68 (3.2)	60 (3.2)	
Family history of depression, N (%)			< .0001
Yes	991 (45.9)	1191 (64.4)	
No	1166 (54.1)	659 (35.6)	
Family history of mood disorder, N (%)			< .0001
Yes	1024 (47.5)	1241 (67.1)	
No	1132 (52.5)	608 (32.9)	
Family history of suicide, N (%)			< .0001
Yes	47 (2.2)	95 (5.2)	
No	2111 (97.8)	1748 (94.8)	
Age, mean ± SD, y	40.3 ± 13.7	40.7 ± 12.8	.2590
Education, mean ± SD, y	13.6 ± 3.4	13.2 ± 3.0	< .0001
Age at onset of first MDD, mean ± SD, y	27.0 ± 14.7	23.7 ± 13.9	< .0001
Number of MDEs, mean ± SD	4.9 ± 8.5	6.0 ± 10.1	.0005
Length of episode, mean ± SD, mo	23.7 ± 49.0	25.6 ± 55.2	.2665
Length of illness, mean ± SD, y	13.3 ± 12.6	17.1 ± 13.4	< .0001

[a]Post hoc comparisons (Bonferroni corrected p < .0167 considered to be statistically significant): less than high school vs. high school to college graduate (p = .3436), less than high school vs. beyond college graduate (p = .0043), high school to college graduate vs. beyond college graduate (p = .0071).

[b]Post hoc comparisons (Bonferroni corrected p < .0083 considered to be statistically significant): married vs. never married (p = .6176), married vs. widowed (p = .6614), married vs. divorced (p = .0021), never married vs. divorced (p = .0009), never married vs. widowed (p = .5242), divorced vs. widowed (p = .3822).

Abbreviations: MDD = major depressive disorder, MDE = major depressive episode.

Table 2. Baseline Depressive Severity, Quality of Life, and Functioning Measures Associated With Family History of Substance Use Disorder (SUD)

		Negative Family History of SUD		Positive Family History of SUD		Unadjusted	Adjusted
Measure[a]	N	Mean ± SD	Adjusted Mean	Mean ± SD	Adjusted Mean	p Value	p Value[b]
HAM-D_{17} (ROA)	3689	19.5 ± 6.6	20.3	20.5 ± 6.4	21.0	< .0001	.0012
IDS-C_{30}	3675	34.9 ± 11.7	36.4	36.4 ± 11.3	37.4	< .0001	.0100
QIDS-SR_{16}	3986	15.2 ± 4.3	16.0	15.8 ± 4.3	16.3	< .0001	.0459
SF-12-physical	3675	49.7 ± 12.0	49.3	48.8 ± 11.9	47.9	.0318	.0006
SF-12-mental	3675	26.8 ± 8.7	26.7	26.6 ± 8.6	27.1	.6587	.2780
Q-LES-Q	3675	42.5 ± 15.5	40.1	40.9 ± 14.9	38.9	.0013	.0180
WSAS	3675	23.1 ± 9.5	23.9	24.0 ± 9.1	24.6	.0017	.0378

[a]Higher score on the HAM-D_{17} (ROA), IDS-C_{30}, and QIDS-SR_{16} indicate greater severity. Higher score on the WSAS indicates worse functioning. Higher score on the SF-12 and Q-LES-Q indicate better health and quality of life, respectively.
[b]Models adjusted for age at MDD onset, education, ethnicity, sex, attempted suicide, family history of mood disorder, and personal history of SUD.
Abbreviations: HAM-D_{17} (ROA) = 17-item Hamilton Rating Scale for Depression (Research Outcomes Assessor), IDS-C_{30} = 30-item Inventory of Depressive Symptomatology–Clinician-Rated, QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology–Self-Report, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SF-12 = Short Form Health Survey, WSAS = Work and Social Adjustment Scale.

female (p = .0013). There was a significant difference in the educational distribution (p = .0120). Participants with a positive family history were less likely to have achieved a high school education (p = .0043) or to have an advanced degree (p = .0071). There was a significant difference in the distribution of marital status (p = .0044). Family-history positive participants were less likely to be married and more likely to be divorced than family-history negative participants. Additionally, as compared to the family-history negative participants, family-history positive participants were more likely to be less than 18 years of age at the onset of MDD (p < .0001), report more than 1 major depressive episode (p < .0001), have attempted suicide (p < .0001), have a family history of depression (p < .0001) or any mood disorder (p < .0001), and have a family history of suicide (p < .0001). In each of these instances, statistical significance was based on a p value less than .05. As a conservative cutoff to identify potential confounding variables, we used a p < .05 for the 19 comparisons. If one were to consider correcting for multiple comparisons using Bonferroni correction, the following characteristics would have remained statistically significant: sex, age at onset less than 18 years versus 18 years or older, recurrence, attempted suicide, family history of depression, family history of mood disorder, family history of suicide, education, mean age at onset of first MDD, and length of illness.

The impact of family history of SUD on depressive severity, quality of life, and functioning is presented in Table 2. While there were statistically significant differences for a number of the measures, none were clinically significant. For example, the difference in severity of depression as measured by the mean IDS-C_{30}, adjusted for sociodemographic and clinical characteristics, is statistically significant (p = .0100), although the mean scores differ only by 1 point (36.4 for family-history negative vs. 37.4 for family-history positive).

After adjustment was made for age at MDD onset, education, ethnicity, gender, attempted suicide, family history of mood disorder, baseline IDS-C_{30} score by the Research Outcomes Assessor, and personal history of SUD, participants with a positive family history were more likely to report midnocturnal insomnia (OR = 1.299, 95% CI = 1.080 to 1.562) and were less likely to report hypersomnia (OR = 0.847, 95% CI = 0.722 to 0.993), sad mood (OR = 0.614, 95% CI = 0.384 to 0.980), and negative outlook on the future (OR = 0.767, 95% CI = 0.644 to 0.913). With the same adjustments, Table 3 shows the presence/absence of psychiatric comorbidities identified by the PDSQ associated with a family history of SUD. Family-history positive participants were more likely to report posttraumatic stress disorder (PTSD), alcohol use disorder, drug use disorder, and generalized anxiety disorder. Furthermore, family-history positive participants reported an overall greater number of Axis I concurrent comorbidities as compared to family-history negative participants (p < .0001).

In addition, the analyses were repeated without adjustment for early age at MDD onset, female sex, and previous history of suicide attempts. The differences between these results and those described above or listed in Tables 2 and 3 were trivial, and the findings of significance did not change for any item.

DISCUSSION

Nearly half of the participants with MDD in this large clinical sample reported a positive family history of SUD. Noteworthy differences were found in those with a positive as opposed to negative family history of SUD. Those with a positive family history of SUD were less likely to be Hispanic and more likely to be female, had a younger age at onset of MDD, and were more likely to have an adolescent onset compared to family-history negative

Table 3. Concurrent Axis I Disorders Associated With Family History of Substance Use Disorder (SUD)

Psychiatric Comorbidity	Negative Family History of SUD, N (%)	Positive Family History of SUD, N (%)	Odds Ratio	95% Confidence Interval	Adjusted Odds Ratio[a]	Adjusted 95% Confidence Interval
OCD			1.145	0.957 to 1.371	1.096	0.904 to 1.328
Present	280 (13.2)	272 (14.8)				
Absent	1845 (86.8)	1565 (85.2)				
Panic disorder			1.197	0.989 to 1.450	1.112	0.907 to 1.363
Present	237 (11.2)	240 (13.1)				
Absent	1888 (88.8)	1597 (86.9)				
Social phobia			1.225	1.068 to 1.406	1.064	0.920 to 1.231
Present	577 (27.2)	576 (31.4)				
Absent	1544 (72.8)	1258 (68.6)				
PTSD			1.226	1.041 to 1.443	1.197	1.008 to 1.422
Present	349 (16.4)	356 (19.4)				
Absent	1777 (83.6)	1479 (80.6)				
Agoraphobia			1.195	0.979 to 1.459	1.142	0.921 to 1.417
Present	215 (10.1)	218 (11.9)				
Absent	1905 (89.9)	1616 (88.1)				
Alcohol use disorder			2.200	1.802 to 2.686	…	…
Present	171 (8.1)	297 (16.2)				
Absent	1953 (91.9)	1542 (83.8)				
Drug use disorder			2.072	1.625 to 2.643	…	…
Present	111 (5.2)	189 (10.3)				
Absent	2008 (94.8)	1650 (89.7)				
Somatoform disorder			0.800	0.529 to 1.210	0.734	0.471 to 1.143
Present	56 (2.6)	39 (2.1)				
Absent	2065 (97.4)	1797 (97.9)				
Hypochondriasis			0.940	0.690 to 1.281	1.015	0.727 to 1.418
Present	93 (4.4)	76 (4.1)				
Absent	2027 (95.6)	1762 (95.9)				
Bulimia nervosa			1.159	0.959 to 1.402	0.992	0.809 to 1.215
Present	245 (11.5)	241 (13.1)				
Absent	1882 (88.5)	1597 (86.9)				
GAD			1.364	1.170 to 1.591	1.203	1.021 to 1.416
Present	393 (18.5)	435 (23.7)				
Absent	1728 (81.5)	1402 (76.3)				
Number of Axis I disorders						
0	974 (46.2)	763 (41.9)	…	…	…	…
1	532 (25.2)	436 (24.0)	1.046	0.893 to 1.225	0.958	0.812 to 1.131
2	279 (13.2)	267 (14.7)	1.222	1.008 to 1.481	1.053	0.859 to 1.291
3	137 (6.5)	158 (8.7)	1.472	1.149 to 1.886	1.280	0.986 to 1.662
≥ 4	186 (8.8)	195 (10.7)	1.338	1.072 to 1.671	1.156	0.909 to 1.470

[a]Models adjusted for age at MDD onset, education, ethnicity, sex, attempted suicide, family history of mood disorder, and personal history of SUD.
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder.
Symbol: … = not applicable.

participants. The earlier onset, in part, explains the longer total duration of depressive illness as compared to family-history negative participants. In addition, participants with a positive family history of SUD were more likely to have recurrent depression, more major depressive episodes, and a positive family history of depression or mood disorder. These findings are consistent with previously reported distinctions in depressive clinical presentations, i.e., a more recurrent pattern of MDD in those patients with a family history of SUD.

In general, there were few differences in the presentation of MDD symptomatology at baseline between those with and without a positive family history of SUD. However, substantial differences were found in concurrent psychiatric comorbidity. The family-history positive group had more concurrent Axis I disorders, specifically PTSD, alcohol and drug use disorders, and generalized anxiety disorder, as compared to the family-history negative group.

Higher rates of concurrent PTSD are consistent with findings from a recent smaller study that compared the clinical features of nonalcoholic patients with MDD (N = 209) without a history of alcoholism in first-degree relatives with those of nonalcoholic MDD patients with a history of alcoholism in first-degree relatives (N = 73).[24] The study participants were drawn from participants in mood disorder research at a university hospital. PTSD and childhood physical/sexual abuse were both significantly more likely in those with both MDD and a positive family history of alcoholism. However, after adjustments were made for gender, the higher prevalence of PTSD declined to a trend level for significance. The study also found that participants who had MDD with a family history of alcohol use disorders were more often female and were

slightly younger than participants with MDD without a family history of alcoholism.

Of clinical importance, the current study found that family-history positive participants were substantially more likely than family-history negative participants to have attempted suicide (21% vs. 13%) and to have a family history of suicide (5% vs. 2%). Unfortunately, the study did not collect details on the nature or lethality of the attempted suicides, or the nature of suicide in family members. Therefore, we are unable to comment on the "serious" versus "nonserious" nature of the suicide attempts or to make comparisons with previous studies. Other studies have found that MDD patients with a positive family history reported more suicide attempts, most commonly "nonserious" attempts, than depressed patients with a negative family history.[10,23] Earlier age at onset of depression and the greater frequency of MDD episodes may contribute to the increased frequency of suicide attempts in family-history positive patients.

Overall, our results indicate that depressed individuals with a positive family history of SUD are at greater risk for psychopathology—perhaps due to complex environmental and genetic factors.[25] A large study[26] of monozygotic male veteran twins (N = 1874) found that familial factors (i.e., inheritance and/or experiences shared by siblings) influence the association between MDD and an alcohol use disorder; however, the association between MDD and drug use disorders are more likely explained by nonfamilial factors.

The current study demonstrates that family-history positive patients may have difficulties in establishing and maintaining a marriage and in achieving educational goals. The results also suggest that family-history positive patients have a more severe depression, as defined by younger age at onset, longer duration of illness, greater likelihood of recurrent depression, more depressive episodes, and higher rates of attempted suicide than the family-history negative patients. These results support the notion that MDD patients with a family history of SUD represent a distinctive subgroup of MDD.

The strengths of this study include its large, prospectively defined, representative sample that includes substantial minority and ethnic representation, as well as participants from treatment settings that include both primary care and psychiatric specialty clinics. Even so, since the participants had to qualify for a clinical trial, the sample may not fully represent the general treatment-seeking population. To mitigate this possible limitation, STAR*D used inclusion/exclusion criteria designed to enroll participants from a general "real-world" patient population and did not recruit from advertisements. Another study limitation is that family history of SUD was based on the clinicians' general psychiatric assessment of a participant's self-report rather than direct evaluation of the family members. Psychiatric diagnoses obtained by personal interview are only moderately reliable, and family history reports are systematically biased.[27] However, the estimates in the current study are consistent with previous findings.

Andreason et al.[28] compared self-reported diagnostic criteria on 2216 first-degree relatives of depressed patients. The study utilized a consensus of 2 Family History Research Diagnostic Criteria interviews and found a sensitivity of 52% and a specificity of 96%. These results indicate that collecting family history through a patient's self-report is a valid source of information.[28] However, in the case of the current study, there may be reduced sensitivity with a single report. The utilization of a clinician-administered interview to obtain information on a patient's family history is clinically meaningful because it mirrors a routine clinical assessment and evaluation.

In conclusion, among patients with nonpsychotic MDD, those who are non-Hispanic or female are more likely to have a family history of SUD. Furthermore, MDD patients with a family history of SUD may be at a greater risk of psychopathology and at a greater risk for attempted suicide than those without a family history of SUD. These findings represent important clinical features to be considered in the evaluation and treatment planning of patients with MDD. These findings confirm previous speculations that depression with a positive family history of SUD is a distinct and more recurrent course of illness. Given the improved technology for genetic biomarkers currently available, follow-up research to this current study and earlier linkage studies[29–31] may now be conducted to determine whether patients with MDD and a family history of SUD have a biologically distinct subtype of MDD. Whether a personal or family history of SUD is associated with different treatment outcomes is also of interest and will be the topic of future STAR*D outcome analyses.

Acknowledgments: The authors acknowledge the administrative support of VA Research and Development at participating VA Medical Centers, as well as the editorial support of Jon Kilner, M.S., M.A. (Pittsburgh, Pa.). Mr. Kilner is an independent contractor hired by the University of Texas Southwestern Medical Center at Dallas to provide writing/editing services and has no financial conflicts or disclosures. The authors also thank the secretarial support of Fast Word Information Processing, Inc. (Dallas, Tex.).

Financial disclosure: **Dr. Davis** has received research support from Abbott, Bristol-Myers Squibb, Eisai Pharmaceuticals, Forest, Ortho McNeil, Janssen, VA, NIMH, Shire, AstraZeneca, and Southwestern Oncology Group; is a consultant for Cyberonics, Abbott, Bristol-Myers Squibb, and Shire; is a speaker for Abbott, Cyberonics, Bristol-Myers Squibb, and Sanofi-Aventis; and has equity holdings in Pfizer. **Dr. Gaynes** has received grant/research support from the Agency for Healthcare Research and Quality, NIMH, Ovation Pharmaceuticals, Pfizer, and the Robert Wood Johnson Foundation; has received honoraria as a speaker from GlaxoSmithKline; is a consultant for Pfizer, Shire, and Wyeth-Ayerst; and has received the NIMH Career Development Award. **Dr. Trivedi** has received research support from Bristol-Myers Squibb, Cephalon, Corcept Therapeutics, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Merck, NIMH, the National Alliance for Research on Schizophrenia and

Depression, Novartis, Pfizer, Pharmacia & Upjohn, Predix, Solvay, and Wyeth-Ayerst; has participated in advisory boards and is a consultant for Abbott, Akzo (Organon), AstraZeneca, Bayer, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Johnson & Johnson, Meade Johnson, Neuronetics, Parke-Davis, Pfizer, Pharmacia & Upjohn, Sepracor, Solvay, and Wyeth-Ayerst; and has participated in speakers boards for Abdi Brahim, Akzo (Organon), Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Pharmacia & Upjohn, Solvay, and Wyeth-Ayerst. **Dr. Wisniewski** is a consultant for Cyberonics, ImaRx Therapeutics, and Bristol-Myers Squibb. **Dr. Fava** has received research support from Abbott, Alkermes, Aspect Medical Systems, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, J & J, Lichtwer Pharma, Lorex, Novartis, Organon, PamLab, Pfizer, Pharmavite, Roche, Sanofi/Synthelabo, Solvay, and Wyeth-Ayerst; is an advisor/consultant for Aspect Medical Systems, AstraZeneca, Bayer AG, Best Practice Project Management, Biovail, BrainCells Inc., Bristol-Myers Squibb, Cephalon, Compellis, Cypress, Dov, Eli Lilly, EPIX, Fabre-Kramer, Forest, GlaxoSmithKline, Grunenthal, Janssen, Jazz, J & J, Knoll, Lundbeck, MedAvante, Merck, Neuronetics, Novartis, Nutrition 21, Organon, PamLab, Pfizer, PharmaStar, Pharmavite, Roche, Sanofi/Synthelabo, Sepracor, Solvay, Somaxon, Somerset, Takeda, and Wyeth-Ayerst; is a speaker for AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Novartis, Organon, Pfizer, PharmaStar, and Wyeth-Ayerst; and has equity holdings in Compellis and MedAvante. **Dr. Shelton** has received grant/research support from Eli Lilly, GlaxoSmithKline, Janssen, Pfizer, Roehn-Polenc-Rorer, Sanofi, SmithKline Beecham, Wyeth-Ayerst, Zeneca, and Abbott; is a consultant for Pfizer and Janssen; and is a member of the speakers bureau for Bristol-Myers Squibb, Eli Lilly, Janssen, Pfizer, SmithKline Beecham, Solvay, Wyeth-Ayerst, and Abbott. **Dr. Alpert** has received grant/research support from Abbott, Alkermes, Lichtwer Pharma, Lorex, Aspect Medical Systems, AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, J & J, Novartis, Organon, PamLab, Pfizer, Pharmavite, Roche, Sanofi/Synthelabo, Solvay, and Wyeth-Ayerst; is a consultant for Eli Lilly, PamLab, and Pharmavite; and has received speakers' honoraria from Eli Lilly, Janssen, and Organon. **Ms. Frazier**, **Ms. Barkin**, and **Drs. Kashner** and **Rush** report no additional financial or other relationships relevant to the subject of this article.

REFERENCES

1. Grant BF, Hasin DS, Dawson DA. The relationship between DSM-IV alcohol use disorders and DSM-IV major depression: examination of the primary-secondary distinction in a general population sample. J Affect Disord 1996;38:113–128
2. Williams RA, Hagerty BM, Yousha SM, et al. Factors associated with depression in Navy recruits. J Clin Psychol 2002;58:323–337
3. Merikangas KR, Risch NJ, Weissman MM. Comorbidity and co-transmission of alcoholism, anxiety and depression. Psychol Med 1994;24:69–80
4. McAvay G, Nunes EV, Zaider TI, et al. Physical health problems in depressed and nondepressed children and adolescents of parents with opiate dependence. Depress Anxiety 1999;9:61–69
5. Nurnberger JI, Wiegand R, Bucholz K, et al. A family study of alcohol dependence: coaggregation of multiple disorders in relatives of alcohol-dependent probands. Arch Gen Psychiatry 2004;61:1246–1256
6. Reich W, Earls F, Frankel O, et al. Psychopathology in children of alcoholics. J Am Acad Child Adolesc Psychiatry 1993;32:995–1002
7. Winokur G. The division of depressive illness into depression spectrum disease and pure depressive disease. Int Pharmacopsychiatry 1974;9:5–13
8. Coryell W, Winokur G, Keller M, et al. Alcoholism and primary depression: a family study approach to co-existing disorders. J Affect Disord 1992;24:93–99
9. Cadoret RJ, Winokur G, Langbehn D, et al. Depression spectrum disease, 1: the role of gene-environment interaction. Am J Psychiatry 1996;153:892–899
10. Winokur G, Coryell W. Familial subtypes of unipolar depression: a prospective study of familial pure depressive disease compared to depression spectrum disease. Biol Psychiatry 1992;32:1012–1018
11. Fava M, Rush AJ, Trivedi MH, et al. Background and rationale for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Psychiatr Clin North Am 2003;26:457–494
12. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced Treatment Alternatives to Relieve Depression (STAR*D): rationale and design. Control Clin Trials 2004;25:119–142
13. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
14. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
15. Trivedi MH, Rush AJ, Ibrahim HM, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med 2004;34:73–82
16. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996;26:477–486
17. Zimmerman M, Mattia JI. A self-report scale to help make psychiatric diagnoses: the Psychiatric Diagnostic Screening Questionnaire. Arch Gen Psychiatry 2001;58:787–794
18. Rush AJ, Zimmerman M, Wisniewski SR, et al. Comorbid psychiatric disorders in depressed outpatients: demographic and clinical features. J Affect Disord 2005;87:43–55
19. Mundt JC. Interactive voice response systems in clinical research and treatment. Psychiatr Serv 1997;48:611–612
20. Kobak KA, Greist JH, Jefferson JW, et al. Computerized assessment of depression and anxiety over the telephone using interactive voice response. MD Comput 1999;16:64–68
21. Ware JE Jr, Sherbourne DC. The MOS 36-item Short Form Health Survey (SF-36), 1: conceptual framework and item selection. Med Care 1992;30:473–483
22. Mundt JC, Marks IM, Shear MK, et al. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry 2002;180:461–464
23. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q): a new measure. Psychopharmacol Bull 1993;29:321–326
24. Oquendo SL, Conason AH, Brent DA, et al. Clinical features of depressed patients with or without a family history of alcoholism. Acta Psychiatr Scand 2005;112:266–271
25. Jacob T, Waterman B, Heath A, et al. Genetic and environmental effects on offspring alcoholism: new insights using an offspring-of-twins design. Arch Gen Psychiatry 2003;60:1265–1272
26. Lin N, Eisen SA, Scherrer JF, et al. The influence of familial and non-familial factors on the association between major depression and substance abuse/dependence in 1874 monozygotic male twin pairs. Drug Alcohol Depend 1996;43:49–55
27. Kendler KS, Prescott CA, Jacobson K, et al. The joint analysis of personal interview and family history diagnoses: evidence for validity of diagnosis and increased heritability estimates. Psychol Med 2002;32:829–842
28. Andreasen N, Rice J, Endicott J, et al. The family history approach to diagnosis. Arch Gen Psychiatry 1986;43:421–429
29. Wilson AF, Tanna VL, Winokur G, et al. Linkage analysis of depression spectrum disease. Biol Psychiatry 1989;26:163–175
30. Tanna VL, Wilson AF, Winokur G, et al. Possible linkage between alcoholism and esterase-D. J Stud Alcohol 1988;49:472–476
31. Tanna VL, Wilson AF, Winokur G, et al. Linkage analysis of pure depressive disease. J Psychiatr Res 1989;23:99–107