Association Between Treatment-Emergent Suicidal Ideation With Citalopram and Polymorphisms Near Cyclic Adenosine Monophosphate Response Element Binding Protein in the STAR*D Study

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Context: A small subset of patients with depression exhibit new or worsening suicidal thoughts or behavior during short-term treatment with antidepressants. Because cyclic adenosine monophosphate response element binding (CREB) protein has been implicated in both antidepressant mechanisms and suicide, the CREB1 gene represents a gene that possibly influences the risk for treatment-emergent suicidality.

Objective: To examine polymorphisms that span CREB1, which was previously associated with anger expression in men with major depressive disorder, for association with new or worsening suicidality.

Design: Nested case-control study derived from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a multicenter, prospective, open, 12-week effectiveness trial from July 1, 2001, to September 30, 2006.

Setting: Outpatient primary care and psychiatric clinics.

Patients: Individuals with nonpsychotic major depressive disorder for whom DNA was available and who did not report suicidal ideation at study entry were subsequently treated with citalopram hydrobromide for up to 12 weeks.

Main Outcome Measure: Emergent suicidal ideation, defined as a score of 2 or higher on any postbaseline visit for participants whose baseline score was 0 or 1 on the 16-item Quick Inventory of Depressive Symptomatology–Clinician Rated item.

Results: Of 1447 participants, 124 (8.6%) subsequently reported suicidality on at least 1 visit; these individuals were compared with the remaining 1324 participants. Of 5 single nucleotide polymorphisms (SNPs) examined, none were significantly associated with treatment-emergent suicidality overall. However, 2 SNPs revealed a gene-by-sex interaction with suicidality. Among the 539 men, these 2 SNPs and 2 of the 5 SNP haplotypes were significantly associated with new-onset suicidality.

Conclusions: Polymorphisms that span CREB1 were associated with treatment-emergent suicidality among men with depression, extending an observation of association with male anger expression in a prior independent cohort. If replicated, this finding would suggest that pharmacogenetic testing could facilitate the identification of the small subset of individuals at greater risk during short-term antidepressant treatment.

Arch Gen Psychiatry. 2007;64:689-697

Despite a number of early case reports indicating emergence or worsening of suicidal thinking or behavior after initiation of desipramine hydrochloride and selective serotonin reuptake inhibitors, several meta-analyses of antidepressant medication trials in major depressive disorder found no significant difference in risk relative to placebo. Indeed, an examination of health-plan data found a decrease in suicide risk after initiation of treatment with antidepressants.

On the other hand, although most individuals are helped by antidepressant medication, a subgroup may still experience symptomatic worsening. This concern led the Food and Drug Administration to mandate a labeling change for antidepressants. Regardless of treatment specificity, nearly all antidepressant medication studies find that some patients experience suicidality after treatment initiation. For example, in a large open study of fluoxetine hydrochloride, 14% of patients reported emergence of suicidal thoughts after treatment initiation. Identification of this subgroup before treatment would have tremendous clinical utility.

Family studies reviewed by Brent and Mann indicate that suicide attempts and completed suicide show familial aggregation, which persists even after adjustment for the presence of psychiatric dis-
order. Based on large twin registry studies, estimates of the heritability of suicidal behavior are in the range of 30% to 55%. We hypothesized that, as with suicidal behavior in general, propensity to develop suicidal thinking during antidepressant treatment might itself be genetically influenced. In particular, converging lines of evidence implicate the transcription factor cyclic adenosine monophosphate (cAMP) response element binding (CREB) protein, coded by the CREB1 gene, in antidepressant response and suicide.

In addition, we have recently observed that single nucleotide polymorphisms (SNPs) near this gene are associated with variation in anger expression among male patients with MDD, a trait that has been associated with suicidality.

Therefore, we examined the possible association between polymorphisms near CREB1 and emergence of suicidal thoughts and behavior during antidepressant treatment in a cohort from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a large multicenter study of patients treated openly with citalopram hydrobromide for 12 to 14 weeks.

**METHODS**

**CLINICAL METHODS**

STAR*D was a multicenter trial in which patients initially received first-line treatment with the selective serotonin reuptake inhibitor citalopram. The methods of the STAR*D study are described in detail elsewhere and are summarized herein.

**STUDY ORGANIZATION**

The STAR*D study was conducted at 14 regional centers that oversaw 41 sites that consisted of 18 primary care and 23 psychiatric care settings across the United States. Research outcomes were collected by telephone interviews conducted by a small team of trained research outcome assessors masked to treatment and by telephone-based interactive voice response. The research outcome assessors received extensive training in the administration of efficacy measures, with interrater reliability assessed periodically.

**STUDY POPULATION**

This report presents data from the 1879 participants who entered level 1 (citalopram) treatment in the STAR*D study for whom DNA was available. The study recruited only individuals who sought treatment at the clinical sites; advertising to recruit participants was not permitted. Participants were informed of all risks, benefits, and adverse events associated with each study treatment, and they provided written informed consent before study entry. Participants were not required to participate in the genetic portion of the protocol, which was initiated approximately 12 months after study initiation. The study protocol was approved by institutional review boards at all participating regional centers, the national coordinating center, and the data coordinating center. The study was overseen by the National Institute of Mental Health data and safety monitoring board.

Participants met broadly inclusive and minimally exclusive criteria to enroll a representative sample. Men and women outpatients aged 18 to 75 years with a DSM-IV diagnosis of nonpsychotic MDD, with a baseline score of 14 or higher on the 17-item Hamilton Rating Scale for Depression (HRSD17) determined by the clinical research coordinator, and for whom the treating physician had determined that outpatient antidepressant treatment was safe and appropriate were enrolled. Exclusion criteria included a well-documented history of nonresponse or intolerability in the current major depressive episode to adequate doses of 1 or more medications used in the first 2 treatment steps; lifetime diagnosis of MDD with psychotic features, schizophrenia, schizoaffective disorder, or bipolar disorder; a current primary diagnosis of eating disorder or obsessive-compulsive disorder; presence of severe, unstable concurrent psychiatric conditions likely to require hospitalization within 6 months (eg, severe alcohol dependence with recent detoxification admissions); presence of concurrent medical or psychiatric conditions or concomitant medications that contraindicate a protocol treatment; and pregnancy or intent to conceive within the 9 months subsequent to study entry.

**RESEARCH OUTCOME ASSESSMENTS**

The clinical research coordinator at each study site completed the HRSD17 at baseline, reviewed inclusion and exclusion criteria, and completed the 16-item Quick Inventory of Depressive Symptomatology (QIDS-C16), a clinician-rated scale that assesses 9 diagnostic symptoms and domains of MDD, at each visit. The research outcome assessor conducted a telephone interview with study participants within 72 hours of the baseline and subsequent visits to complete the baseline HRSD17 and the 30-item Inventory of Depressive Symptomatology–Clinician Rated (IDS-C30).

**INTERVENTION**

All participants received citalopram hydrobromide using dosing guidelines that advised beginning at 20 mg/d and then increasing to 40 mg/d by week 4 and to 60 mg/d by week 6. Dose adjustments were based on guidelines that reflect duration of treatment at current dose, symptom changes, and adverse effect burden, with flexibility allowed based on clinician impression of patient status. The protocol advised treatment visits at 2, 4, 6, 9, and 12 weeks (with an optional visit at week 14 if needed). Patients could discontinue use of citalopram before 12 weeks in the event of intolerable adverse effects that required change in medication, inability to increase to an optimal dose because of adverse effects or patient preference, or presence of significant depressive symptoms (defined as QIDS-C score ≥9) after 9 weeks at the maximum tolerated dose. Concomitant treatments for current general medical conditions; for associated symptoms of depression, including insomnia, anxiety, and agitation; and for citalopram adverse effects were permitted based on clinical judgment. However, stimulants, anticonvulsants, anxiolytics, alprazolam, nonprotocol antidepressants other than trazodone (≤200 mg) at bedtime for insomnia, and psychotherapies for depressive symptoms were not permitted.

**GENOTYPING METHODS**

We first identified all validated SNPs in a region that included CREB1 and flanking regions (115 kilobases in all) using the International HapMap Project Phase 1c database, which yielded a total of 44 SNPs. The Tagger program, which examines pairwise and multilocus linkage disequilibrium to determine the minimum set of SNPs necessary to capture all common genetic variation in a region, identified 5 tags sufficient to capture all exonic or putative promoter-region HapMap SNPs in CREB1, with a minimum r2 of 0.8 (mean r2 of 0.93). Subse-
In light of previous analyses that indicate sex-specific effects of CREB1 in depression liability, which show an association in women but not men, as well as anger expression, which show an association in men but not women, we also used WHAP to formally test for sex-related heterogeneity in the effect of CREB1 (ie, a gene-by-sex interaction). When this test result was statistically significant, we proceeded as planned to examine within-sex associations separately. This gene-by-sex interaction was the only subgroup analysis specified a priori. (Although permutation accounts for testing multiple correlated SNPs within a gene [ie, controls α at the genelevel], Pvalues for single-marker associations are otherwise reported without correction for multiple comparisons; because 2 primary sets of tests were performed [the sample as a whole and male cohort alone], Bonferroni correction would require P<0.025 for statistical significance, although since the tests are not truly independent, this represents a conservative threshold.

HAPLOTYPE AND CONDITIONAL TESTING

Haplotype analyses were also conducted using WHAP. The initial haplotype test is an omnibus test for any joint effect of all haplotypes observed (minor allele frequency, ≥0.01). WHAP accounts for any potential ambiguity in inferred haplotypes by using a weighted likelihood approach to test for association conditional on the posterior distribution of possible haplotypic phases given the multilocus genotype for each individual. When the omnibus test result was statistically significant, we then performed haplotype-specific tests (ie, 1- and 2df tests of each haplotype vs all others). Because HapMap data indicated a single block of linkage disequilibrium that spanned the 5 markers, haplotypes that used all 5 markers were examined.

ADDITIONAL ANALYSES

Comparisons of clinical features between groups used t tests or χ² tests, as appropriate. To generate Kaplan-Meier survival curves for illustrative purposes, participant data were censored at time of dropout, completion of 90 days, or after emergence of suicidality. For examination of the effects of covariates such as cotreatment with a sedative or hypnotic, logistic regression was used. These analyses were performed using Stata statistical software, version 9.0 (Stata Inc, College Station, Tex).

RESULTS

Participants who provided DNA were generally similar to the total STAR*D population in sociodemographic and clinical features, as has been reported elsewhere. However, since the DNA sample collection began months after study initiation, those providing DNA samples were more likely to have been in follow-up and to have achieved a good outcome. Figure 1 shows how the analytic sample was generated. Of 1879 individuals for whom DNA was available, 38 did not remain in the study for at least 1 week, leaving 1841 in the risk set (none of these 38 are known to have made a suicide attempt). Among these 1841, 394 scored 2 or higher on item 12 at study entry, which left 1447 in the risk set. Of these 1447, 123 (8.5%) scored 2 or higher on item 12 (ie, reported suicidal ideation) on at least 1 postbaseline visit.

Those who did or did not develop suicidal ideation during treatment were generally similar in baseline characteristics (Table 1). Individuals who developed suicidal ideation were significantly more likely to report...
C16, or HRSD17, as a covariate (results not shown). While the study did not show a significant association with suicidality (Table 2 and Figure 2), these tests indicated that 2 of 8 haplotypes were significantly associated (P=.004 and P=.009). The most common haplotype appears to be protective (ie, to be underrepresented among those who developed suicidal ideation).

The primary analyses indicated a sex-specific association between 2 SNPs that flanked CREB1 and treatment-emergent suicidality. To examine the possibility that CREB1 polymorphisms were associated with proneness to suicidality before treatment, rather than treatment-emergent suicidality in particular, men with and without suicidality at study entry were compared. No statistically significant association was noted between any SNP and the presence or absence of baseline suicidality. Likewise, no evidence of association was noted between any SNP and history of lifetime suicide attempt.

We also examined the potential confounding effect of sedative or hypnotic use during citalopram treatment, as allowed by the protocol. Among the male participants, 111 (21%) of 539 received sedative or hypnotic cotreatment, including 92 (19%) of 485 with no suicidality and 19 (35%) of 54 with suicidality (χ²=7; P=.008). Individuals who received sedative or hypnotic cotreatment were significantly more likely to experience suicidality (P=.02; OR, 2.3; 95% confidence interval [CI], 1.2-4.5). However, in a regression model, rs4675690 remained significantly associated with suicidality after adjustment for presence or absence of cotreatment (OR, 1.91; 95% CI, 1.3-2.9).

Finally, because previous studies have suggested that antidepressant-associated suicidality often occurs in the first month of treatment, we performed a secondary analysis in which suicidality was divided by epoch (ie, new suicidality occurring within 30 days, between 30 and 60 days, and beyond 60 days). For the initial 30 days, statistically significant association (P<.003; OR, 2.3; 95% CI, 1.3-3.9) remained between rs4675690 and new suicidality. However, for suicidality emerging after 30 days, no statistically significant association was evident (P>.05).

In this analysis of 1447 outpatients with MDD without suicidality who initiated citalopram treatment, 8.6% subsequently reported emergence of such ideation during short-term antidepressant treatment. Among men, risk of emergence of suicidality was associated with 2 SNPs that flanked CREB1 that were previously implicated in a measure of anger expression in an independent cohort of men with MDD. The present finding therefore partially replicates and extends the initial association with a quantitative trait in our previous cohort. Notably, the risk alleles in our cohort correspond to those associated with lower outward expression of anger in a previous cohort with MDD, consistent with models associating suicidality with inwardly rather than outwardly directed anger, particularly among men.

To our knowledge, this finding represents the first association between a genetic polymorphism and antidepressant-associated suicidality. The STAR*D study cohort is one of few with sample sizes sufficient to allow examination of this uncommon but clinically important outcome.
The rate of suicidal ideation emergence is similar to or slightly less than that observed in other studies. For example, in a previous group of 400 fluoxetine-treated patients, 14.3% subsequently had emergence or worsening of suicidality on at least one subsequent visit throughout 12 weeks. Similarly, a previous meta-analysis that included fluoxetine found worsening of the suicidal ideation score (HRSD3 score increasing by any amount) in 15.3%. Of note, only 1 participant in the STAR*D genetics cohort made a suicide attempt, and there were no completed suicides.

In addition to multiple linkage peaks identified in a genomewide linkage survey, a number of candidate gene studies have reported associations with suicide or suicide attempts, although most have not been replicated; these include studies of the serotonin transporter, tryptophan hydroxylase, and other monoaminergic genes. Association studies such as this one may yield false-positive results when the prior probability of association is low. Importantly, therefore, CREB1 represented a particularly appealing functional candidate gene because its product is known to be associated with antidepressant effects and suicide. Region-specific alterations in CREB protein activity have been observed in animal models of antidepressant treatment. In humans, changes in CREB protein expression and phosphorylation have been demonstrated in those committing suicide, and the CREB1 region has been linked to MDD. Finally, we recently observed an association between the same CREB1 poly-

| Table 1. Clinical Features of Genotyped STAR*D Participants Without Suicidality at Study Entry |
|-------------------------------------------------|----------------|----------------|----------------|----------------|----------------|
| Treatment-Associated Suicidality                | No (n = 1324) | Yes (n = 124)  | Total (N = 1447) | Significance Test | P Value       |
| Mean (SD)*                                      |                |                |                  |                  |               |
| Current age, y                                   | 42.5 (13.4)    | 42.3 (13.2)    | 42.5 (13.4)      | 0.3              | .80           |
| Age at first episode, y                         | 26.7 (14.8)    | 24.4 (13.8)    | 26.5 (14.8)      | 1.7              | .10           |
| Baseline HRSD17 score                           | 19.0 (6.3)     | 21.0 (6.4)     | 19.2 (6.3)       | -3.3             | <.001         |
| Baseline IDS-C score                            | 34.0 (11.1)    | 37.9 (11.6)    | 34.3 (11.2)      | -3.6             | <.001         |
| Baseline QIDS-C score                           | 15.6 (3.1)     | 17.0 (3.3)     | 15.7 (3.1)       | -4.9             | <.001         |
| No. (%)*                                        |                |                |                  |                  |               |
| Male                                            | 486 (36.7)     | 54 (43.6)      | 539 (37.3)       | 2.3              | .10           |
| White                                           | 1050 (79.3)    | 94 (75.8)      | 1143 (79.0)      | 0.8              | .40           |
| Recurrent depression                            | 913 (74.8)     | 95 (78.2)      | 1007 (75.5)      | 3.4              | .10           |
| Hopelessness, baseline‡                         | 692 (52.3)     | 99 (80.5)      | 791 (54.7)       | 36.2             | <.001         |
| History of suicide attempt                      | 150 (11.4)     | 22 (17.70)     | 172 (11.8)       | 4.4              | .04           |

Abbreviations: HRSD17, 17-item Hamilton Rating Scale for Depression; IDS-C, Inventory of Depressive Symptomatology–Clinician Rated; QIDS-C, Quick Inventory of Depressive Symptomatology–Clinician Rated.

* t test.
† x2 test.
‡ Hopelessness was defined as a QIDS-C item 12 score of 1.

| Table 2. Single Marker and Haplotype Test Results for Association With Treatment-Emergent Suicidality for All Participants and a Male-Only Subset |
|-------------------------------------------------|----------------|----------------|----------------|----------------|----------------|
| rs2709376 rs2253206 rs759966 rs7594560 rs4675690 Freq (Males) | Freq (Males: SI+) | Freq (Males: SI−) | Empirical P Value (Males) | Empirical P Value (Males: SI+) | Empirical P Value (Males: SI−) |
| Hap1                                           | C A A A T C    | 0.25            | 0.14            | 0.26            | .004           |
| Hap2                                           | C G G T T T    | 0.23            | 0.28            | 0.22            | .16            |
| Hap3                                           | C G G T C T    | 0.19            | 0.15            | 0.19            | .21            |
| Hap4                                           | C A G T T T    | 0.09            | 0.16            | 0.08            | .009           |
| Hap5                                           | C G G C T T    | 0.08            | 0.07            | 0.08            | .45            |
| Hap6                                           | C A G T C T    | 0.07            | 0.09            | 0.07            | .55            |
| Hap7                                           | T A G T C T    | 0.03            | 0.04            | 0.03            | .84            |
| Hap8                                           | T A G C T T    | 0.03            | 0.05            | 0.03            | .16            |
| Hap9                                           | T A G T G T    | 0.01            | 0.03            | 0.01            | .10            |
| Hap10                                          | T G A A T T    | 0.01            | 0.01            | 0.01            | .88            |
| Minor allele                                   | T G A C T      |                |                |                |                |
| MAF (all participants)                         | 0.08           | 0.39            | 0.28            | 0.11            | 0.46           |
| Empirical P value (all participants)           | .21            | .86             | .14             | .86             | .13            |
| SNP-by-sex P value                             | .76            | .79             | .02             | .39             | .007           |
| MAF (all males)                                | 0.09           | 0.49            | 0.28            | 0.1             | 0.46           |
| MAF (males: SI+)                               | 0.11           | 0.49            | 0.17            | 0.09            | 0.59           |
| MAF (males: SI−)                               | 0.08           | 0.5             | 0.29            | 0.1             | 0.44           |
| Empirical P value (males)                      | 0.36           | 0.87            | 0.005           | 0.70             | 0.005          |

Abbreviations: Freq, haplotype frequency; MAF, minor allele frequency; SI+, emergence of suicidality; SI−, no suicidality; SNP, single nucleotide polymorphism.

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In addition to multiple linkage peaks identified in a genomewide linkage survey, a number of candidate gene studies have reported associations with suicide or suicide attempts, although most have not been replicated; these include studies of the serotonin transporter, tryptophan hydroxylase, and other monoaminergic genes. Association studies such as this one may yield false-positive results when the prior probability of association is low. Importantly, therefore, CREB1 represented a particularly appealing functional candidate gene because its product is known to be associated with antidepressant effects and suicide. Region-specific alterations in CREB protein activity have been observed in animal models of antidepressant treatment. In humans, changes in CREB protein expression and phosphorylation have been demonstrated in those committing suicide, and the CREB1 region has been linked to MDD. Finally, we recently observed an association between the same CREB1 poly-
with suicide. We thus hypothesized that antidepressant treatment might provide an additional stress in a subset of male patients with MDD with an underlying diathesis and that this diathesis would be associated with CREB1 polymorphisms.

An important question in interpreting these results is their treatment specificity, that is, to what extent might they reflect risk associated with the antidepressant citalopram vs natural fluctuation in illness severity or placebo response. Without a placebo comparator, we cannot directly address this question. Notably, patients often initiate antidepressant treatment when their symptoms are most severe, which could contribute to an apparently elevated early risk of suicidality. However, we note that the SNPs associated with treatment-emergent suicidality did not demonstrate association with suicidality at baseline.

A key limitation in the present study is the reliance on a single rating scale item that captures suicidal ideation. Of note, similar single-item measures exhibit excellent interrater reliability and correlate well with the Beck Scale for Suicide Ideation. Such a measure also has predictive validity: a 20-year prospective study found that individuals who scored 2 or higher on item 3 of the HRSD were 4.9 times as likely to commit suicide as individuals scoring lower than 2; other studies also support the predictive role, even if imperfect, of suicidal thoughts.

We also note that neither of the 2 SNPs with evidence of association lie in coding regions; rs4675690 is 3’ to the coding region of CREB1, adjacent to a second gene (LOC151194, similar to hepatocellular carcinoma–associated antigen HCA557b, which is known to be expressed in the brain), whereas rs7659963 is in the 3’ untranslated region for both genes. Although a less likely a priori candidate, LOC151194 cannot be excluded as mediating the observed association (eTable). Our SNPs tagged (with r² > 0.8) all but 2 of the known HapMap SNPs in the region with minor allele frequency greater than or equal to 0.05 (Single Nucleotide Polymorphism database of the National Center for Biotechnology Information, build 125: http://www.ncbi.nlm.nih.gov/SNP/index.html). There is currently only 1 known (noncoding) exonic SNP in CREB1 in this database. Thus, if CREB1 influences treatment-emergent suicidality, the causal variant remains to be determined, because none of the polymorphisms directly assayed here are known to affect CREB1 expression or function. Of note, the tagging approach captures common variations but may not account for SNPs not included in HapMap or those with low (<5%) minor allele frequency. Finally, we cannot entirely exclude the possibility of spurious association arising from population stratification, despite the persistence of association when the cohort is limited to white individuals.

The sex-specific nature of the association is intriguing and merits further study. We hypothesized a gene–by-sex interaction based on evidence from a prior study of CREB1 and anger expression in MDD. Interestingly, Zubenko et al reported linkage between the CREB1 region and recurrent, early-onset MDD in women but not men. Female patients with depression may express lower levels of anger or irritability in general; in the same way, their antidepressant response phenotype may differ from that of men.

Regardless of specificity, the associations noted between symptoms and suicidal thinking have potential
clinical implications in identifying a higher-risk subgroup among depressed patients; interventions that benefit most patients may still be associated with worsening in a small subset.\textsuperscript{13,15} The ability to identify this group could allow both patients and clinicians to proceed with antidepressant use with greater confidence or focus more attention on the high-risk group. Before consideration of clinical application of these findings, the confirmation in other antidepressant trial data sets, particularly those with placebo control, will be critical to clarify their specificity and generalizability.

Submitted for Publication: June 12, 2006; final revision received September 26, 2006; accepted October 20, 2006.

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Financial Disclosure: Dr Perlis discloses the following: Research support: Eli Lilly & Company, Elan/Eisai, National Institute of Mental Health, NARSAD, Bowman Family Foundation, American Philosophical Society; Advisory/consulting: AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Company, Pfizer Inc; Speaking: AstraZeneca, Bristol-Myers Squibb Company, Eli Lilly & Company, GlaxoSmithKline, Pfizer Inc; Equity holdings: none; Royalty/patent, other income: none. Dr Fava discloses the following: Research support: Abbott Laboratories, Alkermes, Aspect Medical Systems, Astra-Zeneca, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc, GlaxoSmithKline, J & J Pharmaceuticals, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, Novartis, Organon Inc, PamLab, LLC, Pfizer Inc, Pharmavite, Roche, Sanofi/Synthelabo, Solvay Pharmaceuticals, Inc, Wyeth-Ayerst Laboratories; Advisory boards/consulting: Aspect Medical Systems, Astra-Zeneca, Bayer AG, Biovail Pharmaceuticals Inc, BrainCells, Inc, Bristol-Myers Squibb Company, Cephalon, Compellis, Cypress Pharmaceuticals, Dov Pharmaceuticals, Eli Lilly & Company, EPIX Pharmaceuticals, Fabre-Kramer Pharmaceuticals Inc, Forest Pharmaceuticals Inc, GlaxoSmithKline, Grunenthal GmbH, Janssen Pharmaceutical, Jazz Pharmaceuticals, J & J Pharmaceuticals, Knoll Pharmaceutical Company, Lundbeck, MedAvante, Inc, Neuronechts, Novartis, Nutrition 21, Organon Inc, PamLab, LLC, Pfizer Inc, PharmaStar, Pharmavite, Roche, Sanofi/Synthelabo, Seprazol, Solvay Pharmaceuticals, Inc, Somaxon, Somerset Pharmaceuticals, Wyeth-Ayerst Laboratories; Speaking: Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc, GlaxoSmithKline, Novartis, Organon Inc, Pfizer Inc, PharmaStar, Wyeth-Ayerst Laboratories; Equity holdings: Compellis, MedAvante; Royalty/patent, other income: none. Dr Trivedi discloses the following: Research support: Bristol-Myers Squibb Company, Cephalon, Inc; Concept Therapeutics, Inc; Cyberonics, Inc; Eli Lilly & Company, Forest Pharmaceuticals; GlaxoSmithKline; Janssen Pharmaceutical; Merck; National Institute of Mental Health; National Alliance for Research in Schizophrenia and Depression; Novartis; Pfizer Inc; Predix Pharmaceuticals; Wyeth-Ayerst Laboratories; Advisory boards/consulting: Abbott Laboratories, Inc; Akzo (Organon Pharmaceuticals Inc); Bayer; Bristol-Myers Squibb Company; Cyberonics, Inc; Forest Pharmaceuticals; GlaxoSmithKline; Janssen Pharmaceutical Products, LP; Johnson & Johnson PRD; Eli Lilly & Company; Meade Johnson; Parke-Davis Pharmaceuticals, Inc; Pfizer, Inc; Pharmacia & Upjohn; Seprazol, Solvay Pharmaceuticals, Inc; Wyeth-Ayerst Laboratories; Equity holdings: None (exclude mutual funds/blinded trusts); Royalty/patent, other income: none. Dr Rush discloses the following: Speaker’s bureau: Cyberonics, Inc; Forest Pharmaceuticals, Inc; GlaxoSmithKline; Advisory boards/consultant: Advanced Neurmodulation Systems, Inc; Best Practice Project Management, Inc; Bristol-Myers Squibb Company, Cyberonics, Inc; Eli Lilly & Company, Forest Pharmaceuticals, Inc; Gerson Lehman Group; GlaxoSmithKline; Healthcare Technology Systems, Jazz Pharmaceuticals; Merck & Company; Neuronechts; Ono Pharmaceuticals, Inc; Organon Pharmaceuticals, Inc; Personality Disorders Research Corp; Urban Institute; Wyeth-Ayerst Laboratories, Inc; Research support: Robert Wood Johnson Foundation, National Institute of Mental Health, Stanley Medical Research Institute; Royalties: Guilford Publications, Healthcare Technology Systems; Stock: Pfizer, Inc. Dr Smoller discloses the following: Honoraria: Hoffman-La Roche, Inc; Advisory board/consultant: Roche Diagnostics Corporation; Research support: National Institute of Mental Health and the National Alliance for Research in Schizophrenia and Depression.

Funding/Support: The STAR\textsuperscript{D} study is supported by federal funds from the National Institute of Mental Health under contract N01 MH-90003 to the University of Texas Southwestern Medical Center at Dallas (Dr Rush, principal investigator). Dr Perlis is supported by National Institute of Mental Health grant K23MH67060, a NARSAD Young Investigator Award, and a grant from the Bowman Family Foundation.

Acknowledgment: We appreciate the support of Forest Laboratories for providing citalopram at no cost to the STAR\textsuperscript{D} study. We thank Stephen Wisniewski, PhD, and Heather Eng, BA, for providing the clinical data. We thank the STAR\textsuperscript{D} Research Team, who conducted the clinical study and obtained clinical data and the blood samples for these analyses. Finally, we thank the study participants, without whom this study would not have been possible.

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