ORIGINAL ARTICLE

Selecting Among Second-Step Antidepressant Medication Monotherapies

Predictive Value of Clinical, Demographic, or First-Step Treatment Features

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Context: Little is known about selecting among second-step medications for major depressive disorder after intolerance or lack of remission with an initial selective serotonin reuptake inhibitor.

Objective: To determine whether sociodemographic, clinical, or first-step treatment features predict remission with or intolerance overall or differentially to any 1 of 3 second-step medications after an unsatisfactory outcome with citalopram hydrobromide.

Design: An equipoise stratified randomized study. Participants were recruited from July 17, 2001, through April 20, 2004.

Setting: Public or private sector primary care (n=18) and psychiatric care (n=23) settings across the United States.

Participants: Representative outpatients aged 18 to 75 years with nonpsychotic major depressive disorder (N=727).

Interventions: Sustained-release bupropion hydrochloride was started at 150 mg/d and incrementally increased to 400 mg/d. Sertraline hydrochloride was started at 50 mg/d and incrementally increased to 200 mg/d. Extended-release venlafaxine hydrochloride was started at 37.5 mg/d and incrementally increased to 375 mg/d.

Main Outcome Measures: The 16-item Quick Inventory of Depressive Symptomatology, Self-Rated and the Frequency, Intensity, and Burden of Side Effects Rating.

Results: Remission was more likely among participants who were white, employed, cohabiting or married, or privately insured or who had prior intolerance to citalopram or at least a response to citalopram, and no prior suicide attempts. Remission was less likely among participants with concurrent generalized anxiety, obsessive-compulsive, panic, or posttraumatic stress disorders; social phobia; anxious or melancholic features; or more severe depression. Intolerance was less likely for Hispanic participants, but more likely for participants with previous suicide attempts or intolerance to citalopram. Participants with concurrent substance use were less likely to remit (odds ratio, 0.37) and more likely not to tolerate extended-release venlafaxine. Intolerance to citalopram was associated with intolerance to sertraline ($P=.04$).

Conclusions: Clinical, demographic, and treatment history were of little value in recommending 1 medication vs another as a second-step treatment for major depressive disorder. Participants most likely to remit in the second step had less Axis I psychiatric disorder comorbidity, less social disadvantage, and at least a response to citalopram in the first step.

Trial Registration: clinicaltrials.gov Identifier: NCT00021528

Arch Gen Psychiatry. 2008;65(8):870-881

MAJOR DEPRESSIVE DISORDER (MDD) is typically resistant to treatment. Effectiveness studies of patients similar to those treated in a typical clinical practice have found that only 11% to 30% of patients reach remission with initial treatment, even after 8 to 12 months.[1-4] Therefore, most patients with MDD will require a second-step treatment. Unfortunately, little information is available regarding the comparative efficacy of antidepressant medications as second-step treatments for MDD. Consequently, the selection of second-step medications presently relies on a trial-and-error approach.

An important step in determining comparative treatment efficacy is identifying patient sociodemographic, clinical, and first-step treatment features that are asso-

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ciated with the efficacy of particular treatments. Similar work has been done regarding first-step treatments for MDD. In first-step treatment with citalopram hydrobromide,[5] the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial[6,7] found that more concurrent general medical conditions (GMCs), more concurrent Axis I psychiatric disorders, minority racial/ethnic status, poorer quality of life/perceived function, and greater initial depressive symptom severity were associated with a lower likelihood of reaching remission.

Unfortunately, attempts to identify specific features that recommend one first-step medication over another have generally not revealed clinically useful indicators of (1) whether a particular first-step treatment will be effective or well tolerated for patients with specific characteristics or (2) which of 2 or more different first-step treatments is preferred for patients with specific features.[8-14] However, the chances of finding such indicators is likely higher during second-step treatment because patients who will remit solely from nonpharmacological treatment effects (ie, placebo responders) are less likely to enter second-step treatment.

The second step of STAR*D examined the baseline sociodemographic and clinical features, first-step treatment features, and second-step treatment outcomes of participants who were randomly assigned to second-step treatments following nonremission or intolerance to an adequate trial of first-step citalopram treatment. Second-step treatment options included 3 medications with different pharmacological effects: sustained-release buproprion hydrochloride (bupropion-SR; norepinephrine/dopamine reuptake inhibitor), sertraline hydrochloride (selective serotonin reuptake inhibitor [SSRI]), and extended-release venlafaxine hydrochloride (venlafaxine-XR; serotonin/norepinephrine reuptake inhibitor).[15] Therefore, the participant sample assigned to these 3 treatment options provided an opportunity to develop hypotheses regarding the utility of specific sociodemographic, clinical, or first-step treatment features in predicting efficacy of or intolerance to specific medications (predictors) and for identifying features that might recommend a particular medication for specific patients (moderators). Analyses such as this one could help to better match particular medications to specific patients.

The following questions were addressed:

- What sociodemographic, clinical, or first-step treatment features are general predictors of outcome (ie, remission or intolerance) during a second-step medication switch?
- Do any sociodemographic, clinical, or first-step treatment features usefully predict remission or intolerance with specific second-step switch medications?

METHODS

PARTICIPANTS

From July 17, 2001, through April 20, 2004, STAR*D enrolled treatment-seeking outpatients aged 18 to 75 years who had a primary clinical diagnosis of nonpsychotic MDD,[16] confirmed by a *DSM-IV* checklist completed by trained clinical research coordinators. Patients were recruited from primary care (n=18) and psychiatric care (n=23) clinical settings across the United States that serve the public and private sector. Broad inclusion and minimal exclusion criteria[6] were used to enhance the generalizability of findings.[6,7]

All participants received citalopram as the initial treatment (first step).[5] Participants eligible for second-step treatments had either not remitted or were intolerant to citalopram. *Nonremission* was defined as a score of 5 or less on the 16-item Quick Inventory of Depressive Symptomatology–Clinician-Rated (QIDS-C_{16})[17,18] obtained at the last visit during citalopram treatment. The formation of this sample is described in detail elsewhere.[15]

Treatment options were assigned using an equipoise stratified randomized design.[19] Participants were strongly encouraged to accept all 7 potential second-step treatments (4 switch and 3 augment treatments) but, to mimic clinical practice conditions, participants could opt to exclude certain second-step treatment strategies.[15]

This report evaluates all 727 participants who were randomized in a 1:1:1 ratio to any 1 of 3 second-step medications: bupropion-SR, sertraline, and venlafaxine-XR. Random treatment assignment was conducted separately within each regional center.

All participants provided written informed consent at enrollment into initial treatment with citalopram and again at entry into all second-step treatments. The STAR*D protocol was approved and monitored by the institutional review boards at the national coordinating, data coordinating, and regional centers; relevant clinical sites; and the Data Safety and Monitoring Board of the National Institute of Mental Health (Bethesda, Maryland).

PROTOCOL TREATMENT

Neither participants nor treating clinicians were masked to treatment assignment or dosage to mimic clinical practice, enhance safety, ensure vigorous dosing, and maximize generalizability. A clinical treatment manual (http://www.star-d.org) using measurement-based care[5] recommended starting dosages and dosage changes, based on regular assessment with the QIDS-C_{16} and the self-reported Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)[20] at each treatment visit. Didactic instruction, clinical research coordinator support, and a Web-based monitoring system with feedback[21] were used to assure timely dosage increases in the context of inadequate symptom reduction and acceptable side effects.[5] Treatment was aimed at symptom remission (defined by a QIDS-C_{16} score of 5 or less at the clinic visit).

Citalopram was discontinued without tapering or washout at the initiation of the switch medication. The STAR*D protocol (http://www.star-d.org) provided second-step dosing recommendations. Bupropion-SR was begun at 150 mg/d then raised to 200 mg/d by day 7, 300 mg/d by day 28, and 400 mg/d by day 42. Sertraline was begun at 50 mg/d then raised to 100 mg/d at day 14, 150 mg/d at day 28, and 200 mg/d at day 63. Venlafaxine-XR was begun at 37.5 mg/d then raised to 75 mg/d at day 7, 150 mg/d at day 14, 225 mg/d at day 28, 300 mg/d at day 42, and 375 mg/d at day 63. Dosing recommendations were flexible, based on clinical judgment as informed by the QIDS-C_{16} and FIBSER at each treatment visit.

CONCOMITANT TREATMENTS

Stimulant, anticonvulsant, antipsychotic, mood-stabilizing, nonprotocol antidepressants and potential augmenting medications (eg, buspirone) were prescribed. Otherwise, any concomitant medication was allowed if needed to treat concurrent

GMCs or protocol antidepressant adverse effects (eg, sexual dysfunction), as were anxiolytic medications (except alprazolam) and sedative hypnotic medications (except trazodone at >200 mg/d).

MEASURES

Baseline measures (gathered before beginning first-step citalopram treatment) included the Cumulative Illness Rating Scale[22] to assess for GMCs, the Psychiatric Diagnostic Screening Questionnaire[23,24] to assess concurrent Axis I psychiatric disorders (present at study entry or within 6 months before study entry), and the 30-item Inventory of Depressive Symptomatology–Clinician-Rated[18,25] to assess for depression severity and selected symptom features.[26] Assessments of overall function (Short-Form Health Survey,[27] Work Productivity and Activity Impairment Questionnaire,[28] and Work and Social Adjustment Scale[29]) and satisfaction (Quality of Life Enjoyment and Satisfaction Questionnaire[30]) were collected by an automated interactive voice response telephone system.[31] Anxious,[32] atypical,[26] and melancholic[33] features were defined using items from the Inventory of Depressive Symptomatology–Clinician-Rated or the anxiety subscale[34] of the 17-item Hamilton Rating Scale for Depression.[35,36]

For research purposes, the primary outcome of symptom remission was defined as a total score of 7 or less on the 17-item Hamilton Rating Scale for Depression, obtained via telephone-based structured interviews conducted in English or Spanish by independent, treatment-masked research outcomes assessors within 5 days of entry and exit from each treatment step. Participants who did not provide an exit Hamilton Rating Scale for Depression score were designated a priori as not reaching remission. Secondary outcomes included the Self-Rated 16-Item Quick Inventory of Depressive Symptomatology, Self-Report ($QIDS\text{-}SR_{16}$)[6,7,17,18] and the FIBSER obtained at each treatment visit. *Remission* was defined as a total $QIDS\text{-}SR_{16}$ score of 5 or less at exit from each treatment step. *Response* (without remission) was defined as an improvement of 50% or more above the baseline $QIDS\text{-}SR_{16}$ score at exit from each treatment step. For this report, the $QIDS\text{-}SR_{16}$ was used to define remission and response because all participants completed the $QIDS\text{-}SR_{16}$ at each clinic visit.

Patients could exit treatment at any time because of intolerable adverse effects or after 8 to 9 weeks if minimal symptom reduction occurred. In this sample, 514 (70.7%) of 727 participants completed at least 6 weeks of treatment, and 300 (41.3%) completed at least 12 weeks of treatment.

STATISTICAL METHODS

Descriptive statistics include means and standard deviations for continuous variables and percentages for discrete variables. Logistic regression models were used to identify baseline characteristics associated with remission and intolerance across the 3 treatment groups. The models included main effects for the baseline characteristic of interest and treatment. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. This approach was then repeated by treatment, with these models including only main effects for the baseline characteristic of interest. To determine if the ORs were different across the treatment arms, logistic regression models were fit, which included main effects for treatment and the baseline characteristic of interest, as well as the 2-way interaction between the baseline characteristic and treatment. For this report, we defined a clinically meaningful effect a priori as an OR of 1.3 or more or 0.8 or less regardless of whether statistical significance was obtained.

RESULTS

This report is based on a sample[15] that was previously used to compare overall outcomes of the 3 switch medications following nonremission or intolerance with first-step citalopram treatment (**Table 1**). No variables statistically differentiated participants randomized to each of the 3 second-step medications.

OVERALL PREDICTORS

Predictor analyses examined the overall odds that the presence (vs absence) of selected baseline sociodemographic and clinical features, as well as features of the prior treatment with citalopram, would affect the incidence of remission or intolerance for all participants who underwent a medication switch.

OVERALL PREDICTORS OF EFFICACY

Table 2 shows baseline sociodemographic and clinical features as well as first-step citalopram treatment features, in relation to the likelihood of remission for participants with any second-step medication switch (ie, across treatment groups). For example, white participants were nearly twice as likely as nonwhites to achieve remission. The odds of remission were 60% more likely for employed (vs unemployed) participants. Married or cohabiting participants were 52% more likely to reach remission than those not married or cohabitating. Participants with public insurance were less likely to remit than those with private insurance, as were those with a prior suicide attempt, more concurrent Axis I psychiatric disorders, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, more concurrent GMCs, or anxious or melancholic features. Similarly, those with more severe depression at entry into the second step were less likely to remit than those with less severe depression. Participants who exited first-step citalopram treatment because of intolerance were more likely to remit in the second step, as were those who had at least a response to citalopram in the first step.

OVERALL PREDICTORS OF INTOLERANCE

Table 3 shows the baseline and citalopram-treatment–related features associated with intolerance for all participants (ie, across treatment groups). Hispanic participants were less likely to report intolerance than non-Hispanics. Intolerance was more likely for those with prior suicide attempts and for those with intolerance to citalopram in the first step.

PREDICTORS OF REMISSION WITH SPECIFIC MEDICATIONS

These analyses examined the associations between selected baseline sociodemographic and clinical features and features of first-step treatment with citalopram and remission overall and for each second-step medication.

Table 1. Clinical and Demographic Features of 727 Participants Randomized to Bupropion-SR, Sertraline, or Venlafaxine-XR[a]

Feature	Total (N=727)	Bupropion-SR (n=239)	Sertraline (n=238)	Venlafaxine-XR (n=250)	*P* Value
Age range, y					
18-25	**86** (11.8)	26 (10.9)	24 (10.1)	36 (14.4)	.68
26-35	**163** (22.4)	56 (23.4)	49 (20.6)	58 (23.2)	
36-50	**269** (37.0)	87 (36.4)	96 (40.3)	86 (34.4)	
51-75	**209** (28.7)	70 (29.3)	69 (29.0)	70 (28.0)	
Male sex (vs female)	**300** (41.3)	103 (43.1)	107 (45.0)	90 (36.0)	.10
White race (vs nonwhite)	**551** (75.8)	179 (74.9)	186 (78.2)	186 (74.4)	.58
Hispanic ethnicity (vs non-Hispanic)	**80** (11.0)	23 (9.6)	28 (11.8)	29 (11.6)	.70
Employed (vs unemployed/retired)	**388** (53.4)	132 (55.5)	118 (49.6)	138 (55.2)	.34
Medical insurance					
Any private	**316** (44.6)	106 (44.7)	97 (41.6)	113 (47.3)	.10
Public only	**103** (14.5)	44 (18.6)	28 (12.0)	31 (13.0)	
None	**290** (40.9)	87 (36.7)	108 (46.4)	95 (39.7)	
Married/cohabiting (vs neither)	**288** (39.6)	89 (37.2)	95 (39.9)	104 (41.6)	.61
Age at first episode (<18 y vs ≥18 y)	**268** (37.2)	92 (38.8)	84 (35.9)	92 (36.9)	.80
Recurrent depression (vs first episode)	**499** (75.7)	153 (70.5)	172 (78.5)	174 (78.0)	.09
Ever attempted suicide (vs never)	**125** (17.2)	40 (16.9)	47 (19.7)	38 (15.2)	.41
Family history of depression (vs none)	**387** (53.9)	122 (51.5)	132 (55.9)	133 (54.3)	.62
Presence of Axis I disorders (vs absent)[b]					
Generalized anxiety	**158** (22.1)	53 (22.3)	50 (21.6)	55 (22.4)	.97
Obsessive-compulsive	**101** (14.0)	27 (11.3)	34 (14.5)	40 (16.2)	.30
Panic	**109** (15.2)	41 (17.2)	30 (12.8)	38 (15.4)	.41
Posttraumatic stress	**163** (22.7)	59 (24.9)	52 (22.2)	52 (21.1)	.60
Social phobia	**232** (32.3)	81 (34.0)	65 (27.8)	86 (35.0)	.19
Substance use	**112** (15.6)	27 (11.3)	45 (19.2)	40 (16.3)	.06
No. of Axis I disorders[c]					
0	**254** (35.9)	93 (39.7)	76 (32.9)	85 (35.0)	.37
1	**184** (26.0)	52 (22.2)	74 (32.0)	58 (23.9)	
2	**110** (15.5)	33 (14.1)	33 (14.3)	44 (18.1)	
3	**64** (9.0)	23 (9.8)	19 (8.2)	22 (9.1)	
≥4	**96** (13.6)	33 (14.1)	29 (12.6)	34 (14.0)	
No. of Axis III disorders[d]					
0	**306** (42.1)	103 (43.1)	101 (42.4)	102 (40.8)	.34
1	**168** (23.1)	53 (22.2)	56 (23.5)	59 (23.6)	
2	**114** (15.7)	39 (16.3)	43 (18.1)	32 (12.8)	
3	**62** (8.5)	23 (9.6)	12 (5.0)	27 (10.8)	
≥4	**77** (10.6)	21 (8.8)	26 (10.9)	30 (12.0)	
Psychiatric care (vs primary care)	**437** (60.1)	145 (60.7)	140 (58.8)	152 (60.8)	.88
Chronic index episode (vs nonchronic)[e]	**195** (27.0)	63 (26.6)	67 (28.3)	65 (26.2)	.86
Anxious features (vs absent)	**284** (44.4)	88 (42.1)	97 (45.5)	99 (45.6)	.71
Atypical features (vs absent)	**130** (20.3)	33 (15.8)	47 (22.1)	50 (22.9)	.14
Melancholic features (vs absent)	**121** (18.9)	42 (20.0)	39 (18.3)	40 (18.3)	.88
Severe depression (vs mild/moderate)[f]	**220** (30.4)	77 (32.4)	73 (30.8)	70 (28.1)	.59
Intolerance during the first-step treatment (vs tolerance)[g]	**407** (56.0)	134 (56.1)	132 (55.5)	141 (56.4)	.98
Response during the first-step treatment (vs nonresponse)[h]	**92** (12.7)	33 (13.9)	29 (12.2)	30 (12.0)	.80

Abbreviations: Bupropion-SR, sustained-release buproprion hydrochloride; venlafaxine-XR, extended-release venlafaxine hydrochloride.

[a] Data are presented as number (percentage) of participants unless otherwise indicated. Due to missing data, numbers do not always sum to the total. Sertraline was given as sertraline hydrochloride.

[b] Assessed by the Psychiatric Diagnostic Screening Questionnaire (PDSQ).

[c] Maximum equals 11 of 13 disorders assessed by the PDSQ.

[d] Maximum equals 13 of 14 disorders assessed by the Cumulative Illness Rating Scale.

[e] Duration of index episode for more than 2 years.

[f] Score of 16 or more on the 16-item Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR_{16}).

[g] Exited the study at the first step before week 4 for any reason or after week 4 citing intolerable adverse effects.

[h] Percentage reduction in baseline QIDS-SR_{16} score of 50% or more at the end of treatment.

Table 2 shows the *P* values for the interaction between each clinical or demographic feature and the likelihood of remission for each switch medication. For example, bupropion-SR had an OR of 1.29 of remitting (95% CI, 0.53-3.11) compared with 1.66 (0.83-3.31) for sertraline and 0.38 (0.14-1.01) for venlafaxine-XR. Despite a large number of tests of interaction, only the presence of substance abuse met the test for statistical significance. Thus, this result could be owing to chance alone.

Figure 1 visually summarizes those features for which the association of baseline sociodemographic and clinical features and first-step treatment features was considerably different across the treatment groups. Because this analysis was exploratory (ie, designed to develop hy-

Table 2. Features Associated With Remission Overall and With Each Individual Medication[a]

Feature	Remission Overall	Remission by Medication			*P* Value[c]
		Bupropion-SR (n=239)[b]	Sertraline (n=238)[b]	Venlafaxine-XR (n=250)[b]	
Age range, y					
18-25	1 [Reference]				
26-35	**1.81 (0.97-3.38)**	1.27 (0.40-4.03)	**1.36 (0.45-4.13)**	**3.06 (1.10-8.51)**	.42
36-50	**1.43 (0.78-2.59)**	**1.79 (0.61-5.26)**	1.17 (0.42-3.27)	1.25 (0.45-3.48)	
51-75	1.24 (0.67-2.32)	**1.35 (0.44-4.12)**	0.83 (0.28-2.47)	**1.63 (0.58-4.59)**	
Male sex (vs female)	0.96 (0.69-1.35)	0.89 (0.49-1.61)	1.25 (0.70-2.23)	**0.79 (0.43-1.45)**	.53
White race (vs nonwhite)	**1.99 (1.28-3.10)**	**2.32 (1.07-5.05)**	**1.97 (0.90-4.32)**	**1.75 (0.85-3.62)**	.87
Hispanic ethnicity (vs non-Hispanic)	**1.36 (0.82-2.26)**	**2.03 (0.83-4.95)**	**1.64 (0.71-3.76)**	**0.76 (0.29-1.96)**	.30
Employed (vs unemployed/retired)	**1.60 (1.14-2.25)**	**1.46 (0.80-2.65)**	**1.83 (1.02-3.28)**	**1.52 (0.84-2.75)**	.85
Medical insurance					
Any private insurance	1 [Reference]				
Public only	**0.53 (0.31-0.93)**	**0.54 (0.22-1.29)**	**0.35 (0.11-1.11)**	**0.73 (0.29-1.86)**	.92
None	**0.78 (0.54-1.12)**	**0.77 (0.40-1.47)**	**0.75 (0.41-1.38)**	0.81 (0.43-1.51)	
Married/cohabiting (vs neither)	**1.52 (1.08-2.13)**	**1.36 (0.75-2.45)**	1.28 (0.71-2.29)	**2.01 (1.12-3.60)**	.50
Age at first episode (<18 y vs ≥18 y)	**0.76 (0.53-1.08)**	0.88 (0.48-1.62)	**0.74 (0.40-1.38)**	**0.66 (0.36-1.24)**	.80
Recurrent depression (vs first episode)	**0.78 (0.53-1.16)**	1.05 (0.54-2.02)	**0.76 (0.37-1.52)**	**0.58 (0.29-1.15)**	.48
Ever attempted suicide (vs never)	**0.60 (0.37-0.98)**	**0.56 (0.23-1.35)**	**0.62 (0.28-1.36)**	**0.64 (0.27-1.53)**	.98
Family history of depression (vs none)	1.03 (0.74-1.45)	**1.38 (0.77-2.48)**	**0.80 (0.45-1.43)**	1.01 (0.56-1.81)	.43
Presence of Axis I disorders[d] (vs absent)					
Generalized anxiety	**0.59 (0.38-0.92)**	**0.63 (0.29-1.34)**	**0.52 (0.23-1.14)**	**0.63 (0.30-1.35)**	.92
Obsessive-compulsive	**0.42 (0.23-0.76)**	**0.64 (0.23-1.79)**	**0.32 (0.11-0.94)**	**0.38 (0.14-1.03)**	.62
Panic	**0.42 (0.24-0.75)**	**0.36 (0.13-0.96)**	**0.38 (0.13-1.12)**	**0.55 (0.22-1.38)**	.80
Posttraumatic stress	**0.55 (0.35-0.85)**	**0.60 (0.29-1.26)**	**0.49 (0.22-1.08)**	**0.55 (0.25-1.20)**	.93
Social phobia	**0.58 (0.40-0.86)**	**0.63 (0.33-1.21)**	**0.41 (0.19-0.86)**	**0.72 (0.38-1.34)**	.50
Substance use	1.00 (0.63-1.59)	1.29 (0.53-3.11)	**1.66 (0.83-3.31)**	**0.38 (0.14-1.01)**	**.05**
No. of Axis I disorders[e]					
0	1 [Reference]				
1	0.99 (0.65-1.49)	**0.55 (0.25-1.18)**	**2.09 (1.04-4.21)**	**0.72 (0.34-1.54)**	.22
2	**0.66 (0.39-1.12)**	**0.40 (0.15-1.08)**	0.81 (0.30-2.16)	0.85 (0.38-1.91)	
3	**0.58 (0.30-1.12)**	**0.38 (0.12-1.22)**	**0.56 (0.15-2.14)**	0.85 (0.30-2.42)	
≥4	**0.33 (0.17-0.64)**	**0.32 (0.11-0.92)**	**0.48 (0.15-1.56)**	**0.23 (0.07-0.84)**	
No. of Axis III disorders[f]					
0	1 [Reference]				
1	1.07 (0.71-1.62)	**1.45 (0.71-2.97)**	1.16 (0.57-2.35)	**0.73 (0.35-1.52)**	.81
2	**0.74 (0.45-1.22)**	0.84 (0.36-2.00)	**0.65 (0.28-1.52)**	**0.76 (0.31-1.89)**	
3	**0.67 (0.35-1.30)**	0.99 (0.35-2.78)	**0.49 (0.10-2.37)**	**0.52 (0.18-1.50)**	
≥4	**0.38 (0.19-0.77)**	**0.14 (0.02-1.10)**	**0.58 (0.20-1.69)**	**0.37 (0.12-1.14)**	
Psychiatric care (vs primary care)	1.00 (0.71-1.41)	**0.63 (0.35-1.14)**	1.00 (0.56-1.80)	**1.60 (0.87-2.95)**	**.10**
Chronic index episode (vs nonchronic)[g]	**0.74 (0.50-1.09)**	1.22 (0.64-2.33)	**0.52 (0.26-1.05)**	**0.61 (0.30-1.24)**	**.17**
Anxious features (vs absent)	**0.30 (0.20-0.45)**	**0.25 (0.12-0.52)**	**0.44 (0.23-0.83)**	**0.23 (0.11-0.48)**	.35
Atypical features (vs absent)	1.04 (0.67-1.61)	1.06 (0.46-2.45)	1.10 (0.54-2.24)	0.96 (0.46-2.02)	.97
Melancholic features (vs absent)	**0.43 (0.25-0.73)**	**0.40 (0.16-1.02)**	**0.60 (0.26-1.39)**	**0.29 (0.10-0.85)**	.57
Severe depression (vs mild/moderate)[h]	**0.34 (0.22-0.52)**	**0.38 (0.19-0.78)**	**0.38 (0.18-0.78)**	**0.25 (0.11-0.58)**	.70
Intolerance during the first-step treatment (vs tolerance)[i]	**1.57 (1.11-2.21)**	**1.55 (0.85-2.82)**	**1.74 (0.96-3.16)**	**1.43 (0.79-2.58)**	.90
Response during the first-step treatment (vs nonresponse)[j]	**2.78 (1.77-4.38)**	**2.96 (1.38-6.34)**	**2.31 (1.02-5.20)**	**3.10 (1.41-6.80)**	.86

Abbreviations: See Table 1.
[a] N=727. Data are presented as odds ratio (95% confidence interval) unless otherwise indicated. Sertraline was given as sertraline hydrochloride.
[b] Boldface type indicates clinical significance (odds ratio, ≤0.8 or ≥1.3).
[c] *P* value for interaction between clinical or demographic feature and treatment group. Boldface type indicates clinical significance (*P*≤.20).
[d] Assessed by the Psychiatric Diagnostic Screening Questionnaire (PDSQ).
[e] Maximum equals 11 of 13 disorders assessed by the PDSQ.
[f] Maximum equals 13 of 14 disorders assessed by the Cumulative Illness Rating Scale.
[g] Duration of index episode for more than 2 years.
[h] Score of 16 or more on the 16-item Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR_{16}).
[i] Exited the study at the first step before week 4 for any reason or after week 4 citing intolerable adverse effects.
[j] Percentage reduction in baseline QIDS-SR_{16} score of 50% or more at the end of treatment.

potheses), features with a *P* value of .20 or less were designated as meaningful. These features included substance use disorder (*P*=.05), psychiatric care setting (*P*=.10), and a chronic (>2 years) index episode (*P*=.17). For participants with a chronic index episode, the chances of remission were somewhat higher with bupropion-SR

Table 3. Features Associated With Intolerance Overall and With Each Individual Medication[a]

Feature	Intolerance Overall	Intolerance by Medication			*P* Value[c]
		Bupropion-SR (n=239)[b]	Sertraline (n=238)[b]	Venlafaxine-XR (n=250)[b]	
Age range, y					
18-25	1 [Reference]				
26-35	1.17 (0.62-2.21)	1.22 (0.41-3.62)	**0.77 (0.24-2.44)**	**1.59 (0.55-4.61)**	
36-50	0.99 (0.54-1.80)	1.27 (0.45-3.54)	**0.74 (0.26-2.12)**	0.89 (0.31-2.56)	.76
51-75	**1.34 (0.73-2.45)**	**1.33 (0.47-3.81)**	0.83 (0.28-2.47)	**2.00 (0.72-5.54)**	
Male sex (vs female)	1.19 (0.84-1.69)	1.09 (0.61-1.93)	1.17 (0.63-2.18)	**1.35 (0.72-2.50)**	.88
White race (vs nonwhite)	0.95 (0.64-1.42)	1.04 (0.54-2.00)	1.15 (0.53-2.49)	**0.74 (0.38-1.46)**	.67
Hispanic ethnicity (vs non-Hispanic)	**0.50 (0.26-0.98)**	**0.53 (0.17-1.64)**	**0.59 (0.20-1.80)**	**0.39 (0.11-1.36)**	.88
Employed (vs unemployed/retired)	1.05 (0.74-1.48)	0.88 (0.49-1.56)	1.25 (0.67-2.34)	1.07 (0.58-1.98)	.71
Medical insurance (vs any private insurance)					
Public only	0.93 (0.54-1.58)	**1.76 (0.82-3.75)**	**0.09 (0.01-0.70)**	1.19 (0.43-3.29)	**.01**
None	1.07 (0.74-1.56)	1.11 (0.58-2.12)	**0.59 (0.31-1.14)**	**1.86 (0.96-3.64)**	
Married/cohabiting (vs neither)	1.06 (0.74-1.51)	0.98 (0.54-1.77)	1.24 (0.66-2.33)	1.00 (0.54-1.84)	.84
Age at first episode (<18 y vs ≥18 y)	1.04 (0.73-1.49)	0.98 (0.55-1.76)	**1.72 (0.91-3.24)**	**0.68 (0.36-1.31)**	**.13**
Recurrent depression (vs first episode)	1.29 (0.84-2.00)	0.81 (0.42-1.55)	**5.20 (1.54-17.6)**	1.00 (0.47-2.13)	**.03**
Ever attempted suicide (vs never)	**1.59 (1.04-2.45)**	1.16 (0.55-2.46)	**1.83 (0.89-3.76)**	**1.92 (0.90-4.13)**	.59
Family history of depression (vs none)	1.12 (0.79-1.59)	0.88 (0.50-1.57)	**1.47 (0.77-2.80)**	1.14 (0.61-2.12)	.52
Presence of Axis I disorders[d] (vs absent)					
Generalized anxiety	0.81 (0.52-1.25)	**0.73 (0.36-1.49)**	**0.68 (0.29-1.56)**	1.05 (0.51-2.17)	.69
Obsessive-compulsive	1.27 (0.78-2.05)	1.14 (0.47-2.74)	0.95 (0.39-2.32)	**1.74 (0.81-3.70)**	.57
Panic	**1.43 (0.90-2.25)**	**1.48 (0.72-3.05)**	**2.05 (0.89-4.72)**	0.97 (0.42-2.27)	.47
Posttraumatic stress	1.27 (0.85-1.89)	0.87 (0.45-1.71)	**1.93 (0.96-3.88)**	1.28 (0.63-2.63)	.27
Social phobia	0.88 (0.60-1.28)	0.90 (0.49-1.65)	**0.78 (0.38-1.61)**	0.95 (0.50-1.79)	.92
Substance use	0.86 (0.52-1.41)	**0.57 (0.21-1.58)**	**0.51 (0.20-1.28)**	**1.77 (0.83-3.78)**	**.07**
No. of Axis I disorders[e]					
0	1 [Reference]				
1	**1.43 (0.91-2.25)**	**1.40 (0.66-2.93)**	0.95 (0.42-2.13)	**2.30 (1.01-5.20)**	
2	**1.64 (0.98-2.75)**	**1.44 (0.61-3.40)**	**1.77 (0.70-4.49)**	**1.85 (0.75-4.55)**	.92
3	1.09 (0.56-2.13)	1.01 (0.36-2.87)	**0.76 (0.20-2.96)**	**1.63 (0.51-5.19)**	
≥4	0.90 (0.50-1.64)	**0.77 (0.30-2.01)**	0.85 (0.28-2.59)	1.19 (0.41-3.43)	
No. of Axis III disorders[f]					
0	1 [Reference]				
1	1.12 (0.72-1.74)	**1.30 (0.61-2.76)**	**1.39 (0.60-3.18)**	**0.74 (0.33-1.66)**	
2	1.01 (0.61-1.70)	**1.46 (0.64-3.32)**	**0.74 (0.24-2.02)**	0.91 (0.35-2.36)	.86
3	0.90 (0.46-1.76)	**1.44 (0.53-3.91)**	**0.23 (0.00-1.51)**	0.93 (0.34-2.57)	
≥4	1.15 (0.64-2.07)	**1.65 (0.60-4.55)**	**1.40 (0.44-4.09)**	**0.65 (0.22-1.88)**	
Psychiatric care (vs primary care)	1.26 (0.88-1.80)	1.15 (0.64-2.07)	**2.08 (1.05-4.10)**	0.89 (0.48-1.64)	**.18**
Chronic index episode (vs nonchronic)[g]	0.96 (0.65-1.42)	1.08 (0.57-2.05)	0.98 (0.49-1.97)	0.81 (0.39-1.66)	.84
Anxious features (vs absent)	1.16 (0.80-1.70)	**1.54 (0.83-2.87)**	1.11 (0.56-2.18)	0.88 (0.45-1.72)	.48
Atypical features (vs absent)	0.95 (0.59-1.53)	0.90 (0.38-2.15)	0.95 (0.42-2.17)	0.99 (0.45-2.17)	.99
Melancholic features (vs absent)	**1.44 (0.91-2.27)**	1.20 (0.56-2.55)	**2.50 (1.15-5.43)**	0.99 (0.42-2.32)	.23
Severe depression (vs mild/moderate)[h]	1.00 (0.69-1.46)	**0.67 (0.35-1.26)**	0.99 (0.50-1.96)	**1.59 (0.83-3.03)**	**.17**
Intolerance during the first-step treatment (vs tolerance)[i]	**1.92 (1.33-2.77)**	1.25 (0.70-2.23)	**4.17 (1.97-8.83)**	**1.67 (0.89-3.15)**	**.04**
Response during the first-step treatment (vs nonresponse)[j]	1.19 (0.72-1.97)	**1.64 (0.76-3.56)**	1.00 (0.38-2.61)	0.91 (0.35-2.37)	.58

Abbreviations: See Table 1.
[a] N=727. Data are presented as odds ratio (95% confidence interval) unless otherwise indicated. Sertraline was given as sertraline hydrochloride.
[b] Boldface type indicates clinical significance (odds ratio, ≤0.8 or ≥1.3).
[c] *P* value for interaction between clinical or demographic feature and treatment group. Boldface type indicates clinical significance ($P \leq .20$).
[d] Assessed by the Psychiatric Diagnostic Screening Questionnaire (PDSQ).
[e] Maximum equals 11 of 13 disorders assessed by the PDSQ.
[f] Maximum equals 13 of 14 disorders assessed by the Cumulative Illness Rating Scale.
[g] Duration of index episode for more than 2 years.
[h] Score of 16 or more on the 16-item Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR_{16}).
[i] Exited the study at the first step before week 4 for any reason or after week 4 citing intolerable adverse effects.
[j] Percentage reduction in baseline QIDS-SR_{16} of 50% or more at the end of treatment.

(OR, 1.22; 95% CI, 0.64-2.33) than with sertraline (0.52; 0.26-1.05) or venlafaxine-XR (0.61; 0.30-1.24).

Because these results could be owing to the medication dosage, we examined mean dosages for each switch medication. Mean exit dosage was similar for those with or without a chronic index episode (bupropion-SR, 304 mg/d vs 287 mg/d; sertraline, 141 mg/d vs 139 mg/d [$P=.03$]; venlafaxine-XR, 184 mg/d vs 208 mg/d). Thus,

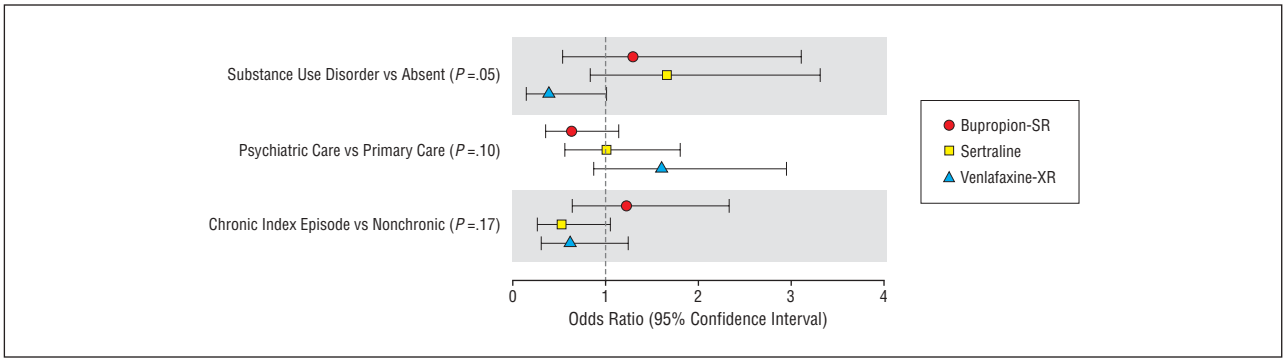

Figure 1. Moderators of remission. Bupropion-SR indicates sustained-release bupropion hydrochloride; venlafaxine-XR, extended-release venlafaxine hydrochloride.

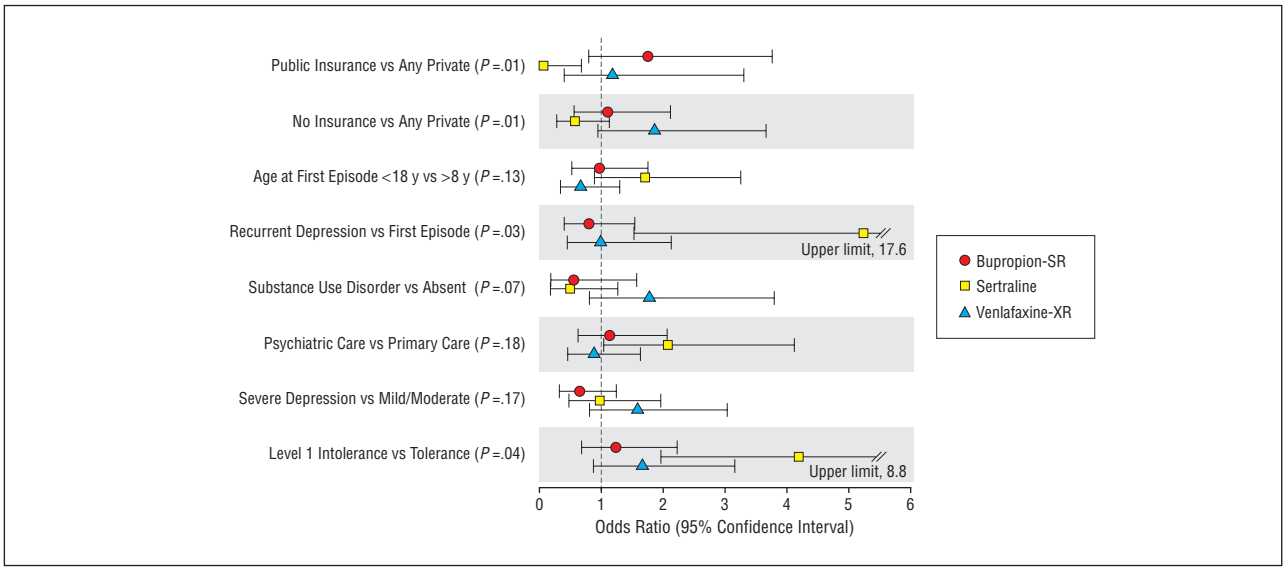

Figure 2. Moderators of intolerance. Bupropion-SR indicates sustained-release bupropion hydrochloride; venlafaxine-XR, extended-release venlafaxine hydrochloride.

differential dosing does not explain the relevance of chronicity to outcomes among the switch medications.

Psychiatric settings tended to be associated with lower chances of remission with bupropion-SR (OR, 0.63; 95% CI, 0.35-1.14) and higher chances of remission with venlafaxine-XR (1.60; 0.87-2.95). Differential dosing between those in primary and psychiatric care settings does not explain this finding (mean exit dosages: bupropion-SR, 281 mg/d vs 294 mg/d; sertraline, 139 mg/d vs 141 mg/d; venlafaxine-XR, 192 mg/d vs 206 mg/d).

Those with substance abuse were significantly less likely to achieve remission with venlafaxine-XR. Participants with substance abuse taking venlafaxine-XR had slightly lower dosages than those without substance abuse (mean exit dosages: bupropion-SR, 305 mg/d vs 287 mg/d; sertraline, 141 mg/d vs 139 mg/d; venlafaxine-XR, 184 mg/d vs 202 mg/d). Therefore, differential dosing might account for the lower remission rate for participants with substance abuse who were taking venlafaxine-XR (vs those without). This lower dosage with venlafaxine-XR could be owing to greater intolerance to venlafaxine-XR among participants with substance abuse (**Figure 2**).

PREDICTORS OF INTOLERANCE WITH SPECIFIC MEDICATIONS

The *P* values in Table 3 refer to the interactions between baseline sociodemographic and clinical features and first-step treatment features and the chances of intolerance for each medication. Only 3 of 27 tests reached the $P < .05$ threshold. Those with only public insurance, compared with the privately insured, had the lowest odds of intolerance with sertraline (OR, 0.09; 95% CI, 0.01-0.70), and the odds of intolerance to bupropion-SR were highest (1.26; 0.82-3.75) (venlafaxine-XR: 1.19; 0.43-3.29). For those with recurrent depression, compared with those having their first episode, the odds of intolerance were highest for sertraline (OR, 5.20; 95% CI, 1.54-17.0), intermediate for venlafaxine-XR (1.00; 0.47-2.13), and lowest for bupropion-SR (0.81; 0.42-1.55). Finally, intolerance to citalopram at the first step was particularly predictive of intolerance to sertraline in the second step (OR, 4.17; 95% CI, 1.97-8.83) compared with venlafaxine-XR (1.67; 0.89-3.15) or bupropion-SR (1.25; 0.70-2.23).

Figure 2 visually summarizes the baseline sociodemographic and clinical features and first-step treatment features that were considerably different across treatment groups. These features included insurance status, ie, public only vs any private ($P=.01$) and none vs any private ($P=.01$); early onset (age <18 years) ($P=.13$); recurrent course ($P=.03$); substance use disorder ($P=.07$); treatment in a psychiatric setting; severe depression at initiation of the second-step medication switch; and intolerance to first-step citalopram treatment.

For example, those with substance use disorder were less likely to exhibit intolerance to bupropion-SR (OR,0.57; 95% CI,0.21-1.58) or sertraline (0.51; 0.20-1.28) but tended to be somewhat more likely to encounter intolerance with venlafaxine-XR (1.77; 0.83-3.78). Note that greater intolerance was found for sertraline among those with a history of recurrence. Also, intolerance to first-step citalopram was significantly predictive of intolerance to the second-step medication, especially regarding intolerance to sertraline. Although having anxious features was associated with lower remission and greater intolerance, it did not recommend 1 medication over another based on chances of remission or chances of intolerance.

COMMENT

To our knowledge, this is the first report to evaluate the relevance of baseline clinical and demographic features and features of first-step treatment in predicting overall and differential likelihood of remission or intolerance to 3 second-step medications.

OVERALL PREDICTORS OF REMISSION

Several baseline sociodemographic and clinical features and first-step treatment features were associated with overall lower chances of remission for these switch medications. Remission was less likely in the context of social disadvantage (eg, being nonwhite, on public insurance, or unemployed), greater depressive illness burden (eg, greater depression severity or prior suicide attempts), and more concurrent Axis I disorders (in particular, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, or social phobia), as well as among participants with more anxious and melancholic features. Atypical features and a chronic index episode were not related to the chances of remission. Furthermore, age at onset of the first episode, treatment setting (psychiatric vs primary care), and the presence of concurrent substance use disorders were not related to the chances of remission with the second-step medication switches. These results are similar to those of our previous report of predictors of remission with citalopram in the first step.[5]

Finally, prior experience with the first-step treatment with citalopram was predictive of remission at the second step. Those with intolerance to citalopram or those who at least had a response to it were more likely to remit overall in the second-step medication switch.

OVERALL PREDICTORS OF INTOLERANCE

Few baseline features were associated with intolerance. Non-Hispanic participants and those with prior suicide attempts or with intolerance to the first-step treatment with citalopram were more likely to be intolerant overall to the second-step medication switch. That is, those with prior suicide attempts were more likely to be intolerant and to not remit. It is possible that those with Axis II disorders could be especially represented in this group. Those who were intolerant to citalopram were more likely to remit and more likely to be intolerant to the second-step medication, particularly sertraline.

PREDICTORS OF DIFFERENTIAL LIKELIHOOD OF REMISSION OR INTOLERANCE

Very few features were clinically useful in selecting from among these 3 second-step switch medications for specific patients. For example, participants with anxious and melancholic features had lower odds of remission overall, compared with participants without these features, but these features did not point to a particular medication that would be more or less likely to produce remission or intolerance. For example, anxious features were not predictive of a lower benefit with bupropion-SR, which is consistent with prior findings in first-step treatment with bupropion-SR and sertraline.[9-12] In contrast to previous studies of serotonin/norepinephrine reuptake inhibitors,[37-39] participants with melancholic features were *not* more likely to remit with venlafaxine-XR than with the other medications. In addition, more Axis I disorders—and, in particular, concurrent panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, and social phobia—were associated with overall lower chances of remission, but these concurrent Axis I disorders did not recommend a serotonin reuptake blocker such as sertraline over other medications.

Response and intolerance to first-step citalopram were associated with greater odds of remission in the second step, but neither was useful in recommending any particular second-step antidepressant to improve the chances of remission. Of interest, intolerance to first-step citalopram did not indicate whether sertraline, the second-step SSRI, would or would not produce remission.

For participants with public insurance or without insurance, intolerance was more likely with venlafaxine-XR and least likely with sertraline. This is perhaps owing to greater general medical comorbidity among these participants.[40,41] Substance use disorders tended to predict greatest intolerance to venlafaxine-XR. Finally, a recurrent history was significantly predictive of intolerance to sertraline.

More important, sex was not predictive of either remission or intolerance for each medication alone, nor did sex recommend 1 medication over another in this second-step switch treatment. Thus, sex is not a basis for selecting among these second-step medications. Studies[42-44] have been inconsistent in suggesting that women might fare better on SSRIs in first-step treatment. This difference in findings between steps could be explained by a greater

responsiveness of women and men to the nonpharmacological effects of the first-step treatment so that, by the second step, this subgroup is not included.

Atypical features were not predictive of either intolerance or remission overall, neither within each medication group nor among medications. Melancholic features were not predictive of differential remission or intolerance. Concurrent Axis I and III disorders and anxious features were unrelated to intolerance.

CLINICAL IMPLICATIONS

Neither cross-sectional symptom features (eg, anxious, atypical, melancholic) nor concurrent Axis I psychiatric disorders can be used to reliably select among second-step medications. The presence of substance use disorders may recommend against using venlafaxine-XR, but this finding requires replication.

Thus, it appears that choosing among second-step medications based on Food and Drug Administration–approved indications is not supported. For example, sertraline, given its established efficacy in patients with posttraumatic stress disorder,[45-47] social phobia,[48-50] and obsessive-compulsive disorder,[51-56] or venlafaxine-XR, given its efficacy in patients with generalized anxiety disorder,[57-59] might have been expected to be more likely to produce remission than bupropion-SR in these patient groups, because bupropion-SR has none of these indications. However, the presence of these concurrent anxiety disorders was associated with a lower likelihood of remission for each of the 3 switch medications to a relatively equivalent degree.

Generally, the presence of more GMCs was associated with a lower likelihood of remission for these switch medications, but the number of GMCs did not recommend 1 switch medication over another. Response to citalopram without remission was uniformly predictive of higher remission rates among the 3 switch medications. Therefore, for patients who respond to first-step citalopram without remission, any of these 3 switch medications are acceptable. Intolerance to citalopram predicted higher remission rates overall for the 3 switch medications, although intolerance to citalopram was predictive of greater intolerance to sertraline in the second-step treatment. For those intolerant to a first-step SSRI, a non-SSRI might be a preferred second-step treatment.

Overall, few clinical or demographic features were of use in selecting among different second-step switch medications. In fact, the number of "predictors" was no greater than chance. To further evaluate these findings, we conducted classification tree analyses that showed that the sensitivities and specificities achieved with these sociodemographic, clinical, and first-step treatment features in predicting either remission or intolerance were only modest (data available from the corresponding author). Thus, most clinical or demographic features are not a sound basis for selecting among second-step switch medications. Prior treatment response with citalopram is a positive predictor overall, but it is not useful in selecting among these switch medications. Intolerance to citalopram is predictive of intolerance to sertraline, but not lack of efficacy, in the second step.

This study has several limitations. Sample sizes were small (only about 25% remitted with each switch medication); generalizability was limited to patients who allowed a switch to the 3 medications being studied; the self-reported Psychiatric Diagnostic Screening Questionnaire was used to diagnose comorbid Axis I psychiatric disorders; and the methods that were used to define atypical, anxious, and melancholic features may have been suboptimal. Also, the measurement-based care provided may have been of higher quality than that found in everyday practice. The use of the nonblinded QIDS-SR_{16} as the primary outcome in this report may be a limitation, although blinded 17-item Hamilton Rating Scale for Depression and QIDS-SR_{16} outcomes were very similar in STAR*D.[15,60] In addition, we had no measure of Axis II (personality) disorders. Furthermore, participant attrition, either from the overall study or with the decision to move to the next treatment step, would affect efficacy and intolerance rates. This fact underscores the need for replication. Even the few positive findings must be viewed as tentative given the number of tests for significance conducted. Prospective testing of these findings is essential.

In sum, these results highlight the limited value of clinical and demographic information in selecting among second-step medication switch treatments for MDD. A greater chance of remission in the second step is predicted by the absence of anxious features, a response to a first-step SSRI, and intolerance to a first-step SSRI. Concurrent substance abuse may recommend against venlafaxine-XR in the second step. Intolerance to the first-step SSRI recommends against using an SSRI in the second step. Better methods, perhaps with biomarkers, to select among second-step medication treatments are needed.

Submitted for Publication: January 15, 2008; final revision received: March 16, 2008; accepted March 25, 2008;
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Author Contributions: Drs Rush, Wisniewski, Warden, and Trivedi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Financial Disclosure: Dr Rush has received research support from the National Institute of Mental Health, the Robert Wood Johnson Foundation, and the Stanley Medical Research Institute; has been on the advisory boards and/or a consultant for Advanced Neuromodulation Systems Inc, AstraZeneca, Best Practice Project Management Inc, Bris-

tol-Myers Squibb, Cyberonics Inc, Eli Lilly and Company, Gerson Lehman Group, GlaxoSmithKline, Jazz Pharmaceuticals, Magellan Health Services, Merck, Neuronetics, Ono Pharmaceutical, Organon Inc, Pam Lab, Personality Disorder Research Corp, Pfizer Inc, The Urban Institute, and Wyeth-Ayerst Laboratories; has been on the speaker's bureau for Cyberonics Inc, Forest Pharmaceuticals, and GlaxoSmithKline; has equity holdings (excluding mutual funds/blinded trusts) in Pfizer Inc; and has royalty income affiliations with Guilford Publications and Healthcare Technology Systems Inc. Dr Wisniewski has been a consultant for Cyberonics Inc (2005-2006), ImaRx Therapeutics Inc (2006), Bristol-Myers Squibb (2007), Organon Inc (2007), and Case Western Reserve University (2007). Dr Warden currently owns stock in Pfizer Inc and has owned stock in Bristol-Myers Squibb within the last 5 years. Dr Davis (2006-2007) has received research support from Abbott Laboratories Inc, AstraZeneca, Bristol-Myers Squibb, Eisai Pharmaceuticals, Ortho McNeil Pharmaceutical Inc, Janssen, the US Department of Veterans' Affairs, the National Institute of Mental Health, Shire, and Southwestern Oncology Group; has received advisory/consulting fees from Abbott, BMS, Cyberonics, and Shire; and has served on speaker's bureaus for Abbott Laboratories, Bristol-Myers Squibb, Cyberonics, and Sanofi-Aventis; and has equity holdings with Pfizer Inc. Dr Fava has received research support from Abbott Laboratories, Alkermes, Aspect Medical Systems, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly and Company, Forest Pharmaceuticals, GlaxoSmithKline, J & J Pharmaceuticals, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, Novartis, Organon Inc, PamLab, Pfizer Inc, Pharmavite, Roche, Sanofi/Synthelabo, Solvay Pharmaceuticals Inc, and Wyeth-Ayerst Laboratories; has served on advisory boards and done consulting for Amarin Aspect Medical Systems, AstraZeneca, Auspex Pharmaceuticals, Bayer AG, Best Practice Project Management Inc, Biovail Pharmaceuticals Inc, BrainCells Inc, Bristol-Myers Squibb, Cephalon, Compellis, CNS Response, Cypress Pharmaceuticals, Dov Pharmaceuticals, Eli Lilly & Company, EPIX Pharmaceuticals, Fabre-Kramer Pharmaceuticals Inc, Forest Pharmaceuticals, GlaxoSmithKline, Grunenthal GmBH, Janssen Pharmaceutica, Jazz Pharmaceuticals, J & J Pharmaceuticals, Knoll Pharmaceutical Company, Lundbeck, MedAvante Inc, Merck, Neuronetics, Novartis, Nutrition 21, Organon Inc, PamLab, Pfizer Inc, PharmaStar, Pharmavite, Precision Human Biolaboratory, Roche, Sanofi/Synthelabo, Sepracor, Solvay Pharmaceuticals Inc, Somaxon, Somerset Pharmaceuticals, Takeda, TetraGenex Inc, Transcept Pharmaceuticals, and Wyeth-Ayerst Laboratories; has served on the speaker's bureau for AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc, GlaxoSmithKline, Novartis, Organon Inc, Pfizer Inc, PharmaStar, and Wyeth-Ayerst Laboratories; and has equity in Compellis and MedAvante. Dr Nierenberg has received research support from Bristol-Myers Squibb, Cederroth, Cyberonics, Forest Pharmaceuticals, Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceutica, Lichtwer Pharma, National Alliance for Research on Schizophrenia and Depression, the National Institute of Mental Health, Pfizer Pharmaceuticals, Stanley Foundation, and Wyeth-Ayerst Laboratories; has served on the speaker's bureau for Bristol-Myers Squibb, Cyberonics, Forest Pharmaceuticals, Eli Lilly and Company, GlaxoSmithKline, and Wyeth-Ayerst Laboratories; and has provided advisory/consulting services to Abbott Laboratories, Brain Cells Inc, Bristol-Myers Squibb, Cederroth, Eli Lilly and Company, GlaxoSmithKline, Genaissance, Innapharma, Janssen Pharmaceutica, Novartis Pharmaceuticals, Pfizer Inc, Sepracor, Shire, and Somerset. Dr Trivedi has been a consultant for Abbott Laboratories Inc, Akzo (Organon Inc), AstraZeneca, Bayer, Bristol-Myers Squibb, Cephalon, Cyberonics Inc, Eli Lilly and Company, Fabre-Kramer Pharmaceuticals Inc, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Johnson & Johnson, Eli Lilly and Company, Meade Johnson, Neuronetics, Parke-Davis Pharmaceuticals, Pfizer Inc, Pharmacia & Upjohn, Sepracor, Solvay Pharmaceuticals Inc, VantagePoint, and Wyeth-Ayerst Laboratories; has served on speaker's bureaus for Abdi Brahim, Akzo (Organon Inc), Bristol-Myers Squibb, Cephalon, Cyberonics Inc, Eli Lilly and Company, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Pharmacia & Upjohn; Solvay Pharmaceuticals Inc, and Wyeth-Ayerst Laboratories; and has also received grant support from Bristol-Myers Squibb, Cephalon Inc, Corcept Therapeutics Inc, Cyberonics Inc, Eli Lilly and Company, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Merck, the National Institute of Mental Health, the National Alliance for Research in Schizophrenia and Depression, Novartis, Pfizer Inc, Pharmacia & Upjohn, Predix Pharmaceuticals, Solvay Pharmaceuticals Inc, and Wyeth-Ayerst Laboratories.

Funding/Support: This project was funded by National Institute of Mental Health contract N01MH90003 to the University of Texas Southwestern Medical Center at Dallas (principal investigator: Dr Rush).

Disclaimer: The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services. Mention of trade names, commercial products, or organizations does not imply endorsement by the US government.

Additional Contributions: Bristol-Myers Squibb, Forest Laboratories, GlaxoSmithKline, King Pharmaceuticals, Organon Inc, Pfizer Inc, and Wyeth-Ayerst Laboratories provided medications at no cost for this trial. We also acknowledge the support of the Research and Development Service at the Veterans' Affairs Medical Centers and the editorial support of Jon Kilner, MS, MA.

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Correction

Missing Information. The "About the Cover" box published in the June issue (2008;65[6]:617) inadvertently omitted the source of one of the images. The sketch of *Les Demoiselles d'Avignon* (1907) by Pablo Picasso was provided by Bridgeman Art Library, New York, NY.