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Bupropion-SR, Sertraline, or Venlafaxine-XR after Failure of SSRIs for Depression

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ABSTRACT

BACKGROUND

After unsuccessful treatment for depression with a selective serotonin-reuptake inhibitor (SSRI), it is not known whether switching to one antidepressant is more effective than switching to another.

METHODS

We randomly assigned 727 adult outpatients with a nonpsychotic major depressive disorder who had no remission of symptoms or could not tolerate the SSRI citalopram to receive one of the following drugs for up to 14 weeks: sustained-release bupropion (239 patients) at a maximal daily dose of 400 mg, sertraline (238 patients) at a maximal daily dose of 200 mg, or extended-release venlafaxine (250 patients) at a maximal daily dose of 375 mg. The study was conducted in 18 primary and 23 psychiatric care settings. The primary outcome was symptom remission, defined by a total score of 7 or less on the 17-item Hamilton Rating Scale for Depression (HRSD-17) at the end of the study. Scores on the Quick Inventory of Depressive Symptomatology — Self Report (QIDS-SR-16), obtained at treatment visits, determined secondary outcomes, including remission (a score of 5 or less at exit) and response (a reduction of 50 percent or more on baseline scores).

RESULTS

Remission rates as assessed by the HRSD-17 and the QIDS-SR-16, respectively, were 21.3 percent and 25.5 percent for sustained-release bupropion, 17.6 percent and 26.6 percent for sertraline, and 24.8 percent and 25.0 percent for extended-release venlafaxine. QIDS-SR-16 response rates were 26.1 percent for sustained-release bupropion, 26.7 percent for sertraline, and 28.2 percent for extended-release venlafaxine. These treatments did not differ significantly with respect to outcomes, tolerability, or adverse events.

CONCLUSIONS

After unsuccessful treatment with an SSRI, approximately one in four patients had a remission of symptoms after switching to another antidepressant. Any one of the medications in the study provided a reasonable second-step choice for patients with depression. (ClinicalTrials.gov number, NCT00021528.)

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*The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial investigators are listed in the Appendix.

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Major depressive disorder is associated with substantial morbidity, mortality, family burden, and health care costs.[1] Since no single treatment is uniformly effective,[2-4] subsequent interventions are often needed. Second-step treatments include augmenting the first agent with a second or discontinuing the first agent and beginning a second (switching). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial used an equipoise, stratified, randomized design to evaluate the relative efficacy and tolerability of various antidepressant treatments for outpatients with nonpsychotic major depressive disorder who had a lack of remission or could not tolerate the selective serotonin-reuptake inhibitor (SSRI) citalopram (Celexa, Forest Pharmaceuticals) or subsequent treatments.[2,4,5]

The SSRIs are common first-step treatments, given their relatively low toxicity and high tolerability. Few randomized trials have compared the efficacy and tolerability of treatment with at least two active second agents after the initial failure of treatment with an SSRI.[6-9] Open case series — typically in symptomatic volunteers with few psychiatric and general medical coexisting conditions[10] — suggest variable response rates (25 to 65 percent) when the first SSRI is switched to a second SSRI,[11-13] to a non-SSRI (an out-of-class switch),[14-16] or to medications that inhibit the uptake of both serotonin and norepinephrine ("dual-action" agents).[17-19]

This report summarizes the overall study design for the first two treatment steps. In the current study, we compared outcomes achieved with three second-step medications: sustained-release bupropion (Wellbutrin SR, GlaxoSmithKline), sertraline (Zoloft, Pfizer), or extended-release venlafaxine (Effexor XR, Wyeth-Ayerst Laboratories).[2,4] These medications are pharmacologically distinct. Sustained-release bupropion, an out-of-class agent, does not inhibit serotonin reuptake. Sertraline, a within-class switch, is an SSRI. Extended-release venlafaxine, a dual-action agent, inhibits the reuptake of both serotonin and norepinephrine.

Remission (as opposed to response) was chosen as the primary outcome. Remission, the virtual absence of depressive symptoms, was the goal of treatment[3,20] and is associated with a better prognosis and day-to-day function than is response (i.e., a reduction in symptoms of at least 50 percent from baseline).[21,22] Generally, in eight-week efficacy trials, remission rates are 35 to 40 percent, and response rates are 50 to 55 percent. Remission rates with citalopram as the first step in STAR*D were 28 to 33 percent, and response rates averaged 47 percent.[23]

Figure 1 (facing page). Overview of Study Design.
BUP-SR denotes sustained-release bupropion, SERT sertraline, VEN-XR extended-release venlafaxine, CT cognitive therapy, CIT citalopram, and BUS buspirone.

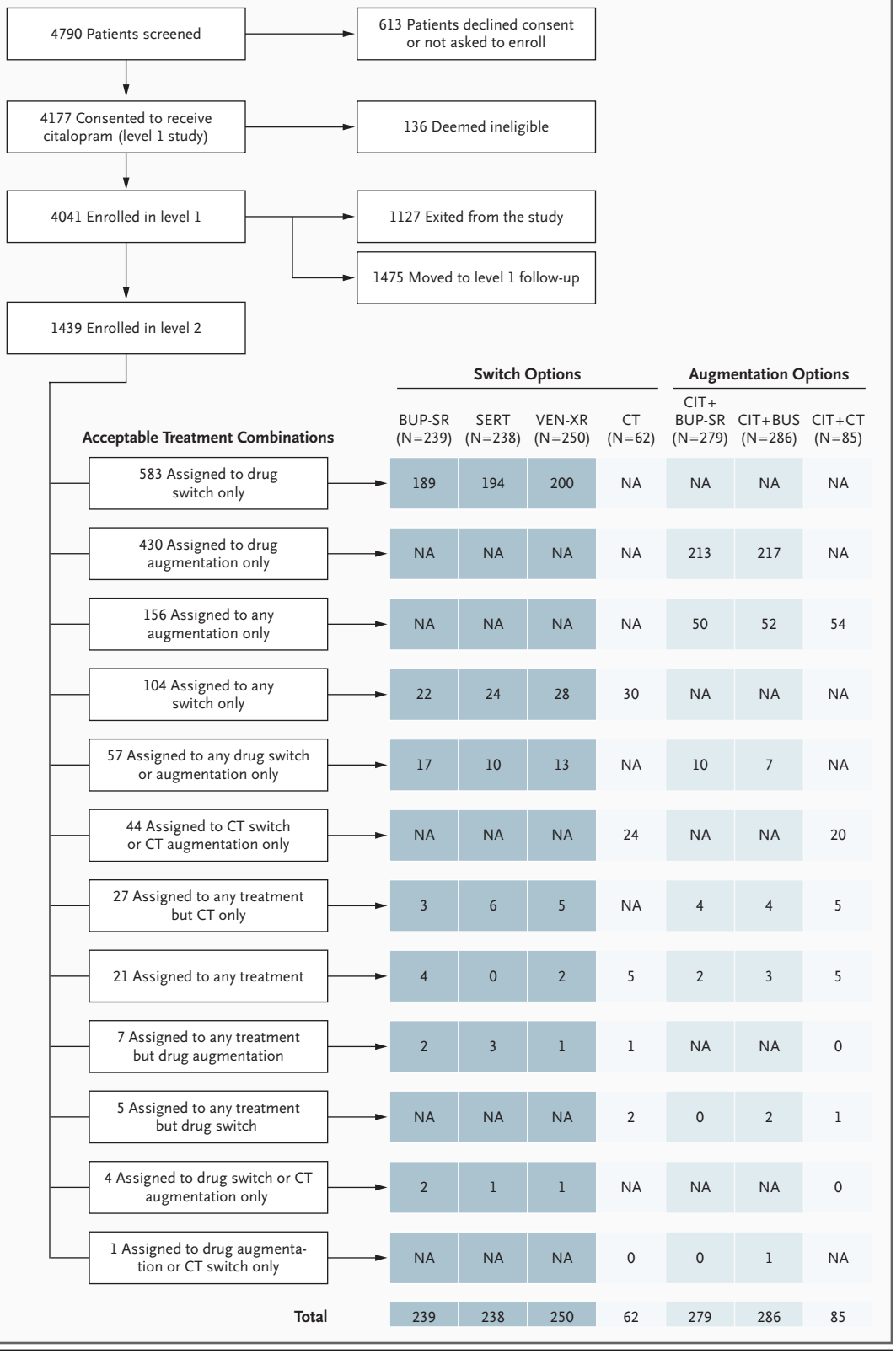
METHODS

PARTICIPANTS

Adult outpatients with a primary clinical diagnosis of nonpsychotic major depressive disorder,[24] as confirmed by a checklist completed by the clinical research coordinators, were enrolled at primary and psychiatric public and private practice settings between July 2001 and August 2004. Broad inclusion and minimal exclusion criteria[4] were used to maximize the generalizability of the findings.[2,4]

All study participants provided written informed consent at enrollment into the initial treatment with citalopram (level 1) and into all secondary treatments (level 2). All participants received citalopram as the initial treatment.[23] Participants who were eligible for second-step treatments either had not had a remission or could not tolerate citalopram. A lack of remission was defined as a score of more than 5 on the 16-item Quick Inventory of Depressive Symptomatology — Clinician Rated (QIDS-C-16)[25,26] at the last level 1 visit; scores can range from 0 to 27, with higher scores indicating greater severity of symptoms.

Figure 1 provides an overview of the study at levels 1 and 2. The study used an equipoise stratified, randomized design[5] in which patients were strongly encouraged to accept all seven potential second-step treatments — the four switch options (including cognitive therapy) and three augmented treatments. However, to mimic practice, patients could opt to exclude certain level 2 treatment options. They could elect to exclude all switch options or all augmentation options, they could accept or decline cognitive therapy within either the switch or augmentation option, or they could accept only cognitive therapy (both as a switch and an augmentation treatment). In this design, the various acceptable



Acceptable Treatment Combinations	Switch Options				Augmentation Options		
	BUP-SR (N=239)	SERT (N=238)	VEN-XR (N=250)	CT (N=62)	CIT+ BUP-SR (N=279)	CIT+BUS (N=286)	CIT+CT (N=85)
583 Assigned to drug switch only	189	194	200	NA	NA	NA	NA
430 Assigned to drug augmentation only	NA	NA	NA	NA	213	217	NA
156 Assigned to any augmentation only	NA	NA	NA	NA	50	52	54
104 Assigned to any switch only	22	24	28	30	NA	NA	NA
57 Assigned to any drug switch or augmentation only	17	10	13	NA	10	7	NA
44 Assigned to CT switch or CT augmentation only	NA	NA	NA	24	NA	NA	20
27 Assigned to any treatment but CT only	3	6	5	NA	4	4	5
21 Assigned to any treatment	4	0	2	5	2	3	5
7 Assigned to any treatment but drug augmentation	2	3	1	1	NA	NA	0
5 Assigned to any treatment but drug switch	NA	NA	NA	2	0	2	1
4 Assigned to drug switch or CT augmentation only	2	1	1	NA	NA	NA	0
1 Assigned to drug augmentation or CT switch only	NA	NA	NA	0	0	1	NA
Total	239	238	250	62	279	286	85

treatments chosen by patients are called acceptability strata. Only the treatments for which patients accepted randomization were compared.[5]

By design, only the treatment groups that included a sufficient number of patients were analyzed to address the primary study aims. For level 2, the primary comparisons were among the three medication switches (sustained-release bupropion, sertraline, and extended-release venlafaxine), which are discussed in this report, and among the two medication augmentations (reported by Trivedi et al. elsewhere in this issue of the *Journal*[27]). Randomization was conducted in a 1:1:1 ratio separately within each regional center and according to which treatments the participants accepted.

The institutional review boards at the national coordinating center, the data coordinating center, and regional centers and at relevant clinical sites and the data safety and monitoring board of the National Institute of Mental Health approved and monitored the protocol.

All authors were involved in study implementation, supervision, data review, and manuscript development. Bristol-Myers Squibb, Forest Pharmaceuticals, GlaxoSmithKline, King Pharmaceuticals, Organon, Pfizer, and Wyeth-Ayerst Laboratories provided medications at no cost for this trial but otherwise had no role in the design, conduct, data analysis, or drafting of the manuscript reporting the results.

PROTOCOL TREATMENT

To mimic clinical practice, enhance safety, ensure a vigorous dosing regimen, and maximize generalizability, all participants and treating clinicians were aware of treatment assignments and doses. A clinical treatment manual (available at www.star-d.org) with an emphasis on measurement-based care[23] recommended starting doses and dose changes on the basis of scores for the clinician-rated (QIDS-C-16) version of the 16-item Quick Inventory of Depressive Symptomatology (a scale ranging from 0 to 27, with higher scores indicating a greater severity of symptoms)[25,26] and the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) (a rating scale that collects information on the frequency, intensity, and burden of side effects, each on a 7-point scale with higher ratings indicating greater severity) obtained at each treatment.[4] (A copy of the manual can be found in the Supplementary Appendix, available with the full text of this article at www.nejm.org.) In addition, didactic instruction, support by the clinical research coordinators, and a centralized monitoring system[28] with feedback ensured timely increases in doses when an inadequate reduction in symptoms occurred in the context of acceptable side effects.[23] Treatment was aimed at symptom remission, which was defined as a QIDS-C-16 score of 5 or less at the clinic visit.

At the initiation of the switch in medications, citalopram was discontinued without a tapering or washout period. The recommended daily dose of sustained-release bupropion was 150 mg for seven days, 200 mg from day 8 to 27, 300 mg from day 28 to 41, and 400 mg from day 42 onward. Sertraline was started at a daily dose of 50 mg and increased to 100 mg at day 14, to 150 mg at day 28, and to 200 mg at day 63. For extended-release venlafaxine, the starting daily dose of 37.5 mg for 7 days was increased to 75 mg from day 8 to 14, to 150 mg from day 15 to 27, to 225 mg from day 28 to 41, to 300 mg from day 42 to 62, and to 375 mg from day 63 onward. Dosing recommendations were flexible and were based on clinical judgment as informed by the FIBSER and the QIDS-C-16 scores at each treatment visit.

CONCOMITANT TREATMENTS

Stimulants, anticonvulsants, antipsychotic agents, mood stabilizers, nonprotocol antidepressant medications, and potential antidepressant augmenting agents (e.g., buspirone) were proscribed. Otherwise, any concomitant medication was allowed as necessary to manage concurrent general medical conditions or the side effects of protocol antidepressants (e.g., sexual dysfunction), as were anxiolytic agents (with the exception of alprazolam) and sedative hypnotic agents (including trazodone, at a dose of 200 mg or less at bedtime, for sleep).

CLINICAL MEASUREMENTS

Information collected at level 1 baseline to describe the study cohort included scores for the Cumulative Illness Rating Scale (CIRS)[29] to assess patients' general medical conditions, the Psychiatric Diagnostic Screening Questionnaire[30,31] to identify coexisting psychiatric disorders, and the 30-item Inventory of Depressive Symptomatology — Clinician Rated[26,32] (IDS-C30) to assess the severity of depression and certain symptom fea-

tures.[33] Assessments of overall function — including the Short-Form Health Survey (SF-12), Work Productivity and Activity Impairment Questionnaire, Work and Social Adjustment Scale (WSAS) — and satisfaction (Quality of Life Enjoyment and Satisfaction Questionnaire [QLESQ]) were collected by an automated interactive-voice-response telephone system.[34]

The primary outcome (i.e., symptom remission) was defined as a total score of 7 or less on the 17-item Hamilton Depression Rating Scale[35] (HRSD-17), which was obtained in telephone-based, structured interviews (in either English or Spanish) conducted by independent research-outcome assessors who were unaware of treatment-group assignment within five days after entry and exit from the study. The secondary outcomes included results on the Quick Inventory of Depressive Symptomatology — Self-Report (QIDS-SR-16)[2,4,25,26] and the FIBSER[4] obtained at each treatment visit. QIDS-SR-16 remission was defined as a total score at study exit of 5 or less, and response was defined as a reduction of 50 percent or more (level 2 baseline to exit) on the QIDS-SR-16.

STATISTICAL ANALYSIS

Summary statistics are presented as means (±SD) for continuous variables and percentages for discrete variables. Parametric and nonparametric analysis-of-variance methods and chi-square tests were used to compare the baseline clinical and demographic characteristics, treatment features, and rates of side effects and serious adverse events among treatment groups.

All analyses were conducted according to the intention to treat.[36] Logistic-regression models were used to determine whether there was an independent treatment effect on remission and response rates, adjusting for the effect of the regional center and acceptability stratum. Thirteen design variables were included in the logistic-regression models to estimate the effect of differences among the 14 regional centers. For this report, eight treatment-acceptability strata for medication switches were possible. These strata were collapsed into two strata ("medication switch only" and "other") because of small numbers of patients in several strata. Thus, one design variable was included in the logistic models to control for the effect of the acceptability. Times to first remission (a score of 5 or less on the QIDS-SR-16) and first response (a reduction in the baseline score of 50 percent or more on the QIDS-SR-16) were defined as the first observed point with the use of data from clinic visits. Log-rank tests were used to compare the cumulative proportion with rates of remission and response among the three treatment groups. Exploratory logistic-regression analyses were used to determine whether there was a differential effect of treatment among patients who could not tolerate treatment in level 1.

At the end of this study, patients with missing HRSD-17 scores were assumed not to have had a remission (as originally defined).[4] To determine whether this assumption affected study results, we conducted sensitivity analyses. The analyses were replicated with the use of two additional methods of imputation, a multiple imputation method[37] and imputed values generated from item-response theory, which mapped total scores on the QIDS-SR-16 to corresponding values on the HRSD-17.[38] Consistent findings indicated that the results were not affected by this approach to missing data.

RESULTS

PATIENTS

Figure 1 shows how the study groups in this trial (and the study by Trivedi et al.[27]) were developed on the basis of the various acceptability strata. Only 21 of 1439 patients (1.5 percent) accepted random assignment to any of the seven level 2 treatments. Furthermore, only 369 of 1439 patients (25.6 percent) included cognitive therapy among any of the acceptable treatments.

Of the 727 participants, 239 received sustained-release bupropion, 238 received sertraline, and 250 received extended-release venlafaxine. The majority of these participants were drawn from two groups who were defined by the treatments that they found acceptable (Fig. 1), mainly from the 583 patients who accepted only the three medication switch treatments and the 104 patients who accepted only the four switch treatments (i.e., the three medication switches plus cognitive therapy alone).

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Participants had index episodes of depression with low function that were defined as recurrent (75.7 percent of the patients), early onset (37.2 percent), or chronic (27.0 percent) (Table 1). The character-

Table 1. Clinical and Demographic Characteristics of Patients.*

Characteristic	Total (N=727)	Sustained-Release Bupropion (N=239)	Sertraline (N=238)	Extended-Release Venlafaxine (N=250)
Age — yr	41.8±12.8	41.9±12.9	42.6±12.7	41.1±12.6
Female sex — no. (%)	427 (58.7)	136 (56.9)	131 (55.0)	160 (64.0)
Race or ethnic group — no. (%)†				
White	551 (75.8)	179 (74.9)	186 (78.2)	186 (74.4)
Black	128 (17.6)	47 (19.7)	39 (16.4)	42 (16.8)
Other	48 (6.6)	13 (5.4)	13 (5.5)	22 (8.8)
Hispanic ethnic group	80 (11.0)	23 (9.6)	28 (11.8)	29 (11.6)
Education — yr	13.3±3.0	13.4±2.9	13.1±3.2	13.4±2.9
Employment status — no. (%)				
Employed	388 (53.4)	132 (55.5)	118 (49.6)	138 (55.2)
Unemployed	299 (41.2)	90 (37.8)	109 (45.8)	100 (40.0)
Retired	39 (5.4)	16 (6.7)	11 (4.6)	12 (4.8)
Monthly income — $	2,039±2,568	2,139±2,744	1,900±2,679	2,077±2,258
Medical insurance — no. (%)				
Private	316 (44.6)	106 (44.7)	97 (41.6)	113 (47.3)
Public	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)
Marital status — no. (%)				
Single (never married)	199 (27.4)	69 (28.9)	67 (28.2)	63 (25.2)
Married or cohabiting	288 (39.6)	89 (37.2)	95 (39.9)	104 (41.6)
Divorced or separated	205 (28.2)	69 (28.9)	64 (26.9)	72 (28.8)
Widowed	35 (4.8)	12 (5.0)	12 (5.0)	11 (4.4)
Age at first major depressive episode				
Mean — yr	25.0±14.0	25.7±14.6	24.8±13.5	24.4±13.8
<18 yr — no. (%)	268 (37.2)	92 (38.8)	84 (35.9)	92 (36.9)
Duration of major depressive disorder — yr	16.9±13.6	16.2±13.6	17.8±13.6	16.8±13.6
No. of major depressive episodes	7.0±12.8	6.7±11.5	6.6±12.2	7.8±14.6
Recurrent major depressive disorder — no. (%)	499 (75.7)	153 (70.5)	172 (78.5)	174 (78.0)
Family history of major depressive disorder — no. (%)	387 (53.9)	122 (51.5)	132 (55.9)	133 (54.3)
Prior suicide attempt — no. (%)	125 (17.2)	40 (16.9)	47 (19.7)	38 (15.2)

istics of the patients were similar to those of the patients who entered level 1 and who could be evaluated.[23] For example, the mean (±SD) scores for the HRSD-17 were 21.8±5.2 at entry into level 1 and 18.9±7.3 at entry into this study. Of the 727 enrollees, 407 patients could not tolerate citalopram (56.0 percent), as defined by the discontinuation of level 1 treatment before four weeks for any reason or after four weeks because of intolerable side effects. The results in the three medication groups were similar. The number of concurrent psychiatric disorders (data not shown) did not differ significantly among the three treatment groups.

TREATMENT FEATURES

Table 2 shows the course of treatment with each medication. All three medications were administered in adequate doses for substantial periods, though only 32.8 percent of patients who received extended-release venlafaxine took more than 225 mg per day.

Table 1. (Continued.)

Characteristic	Total (N=727)	Sustained-Release Bupropion (N=239)	Sertraline (N=238)	Extended-Release Venlafaxine (N=250)
CIRS				
No. of categories‡	3.3±2.4	3.3±2.4	3.3±2.4	3.3±2.3
Total score	4.8±3.9	4.8±4.0	4.7±3.8	4.9±3.9
Psychiatric care — no. (%)	437 (60.1)	145 (60.7)	140 (58.8)	152 (60.8)
Duration of index major depressive episode				
Mean — mo	29.6±65.9	32.1±75.0	28.7±60.6	28.1±61.7
≥2 years — no. (%)	195 (27.0)	63 (26.6)	67 (28.3)	65 (26.2)
SF-12				
Mental§	25.8±8.3	25.8±8.5	25.5±8.7	26.0±7.7
Physical	47.0±12.3	46.7±12.4	47.1±12.3	47.1±12.3
WSAS score¶	25.3±8.7	25.2±8.9	25.6±8.6	25.3±8.6
QLESQ score‖	38.2±15.3	39.2±15.7	36.9±15.0	38.4±15.4
HRSD-17 score (level 2 entry)**	18.9±7.3	18.5±7.7	19.3±6.9	18.9±7.3
IDS-C30 score (level 2 entry)††	34.1±13.0	33.2±13.6	34.3±12.3	34.6±13.1
Anxious features (level 2 entry) — no. (%)‡‡	284 (44.4)	88 (42.1)	97 (45.5)	99 (45.6)
Atypical features (level 2 entry) — no. (%)§§	130 (20.3)	33 (15.8)	47 (22.1)	50 (22.9)
QIDS-C-16 score (level 2 entry)¶¶	14.0±4.5	14.0±4.6	14.0±4.3	13.9±4.7
QIDS-SR-16 score (level 2 entry)¶¶	13.2±4.9	13.3±5.1	13.3±4.7	13.1±5.0
Duration of level 1 treatment — wk	8.0±4.2	7.9±4.2	7.7±4.3	8.4±4.0
Change in QIDS-C-16 score during level 1 — %	4.3±40.2	4.2±33.6	3.5±44.7	5.1±41.6
Citalopram dose at end of level 1 — mg/day	41.6±17.7	41.5±17.8	41.3±17.8	42.0±17.4
Intolerance to level 1 side effects — no. (%)	407 (56.0)	134 (56.1)	132 (55.5)	141 (56.4)

* Plus–minus values are means +SD. Level 1 refers to initial treatment with citalopram. Level 2 refers to second-step treatment (reported in this study) with sustained-release bupropion, sertraline, or extended-release venlafaxine. Because of missing data on some characteristics, the denominators that were used to determine some percentages differ from the total numbers of patients.

† Race or ethnic group was self-reported by patients.

‡ The Cumulative Illness Rating Scale (CIRS) is divided into 13 categories or disorders, with a range of 0 to 13 (e.g., pulmonary and gastrointestinal). Each category is rated for severity, with a range of 0 to 4, with higher numbers indicating greater severity. The total score was calculated by adding up the scores for all categories.

§ The Short Form Health Survey (SF-12) scores range from 0 to 100, with higher scores indicating better function.

¶ The Work and Social Adjustment Scale (WSAS) scores range from 0 to 40, with higher scores indicating worse function.

‖ The Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ) scores range from 0 to 100, with higher scores indicating greater satisfaction.

** The 17-item Hamilton Rating Scale for Depression (HRSD-17) scores range from 0 to 52, with higher scores indicating a greater severity of symptoms.

†† The 30-item Inventory of Depressive Symptomatology — Clinician Rated (IDS-C30) scores range from 0 to 84, with higher scores indicating a greater severity of symptoms.

‡‡ The presence of anxious features was ascertained on the basis of the total score on the anxiety subscale of the HRSD-17.

§§ The presence of atypical features was ascertained on the basis of specific item scores on the IDS-C30.

¶¶ The 16-item Quick Inventory of Depressive Symptomatology — Clinician-Rated and Self-Rated (QIDS-C-16 and QIDS-SR-16) scores range from 0 to 27, with higher scores indicating a greater severity of symptoms.

SYMPTOM OUTCOMES

Remission rates, on the basis of the results on the HRSD-17, did not differ significantly among treatment groups ($\chi^2=3.649$ with 2 df, $P=0.16$). Of 239 patients who received sustained-release bupropion, 51 had a remission (21.3 percent), as did 42 of 238 patients who received sertraline (17.6 percent) and 62 of 250 patients who received extended-release venlafaxine (24.8 percent). The treatments did not differ significantly with respect to the

Table 2. Characteristics of Treatment.*

Characteristic	Sustained-Release Bupropion (N=239)	Sertraline (N=238)	Extended-Release Venlafaxine (N=250)
Duration of treatment			
Mean — wk	8.3±5.0	9.1±5.0	9.3±5.1
<4 wk — no. (%)	60 (25.1)	44 (18.5)	55 (22.0)
<8 wk — no. (%)†	105 (43.9)	94 (39.5)	81 (32.4)
No. of post-baseline clinic visits	3.5±1.6	3.7±1.6	3.8±1.6
Days to first post-baseline visit	16.9±7.0	18.2±11.7	17.0±7.7
Dose at end of study — mg/day	282.7±104.4	135.5±57.4	193.6±106.2
Time received exit dose — wk	6.7±5.1	6.3±3.8	6.4±4.7
Concomitant psychotropic treatments — no. (%)			
Trazodone	37 (15.7)	46 (19.3)	41 (16.5)
Anxiolytics	34 (14.4)	24 (10.1)	28 (11.3)
Sedative or hypnotics	40 (17.0)	42 (17.7)	38 (15.3)

* Plus–minus values are means ±SD. Because of missing data on some characteristics, the denominators that were used to determine some percentages differ from the total numbers of patients.

† P<0.04 for the comparison among the groups. Bonferroni-adjusted post hoc comparisons indicate a significant difference between sustained-release bupropion and extended-release venlafaxine (P=0.009).

QIDS-SR-16 response rates, remission rates, or percent reductions in QIDS-SR-16 scores (Table 3).

The treatments also did not differ significantly with respect to either time to remission (log rank $\chi^2=0.38$, P=0.93) (Fig. 2) or time to response (log rank $\chi^2=0.65$, P=0.72) on the basis of results on the QIDS-SR-16. Among the patients who had a remission, the mean time to remission according to results on the QIDS-SR-16 was 5.4±4.5 weeks (median, 4.0) for those given sustained-release bupropion, 6.2±5.0 weeks (median, 4.9) for those given sertraline, and 5.5±4.7 weeks (median, 4.2) for those given extended-release venlafaxine. Similarly, among patients with a response, according to results on the QIDS-SR-16, the mean time to a response was 5.5±3.5 weeks (median, 4.0) for those given sustained-release bupropion, 6.6±4.3 weeks (median, 5.9) for those given sertraline, and 7.0±4.3 weeks (median, 6.0) for those given extended-release venlafaxine.

TOLERABILITY AND ADVERSE EVENTS

Side effects and serious adverse events were clinically similar among the treatment groups (Table 3). The treatments did not differ significantly in the overall burden of side effects or in the proportion of patients with any serious psychiatric adverse event, though there was a difference in the distribution of the frequency of side effects. Four patients were hospitalized for suicidal ideation or attempted suicide, but none committed suicide during the trial.

DISCUSSION

In the context of the equipoise stratified, randomized design used in this trial, which gave patients choices in their treatment regimen, most patients opted to have their medication either switched or augmented. Few patients chose to do both, thus preventing a definitive comparison of strategies involving augmentation with those involving a switch medication. Our results suggest that such a choice (i.e., both augmentation and a switch medication) is relatively uncommon in practice when patients are provided options.

With regard to the commonly accepted practice of switching medications, approximately one in four depressed patients had a remission of symptoms with sustained-release bupropion, sertraline, or extended-release venlafaxine after either not having had a remission with or being unable to tolerate citalopram therapy. Remission rates did not differ significantly among the three medication groups nor did QIDS-SR-16 response rates, times to QIDS-SR-16 response, change in QIDS-SR-16 scores from baseline to the end of the study, serious adverse events, or measures of tolerability. Remission rates were slightly higher according to results on the QIDS-SR-16 than to results on the HRSD-17, because patients who did not undergo HRSD-17 evaluation at the end of the study were declared a priori not to have had a remission. Of the 209 patients with missing HRSD-17 scores, 26 had a remission (12.4 percent) on the basis of results on the QIDS-SR-16. On the basis of results on the HRSD-17, no differential treatment effect in regard to remission was found between patients who could not tolerate citalopram and those who could tolerate this agent. These findings are generalizable to most adult outpatients with a nonpsychotic major depressive disorder who are treated in primary or specialty care settings.

Rates of response and remission with each switch medication were lower than rates reported in open-label case series of switch medications

Table 3. Treatment Outcomes, Side Effects, and Serious Adverse Events.*

Characteristic	Sustained-Release Bupropion (N=239)	Sertraline (N=238)	Extended-Release Venlafaxine (N=250)
HRSD-17 remission at end of study — no. (%)	51 (21.3)	42 (17.6)	62 (24.8)
QIDS-SR-16 remission at end of study — no. (%)	61 (25.5)	63 (26.6)	62 (25.0)
QIDS-SR-16 response — no. (%)	62 (26.1)	63 (26.7)	70 (28.2)
Change in QIDS-SR-16 score — %	–16.4±52.7	–21.9±41.1	–16.9±72.4
QIDS-SR-16 score at end of study	10.5±6.0	10.1±5.9	10.2±6.1
Maximal frequency of side effects in level 2 — no. (%)†			
No side effects	53 (24.5)	45 (20.6)	43 (19.0)
10–25% of the time	46 (21.3)	68 (31.2)	68 (30.1)
50–75% of the time	73 (33.8)	52 (23.9)	55 (24.3)
90–100% of the time	44 (20.4)	53 (24.3)	60 (26.5)
Maximal intensity of side effects in level 2 — no. (%)			
None	52 (24.1)	43 (19.7)	41 (18.1)
Minimal to mild	45 (20.8)	55 (25.2)	62 (27.4)
Moderate to marked	91 (42.1)	77 (35.3)	80 (35.4)
Severe to intolerable	28 (13.0)	43 (19.7)	43 (19.0)
Maximal burden of side effects in level 2 — no. (%)			
None	62 (28.7)	50 (22.9)	52 (23.0)
Minimal to mild	70 (32.4)	84 (38.5)	73 (32.3)
Moderate to marked	67 (31.0)	59 (27.1)	80 (35.4)
Severe to intolerable	17 (7.9)	25 (11.5)	21 (9.3)
Discontinuation due to intolerance — no. (%)‡	65 (27.2)	50 (21.0)	53 (21.2)
Serious adverse events — no. (%)§	5 (2.1)	10 (4.2)	6 (2.4)
Death, nonsuicide	1	0	0
Medical event with hospitalization	3	8	4
Medical event without hospitalization	0	0	0
Psychiatric hospitalization for detoxification	0	1	0
Psychiatric hospitalization for suicidal ideation or attempt	0	2	2
Psychiatric hospitalization for worsening depression	0	0	0
Psychiatric hospitalization for other psychiatric condition	1	0	0
Suicidal ideation without hospitalization	0	0	0
Serious psychiatric adverse events — no. (%)	1 (0.4)	3 (1.3)	2 (0.8)

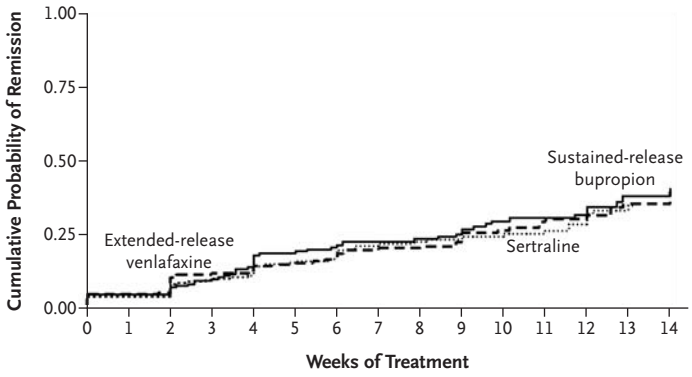
* Plus–minus values are means ±SD. HRSD-17 denotes the 17-item Hamilton Rating Scale for Depression (scores can range from 0 to 52, with higher scores indicating a greater severity of symptoms), and QIDS-SR-16 the 16-item Quick Inventory of Depressive Symptomatology, Self-Rated (scores can range from 0 to 27, with higher scores indicating a greater severity of symptoms). Because of missing data on some characteristics, the numbers of cases do not always add up to the total number of cases in the treatment group, and the percentages do not always sum to 100 because of rounding.

† $P<0.05$ for the comparison among the groups. Bonferroni-adjusted post hoc comparisons found no significant pairwise differences.

‡ This category included all patients who discontinued the study before week 4 regardless of the reason and all who did so at or after week 4 if they cited intolerable side effects as the reason.

§ Patients may have had more than one event.

after failure of treatment with an SSRI. Such series typically involved patients who were not chronically depressed, had few coexisting medical or psychiatric illnesses, and were treated in research clinics.[10] On the basis of results on the HRSD-17, remission rates were also slightly lower than the overall rate of 30 percent with medication augmentation as the second treatment step



No. at Risk							
Sustained-release bupropion	239	191	146	119	89	53	26
Sertraline	238	207	165	135	92	63	30
Extended-release venlafaxine	250	201	159	136	103	62	33
Total	727	599	470	390	284	178	89

Figure 2. Weeks of Treatment until Remission, According to Drug.

(as described by Trivedi et al.[27]). However, these two trial groups of the STAR*D study involved largely distinct groups of patients who had different outcomes with citalopram treatment. Patients in our study had greater rates of intolerance to and somewhat less benefit from citalopram. Although the remission rates in our trial are clinically meaningful, the relatively low rates were probably not due to inadequate doses of medication or to inadequate durations of treatment, given the mean doses at the end of treatment and durations of treatment for each agent. However, the dose of extended-release venlafaxine was less likely to approach the protocol-recommended maximum of 375 mg per day than was the dose of either of the other two drugs.

These findings have important practical implications. Contrary to the belief that intolerance of one SSRI predicts intolerance of another SSRI, sertraline was tolerated as well as sustained-release bupropion, even though 56.0 percent of patients in this trial could not tolerate citalopram. Thus, intolerance to or the lack of efficacy of one SSRI seems not to imply intolerance or lack of efficacy of another SSRI. These results indicate that both within-class and out-of-class medication switches are reasonable choices.

As for the dual-action agent extended-release venlafaxine, post hoc pooled analyses[39,40] have suggested slightly higher remission rates with venlafaxine than with SSRIs when used as first-step treatment. No studies, to our knowledge, have compared venlafaxine with other potentially active medications at the second treatment step. In this study, higher remission rates were not achieved with extended-release venlafaxine than with the more selective agents among patients who could not tolerate or who did not have a remission with citalopram therapy.

Important limitations to this comparison of three switch medications include the lack of placebo control and unblinded delivery of treatment, though assessment of the primary outcome (according to results on the HRSD-17) was done in a blinded fashion, and the QIDS-SR-16 and HRSD-17 ratings were in agreement. A placebo-controlled study is not needed to discern whether these three switch treatments differ, but without a placebo group, we cannot be certain that any of the treatments was specifically effective (i.e., the results were due to the pharmacologic effects of the medication). On the other hand, switching to a placebo after an initial failed treatment would have aroused concern about ethics,[41] might have limited generalizability (if more severely or chronically ill patients had declined to enroll), or might have led to less vigorous administration of drugs, given the high prevalence of coexisting medical conditions among the patients. In addition, since few patients opted for both augmentation of their medication and switching to another drug, we cannot definitively compare these two strategies. Finally, we cannot determine the basis for the choices exercised by patients, since

we did not ask them why they had made such choices.

Among patients who cannot tolerate or who do not have a remission in response to an initial SSRI, approximately one in four patients had a remission on switching to sustained-release bupropion, sertraline, or extended-release venlafaxine; these three drugs had similar efficacy and tolerability. These findings highlight the need for more broadly effective antidepressant treatments.

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This study is dedicated to the memory of Fred Quitkin, M.D., our dear friend and colleague.

APPENDIX

The following investigators participated in the STAR*D trial: *National Coordinating Center* — A.J. Rush, M. Trivedi, D. Warden, M.M. Biggs, K. Shores-Wilson, D. Stegman, M. Kashner; *Data Coordinating Center* — S. Wisniewski, G.K. Balasubramani, J. Luther, H. Eng; *Regional Centers: University of Alabama, Birmingham,* and *Tuscaloosa Veterans Affairs Medical Center, Tuscaloosa, Ala.* — L. Davis, K. Rice, A. Berry, P. Johnson, S. Ambrose, M. Jewell, B. Thomas, E. Waldrop, T. Allen, E. St. John, R. Williams; *University of California, Los Angeles* — A. Leuchter, I. Lesser, I. Cook, M. Epstein, S. Rosenberg, S. Zeim, L. Sulkowski, J. Iribarren, R. Armstrong, A. Rosales, M. Abrams; *University of California, San Diego* — S. Zisook, K. Harless, C. Gonzalez, M. Smith, C. Lawrence, J. Palica, M. Rohrs, M. Capous-Desyllas, K. Ganadjian; *Northwestern University Medical School, Chicago* — W. McKinney, W. Gilmer, C. Kelley, C. Cooler, A. Bauer, J. Fleck, C. Endick: *Psychiatric Research Institute, University of Kansas, Wichita* — S. Preskorn, D. Hilger, A. Klick-Davis, R. Lusk, J. Elmore, D. Soetaert; *Massachusetts General Hospital, Boston* — J. Alpert, M. Fava, A. Nierenberg, A. Farabaugh, T. Petersen, W. Merens, P. Cassano, N. Craven, H. Yang, M. Candrian, R. Fraguas; *University of Michigan, Ann Arbor* — E. Young, S. Marcus, J. Greden, H. Briggs, K. Bullard, A. Kennedy, A. Benway, E. Rickard; *New York State Psychiatric Institute* and *Columbia College of Physicians and Surgeons, New York* — F.M. Quitkin, P. McGrath, J.W. Stewart, H. Sackeim, K. Tate-Brown, S. Rees, C. Smith, A. Couraud, J. Lavelle, K. Broderick; *University of North Carolina, Chapel Hill* — R. Golden, B. Gaynes, J. DeVeaugh-Geiss, A. Ford, S. Barnett, B. Pearson; *Laureate Healthcare System, Tulsa, Okla.* — J. Mitchell, W. Yates, J. Kuehnert, L. Jernigan, B. Williams, J. Hilton; *University of Pittsburgh Medical Center, Pittsburgh* — M. Thase, R.H. Howland, E. Friedman, J. Callan, S. Berman, L. Shutt, C. Spotts; *Vanderbilt University Medical Center, Nashville* — S. Hollon, R. Shelton, M. Lovett, T. Crutcher, T. Patton, J. Hart, R.M. Harris-Turner, D. Lilly, B. Sirles, S. Hicks, N. Harris, S. Addington; *University of Texas Southwestern Medical Center, Dallas* — M. Husain, M. Downing, D. Stegman, E. Shellhorn, B. O'Neal, D. Turner, L. MacLeod, M. Henson, T. Hawley, S. Gardner; *Virginia Commonwealth University, Richmond* — S. Kornstein, R. Schneider, S. Belyea, B. Perry, K. Schmitt, T. Goff, K. Lamoree, M. Britton, C. Glassman.

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