ORIGINAL ARTICLE

Medication Augmentation after the Failure of SSRIs for Depression

Madhukar H. Trivedi, M.D., Maurizio Fava, M.D., Stephen R. Wisniewski, Ph.D., Michael E. Thase, M.D., Frederick Quitkin, M.D., Diane Warden, Ph.D., M.B.A., Louise Ritz, M.B.A., Andrew A. Nierenberg, M.D., Barry D. Lebowitz, Ph.D., Melanie M. Biggs, Ph.D., James F. Luther, M.A., Kathy Shores-Wilson, Ph.D., and A. John Rush, M.D., for the STAR*D Study Team*

ABSTRACT

BACKGROUND

Although clinicians frequently add a second medication to an initial, ineffective antidepressant drug, no randomized controlled trial has compared the efficacy of this approach.

METHODS

We randomly assigned 565 adult outpatients who had nonpsychotic major depressive disorder without remission despite a mean of 11.9 weeks of citalopram therapy (mean final dose, 55 mg per day) to receive sustained-release bupropion (at a dose of up to 400 mg per day) as augmentation and 286 to receive buspirone (at a dose of up to 60 mg per day) as augmentation. The primary outcome of remission of symptoms was defined as a score of 7 or less on the 17-item Hamilton Rating Scale for Depression (HRSD-17) at the end of this study; scores were obtained over the telephone by raters blinded to treatment assignment. The 16-item Quick Inventory of Depressive Symptomatology — Self-Report (QIDS-SR-16) was used to determine the secondary outcomes of remission (defined as a score of less than 6 at the end of this study) and response (a reduction in baseline scores of 50 percent or more).

RESULTS

The sustained-release bupropion group and the buspirone group had similar rates of HRSD-17 remission (29.7 percent and 30.1 percent, respectively), QIDS-SR-16 remission (39.0 percent and 32.9 percent), and QIDS-SR-16 response (31.8 percent and 26.9 percent). Sustained-release bupropion, however, was associated with a greater reduction (from baseline to the end of this study) in QIDS-SR-16 scores than was buspirone (25.3 percent vs. 17.1 percent, $P<0.04$), a lower QIDS-SR-16 score at the end of this study (8.0 vs. 9.1, $P<0.02$), and a lower dropout rate due to intolerance (12.5 percent vs. 20.6 percent, $P<0.009$).

CONCLUSIONS

Augmentation of citalopram with either sustained-release bupropion or buspirone appears to be useful in actual clinical settings. Augmentation with sustained-release bupropion does have certain advantages, including a greater reduction in the number and severity of symptoms and fewer side effects and adverse events. (ClinicalTrials.gov number, NCT00021528.)

From the Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas (M.H.T., D.W., M.M.B., K.S.-W., A.J.R.); the Clinical Psychopharmacology Unit, Massachusetts General Hospital, Boston (M.F., A.A.N.); the Epidemiology Data Center, Graduate School of Public Health, University of Pittsburgh (S.R.W., J.F.L.), and the Department of Psychiatry, University of Pittsburgh School of Medicine (M.E.T.) — both in Pittsburgh; the New York State Psychiatric Institute and the Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York (F.Q.); and the National Institute of Mental Health, Bethesda, Md. (L.R., B.D.L.). Address reprint requests to Dr. Trivedi at the Mood Disorder Program and Clinic, Department of Psychiatry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9119, or at madhukar.trivedi@utsouthwestern.edu.

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

N Engl J Med 2006;354:1243-52.

Numerous studies,[1-7] including one by Rush et al.[8] reported elsewhere in this issue of the *Journal,* have shown that major depressive disorder often requires more than one step of treatment to elicit a remission of symptoms. Frequently, a second medication is added to augment the first.[4,6] Augmentations of an initial selective serotonin-reuptake inhibitor (SSRI) with sustained-release bupropion, buspirone, mirtazapine, or dopamine agonists (e.g., pramipexole, dextroamphetamine, and methylphenidate) have been evaluated largely in open case series conducted in symptomatic volunteers with few psychiatric or general medical coexisting illnesses.[9] No randomized, controlled, prospective trials have directly compared two or more potentially effective second-step augmentation medications, with the exception of a comparison of lithium with thyroid hormone to augment older, tricyclic antidepressants.[10,11]

From July 2001 through August 2004, we compared the efficacy, safety, and tolerability of augmentation of citalopram (Celexa, Forest Pharmaceuticals), an SSRI, with sustained-release bupropion (Wellbutrin SR, GlaxoSmithKline) or buspirone (Buspar, Bristol-Myers Squibb) as a second step of treatment (level 2) in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, which is being conducted in primary and psychiatric care settings.[4,6] These augmented treatments were compared among patients who did not have a remission or who had an intolerance to citalopram.[8,12] Remission of symptoms (rather than response to treatment) was chosen as the primary outcome, because remission is associated with better daily functioning and a better prognosis.

The two commonly used augmentation agents have distinct pharmacologic profiles.[4,6] Buspirone, a partial agonist at the postsynaptic 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) receptor, enhances the activity of SSRIs through the 5HT$_{1A}$ receptors.[13] In contrast, sustained-release bupropion appears to produce antidepressant effects by blocking the reuptake of dopamine and norepinephrine. Buspirone is not viewed as an antidepressant monotherapeutic agent, whereas sustained-release bupropion is.[1] The evidence of the efficacy of either agent as augmentation for SSRIs rests largely on case reports, case series, and small, inconclusive placebo-controlled studies.[5] Augmentation with lithium, a possible second-step addition, was excluded, given its side effects, its toxicity in the case of overdose, and the need for monitoring of blood levels.

METHODS

PATIENT POPULATION AND INCLUSION AND EXCLUSION CRITERIA

Procedures related to written informed consent and monitoring have been described elsewhere.[4,6,8] All the authors had essential roles in study implementation and supervision, data review, and manuscript development. Medications were supplied to the study at no cost by Bristol-Myers Squibb, Forest Pharmaceuticals, GlaxoSmithKline, King Pharmaceuticals, Organon, Pfizer, and Wyeth-Ayerst Laboratories; otherwise these companies had no role in the study design, data accrual, data analysis, or manuscript preparation.

STUDY DESIGN

Participants were randomly assigned to receive one of the two augmentation medications (sustained-release bupropion or buspirone)[6,12] in a 1:1 ratio, stratified according to the acceptability of treatment and to regional center. Patients who did not have a remission with or who had an intolerance to citalopram alone were eligible for this study, as long as they accepted treatment options that included augmentation with sustained-release bupropion or buspirone. During the trial, the citalopram dose was kept constant (but it could be reduced if side effects occurred). The initial dose of sustained-release bupropion was 200 mg per day during weeks 1 and 2, increasing to 300 mg per day by week 4 and to 400 mg per day (the final dose) during week 6. The starting dose of buspirone was 15 mg per day during week 1, increasing to 30 mg per day during week 2, and then to 45 mg per day during weeks 3 through 5, with a final, maximal dose of 60 mg per day during week 6. Both drugs were taken twice daily.

PROTOCOL TREATMENT

The aim of augmentation treatment was defined a priori as a remission of symptoms — defined as a score of 5 or less on the 16-item Quick Inventory of Depressive Symptomatology, clinician-rated (QIDS-C-16), which assesses the core symptoms of major depression and on which scores range from 0 to 27, with higher scores indicating greater symptom severity. Clinic visits were rec-

ommended at baseline and weeks 2, 4, 6, 9, and 12. Patients with at least a response (defined as a reduction of 50 percent or more in the baseline total QIDS-C-16 score at 12 weeks) and an acceptable level of tolerability could receive treatment for another 2 weeks to determine whether remission would occur with additional time.

Patients could leave the trial before 12 weeks if intolerable side effects occurred, if a remission that was sustained for at least 2 weeks and preferably 4 weeks occurred before 12 weeks (e.g., patients who had a remission by week 4 and remained in remission by week 6 or 9 could move to follow-up), or if substantial symptoms (as determined by a total QIDS-C-16 score of 9 or more) were still present after 9 weeks at maximally tolerated doses. Concomitant treatments were managed as described elsewhere.[6,8] Protocol treatment involved the measurement of symptoms and side effects at each clinic visit to ensure the quality of care (measurement-based care).[8,14]

CLINICAL MEASUREMENTS

Information with regard to baseline clinical and demographic characteristics, side effects, and adverse events was collected, as described elsewhere.[8] The primary outcome — remission of symptoms — was defined by a score of 7 or less on the 17-item Hamilton Rating Scale for Depression[15] (HRSD-17). Scores can range from 0 to 52, with higher scores indicating more severe depression. Scores were obtained by independent, trained, and certified assessors of research outcomes who were unaware of patients' treatment assignments and used telephone-based, structured interviews (in English or Spanish) with participants at entry into and at the end of this study. Secondary outcomes included the rates of response to treatment (defined as a reduction of 50 percent or more from the baseline Quick Inventory of Depressive Symptomatology — Self-Report [QIDS-SR-16] score at the end of this study) and remission (defined as a total score of 5 or less at the end of this study), on the basis of the QIDS-SR-16 scores obtained at each treatment visit (range, 0 to 27).[16,17]

STATISTICAL ANALYSIS

Summary statistics are presented as described by Rush et al.[8] Logistic-regression models were used to compare rates of remission (according to HRSD-17 and QIDS-SR-16 scores) and response (according to QIDS-SR-16 scores), after adjustment for the effect of regional center treatment-acceptability strata,[8] and baseline characteristics that were not balanced among the treatment groups. There were seven possible treatment-acceptability strata, which were collapsed into three categories (medication augmentation only, medication or cognitive-therapy augmentation, and other), owing to small numbers of patients in several strata. If final HRSD-17 scores were missing, it was assumed that there was a lack of remission (as defined in the original analysis plan).[6] Sensitivity analyses that were performed with the use of two imputation methods yielded results that were consistent with this assumption.[8] With the use of data regarding clinic visits, the times to first remission (as determined by a QIDS-SR-16 score of less than 6) and first response (a reduction of 50 percent or more from the baseline QIDS-SR-16 score) were defined as the first observed point. Log-rank tests compared the cumulative proportion of patients without remission and response in the two treatment groups.

All effectiveness and safety analyses were conducted according to the intention-to-treat principle (i.e., the analyses included all patients randomly assigned to each treatment group, regardless of adherence to protocol, actual treatment received, or subsequent withdrawal from assessments, treatment, protocol deviations, or all of these).[18]

RESULTS

PATIENTS

Overall, 1439 participants enrolled in the second step of treatment (level 2) of the STAR*D trial after intolerance to citalopram developed or they did not have a remission with the use of this agent. The development of the sample of participants is described by Rush et al.[8] The final sample included 565 patients randomly assigned to receive augmentation of citalopram with sustained-release bupropion (279 patients) or buspirone (286 patients). Most of the patients who were randomly assigned to receive one of these two augmentation medications (430 of 565, or 76.1 percent) had accepted their assignment to receive only the two augmentation medications; 102 patients (18.0 percent) had accepted their assignment to all three augmentation options (two medications plus cognitive therapy); the remaining 33 patients (5.8 percent) had accepted their

assignment to other treatment options that included both medication augmentations.[8]

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Table 1 shows the characteristics of the participants. The two groups receiving augmentation with sustained-release bupropion or buspirone did not differ significantly with respect to any of the characteristics, including the rates of concurrent coexisting axis I disorders listed in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (data not shown), except that those assigned to receive citalopram plus sustained-release bupropion had a shorter overall length of illness (15 years) than did those receiving citalopram plus buspirone (17 years) ($P<0.04$).

TREATMENT FEATURES

Both augmentation medications were administered in effective doses and were provided for adequate durations of time to detect a benefit. The mean doses at the end of this study were

Table 1. Clinical and Demographic Characteristics of Patients.*

Characteristic	All Patients (N=565)	Sustained-Release Bupropion (N=279)	Buspirone (N=286)
Age — yr	41.1±12.7	40.8±12.9	41.5±12.6
Female sex — no. (%)	332 (58.8)	172 (61.6)	160 (55.9)
Race — (%)†			
White	441 (78.1)	221 (79.2)	220 (76.9)
Black	95 (16.8)	48 (17.2)	47 (16.4)
Other	29 (5.1)	10 (3.6)	19 (6.6)
Hispanic ethnic group	77 (13.6)	36 (12.9)	41 (14.3)
Education — yr	13.2±3.3	13.5±3.2	13.0±3.4
Employment status — no. (%)			
Employed	307 (54.4)	160 (57.3)	147 (51.6)
Unemployed	236 (41.8)	111 (39.8)	125 (43.9)
Retired	21 (3.7)	8 (2.9)	13 (4.6)
Monthly income — $	2,326±2,981	2,287±2,600	2,363±3,314
Medical insurance — no. (%)			
Private	272 (49.9)	130 (48.1)	142 (51.6)
Public	71 (13.0)	35 (13.0)	36 (13.1)
None	202 (37.1)	105 (38.9)	97 (35.3)
Marital status — no. (%)			
Single (never married)	163 (28.9)	84 (30.1)	79 (27.7)
Married or cohabiting	229 (40.6)	112 (40.1)	117 (41.1)
Divorced or separated	158 (28.0)	73 (26.2)	85 (29.8)
Widowed	14 (2.5)	10 (3.6)	4 (1.4)
Age at first major depressive episode			
Mean — yr	25.2±14.0	26.1±14.4	24.3±13.6
<18 yr — no. (%)	212 (38.1)	101 (36.6)	111 (39.5)
Duration of major depressive disorder — yr‡	16.0±13.1	14.8±12.6	17.3±13.6
No. of major depressive episodes	6.5±13.3	6.1±13.6	6.8±13.0
Recurrent major depressive disorder — no. (%)	421 (79.3)	208 (79.1)	213 (79.5)
Family history of major depressive disorder — no. (%)	288 (51.7)	142 (52.0)	146 (51.4)
Prior suicide attempt — no. (%)	101 (17.9)	50 (17.9)	51 (17.8)

267.5 mg per day for sustained-release bupropion and 40.9 mg per day for buspirone. Patients receiving citalopram plus sustained-release bupropion had a mean (±SD) of 3.8±1.5 clinic visits (Table 2), as compared with 3.8±1.7 visits among patients receiving citalopram plus busprione ($\chi^2=0.03$, P=0.87). Fourteen percent of those receiving citalopram plus sustained-release bupropion received less than four weeks of treatment, as compared with 21.0 percent of those receiving citalopram plus buspirone ($\chi^2=4.79$, P=0.03). The mean duration of treatment at the time of the final dose of the augmentation medication was similar for both groups (7.6 weeks for citalopram plus sustained-release bupropion and 7.1 weeks for citalopram plus buspirone). Those

Table 1. (Continued.)

Characteristic	All Patients (N=565)	Sustained-Release Bupropion (N=279)	Buspirone (N=286)
CIRS			
No. of categories	3.0±2.3	2.8±2.3	3.2±2.3
Total score	4.4±3.9	4.2±3.9	4.5±3.9
Psychiatric care — no. (%)	376 (66.5)	186 (66.7)	190 (66.4)
Duration of index major depressive episode			
Mean — mo	27.1±55.6	26.1±52.9	28.1±58.1
≥2 yr — no. (%)	152 (27.2)	73 (26.5)	79 (27.9)
SF-12 score			
Mental	25.6±8.0	25.0±8.2	26.2±7.7
Physical	48.2±12.2	48.3±12.5	48.1±12.0
WSAS score	25.7±8.6	25.8±8.1	25.6±9.1
QLESQ score	38.2±13.6	37.1±12.9	39.3±14.2
Anxious features — no. (%)	144 (28.9)	67 (27.3)	77 (30.4)
Atypical features — no. (%)	77 (15.5)	30 (12.3)	47 (18.5)
Scores at study entry (level 2)			
HRSD-17	15.8±7.1	15.4±6.8	16.2±7.3
IDS-C-30	28.5±12.6	27.8±12.2	29.2±13.0
QIDS-C-16	11.7±4.2	11.7±4.1	11.7±4.2
QIDS-SR-16	11.3±4.9	11.2±4.7	11.5±5.0
Duration of level 1 treatment — wk	11.9±3.0	11.9±2.9	11.9±3.0
QIDS-C-16 change during level 1 treatment — %	–8.7±42.1	–9.3±44.0	–8.0±40.3
Citalopram (dose at end of level 1) — mg/day	54.9±10.9	54.8±10.9	55.0±10.9
Intolerance to level 1 side effects — no. (%)	51 (9.0)	24 (8.6)	27 (9.4)

* Plus–minus values are means ±SD. CIRS denotes Cumulative Illness Rating Scale; HRSD-17 the 17-item Hamilton Rating Scale for Depression (scores can range from 0 to 52; higher scores indicate increased severity of depressive symptoms); IDS-C-30 the 30-item Inventory of Depressive Symptomatology — Clinician-Rated (scores can range from 0 to 84; higher scores indicate increased severity of depressive symptoms); MDD major depressive disorder; MDE major depressive episode; QIDS-C-16 and QIDS-SR-16, the 16-item Quick Inventory of Depressive Symptomatology — Clinician-Rated and Self-Rated, respectively (scores can range from 0 to 27; higher scores indicate increased severity of depressive symptoms); QLESQ Quality of Life Enjoyment and Satisfaction Questionnaire (scores can range from 0 to 100; higher scores indicate greater satisfaction); SF-12 Short Form Health Survey (scores can range from 0 to 100; higher scores reflect increased perceived function); and WSAS Work and Social Adjustment Scale (scores can range from 0 to 40; higher scores indicate worse function). Level 1 refers to initial treatment with citalopram. Level 2 refers to second-step treatment in this study with augmentation of citalopram with either sustained-release bupropion or buspirone. 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 background was self-reported.

‡ P<0.04.

Table 2. Characteristics of Treatment.*

Characteristic	Sustained-Release Bupropion (N=279)	Buspirone (N=286)
Duration of treatment		
Mean — wk	10.2±4.7	9.2±5.0†
<4 wk — no. (%)	39 (14.0)	60 (21.0)‡
<8 wk — no. (%)	76 (27.2)	101 (35.3)§
No. of post-baseline clinic visits	3.8±1.5	3.8±1.7
Days to first post-baseline visit	19.3±12.9	18.2±8.7
Dose at end of study — mg/dl	267.5±99.8	40.9±16.7
Time received exit dose — wk	7.6±4.1	7.1±4.0
Citalopram dose at end of study — mg/dl	54.2±11.8	54.9±12.2
Concomitant psychotropic treatments — no. (%)		
Trazodone	68 (24.5)	60 (21.1)
Anxiolytics	40 (14.4)	29 (10.2)
Sedatives or hypnotics	51 (18.4)	51 (17.9)

* 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 numbers of total patients.
† P<0.02.
‡ P<0.03.
§ P<0.04.

treated with citalopram plus sustained-release bupropion adhered to treatment longer (10.2 weeks) than did those receiving citalopram plus buspirone (9.2 weeks, P=0.01).

SYMPTOM OUTCOMES

On the basis of HRSD-17 scores, remission rates did not differ significantly between the group given citalopram plus bupropion (29.7 percent [83 of 279 patients]) and the group given citalopram plus buspirone (30.1 percent [86 of 286 patients]; $\chi^2=0.01$; P=0.93). On the basis of QIDS-SR-16 scores, remission rates (39.0 percent for sustained-release bupropion and 32.9 percent for buspirone, P=0.13) and response rates (31.8 percent for sustained-release bupropion and 26.9 percent for buspirone, P=0.21) were not significantly different (Table 3). However, when outcomes were assessed as continuous variables (as is customary in most trials involving the efficacy of antidepressant medication), greater benefit was found with citalopram plus sustained-release bupropion than with citalopram plus buspirone on the basis of percent reductions (from baseline to the end of this study) in QIDS-SR-16 scores (25.3 percent as compared with 17.1 percent, P<0.04). Furthermore, total QIDS-SR-16 scores at the end of this study were significantly lower with citalopram plus sustained-release bupropion treatment than with citalopram plus buspirone (8.0 vs. 9.1, P<0.02). The two groups did not differ significantly with respect to the time to the first QIDS-SR-16 response (log-rank $\chi^2=0.0001$, P=0.99) or to first QIDS-SR-16 remission ($\chi^2=0.0024$, P=0.96) (Fig. 1). For patients who did have a remission, the mean time to a QIDS-SR-16 remission was 6.3 ±4.8 weeks (median, 5.2) for citalopram plus sustained-release bupropion and 5.4±4.4 weeks (median, 4.1) for citalopram plus buspirone. Similarly, the mean time to a QIDS-SR-16 response among patients who had a response was 6.3 ±4.6 weeks (median, 6.0) for citalopram plus sustained-release bupropion and 6.8±3.9 weeks (median, 4.1) for citalopram plus buspirone.

TOLERABILITY AND ADVERSE EVENTS

There were no significant differences between the groups in the maximal frequency, intensity, or burden of side effects (Table 3). Fewer participants taking citalopram plus sustained-release bupropion stopped treatment (i.e., they discontinued the study treatment before four weeks or at or after four weeks, with the reason recorded as due to side effects) because of intolerance than did those taking citalopram plus buspirone (12.5 percent vs. 20.6 percent; $\chi^2=6.86$; P<0.001).

The groups did not differ significantly in terms of the number of patients with one or more serious adverse events (3.6 percent for citalopram plus sustained-release bupropion and 4.2 percent for citalopram plus buspirone; $\chi^2=0.14$; P=0.71). All together, 24 serious adverse events occurred among 22 patients; of these patients, 3 had at least 1 serious psychiatric adverse event with citalopram plus sustained-release bupropion, whereas 6 had a serious psychiatric adverse event with citalopram plus buspirone. No patient committed suicide during this study. One patient with a preexisting cardiac disease died owing to cardiac arrest.

DISCUSSION

Among patients with depression who did not have a remission during a vigorous trial of up to 14 weeks of citalopram or who could not tolerate such therapy, augmentation with sustained-release

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

Characteristic	Sustained-Release Bupropion (N=279)	Buspirone (N=286)
HRSD-17 remission at end of study — no. (%)†	83 (29.7)	86 (30.1)
QIDS-SR-16 remission at end of study — no. (%)	108 (39.0)	94 (32.9)
QIDS-SR-16 response — no. (%)‡	88 (31.8)	77 (26.9)
Change in QIDS-SR-16 score — %†§	−25.3±43.9	−17.1±49.7§
QIDS-SR-16 score at end of study§	8.0±5.3	9.1±5.6§
Maximal frequency of side effects in level 2 — no. (%)		
None	53 (20.3)	58 (22.6)
10–25% of the time	88 (33.7)	89 (34.6)
50–75% of the time	73 (28.0)	68 (26.5)
90–100% of the time	47 (18.0)	42 (16.3)
Maximal intensity of side effects in level 2 — no. (%)		
None	54 (20.7)	58 (22.6)
Minimal to mild	85 (32.6)	74 (28.8)
Moderate to marked	92 (35.2)	98 (38.1)
Severe to intolerable	30 (11.5)	27 (10.5)
Maximal burden of side effects in level 2 — no. (%)		
None	61 (23.4)	73 (28.4)
Minimal to mild	128 (49.0)	104 (40.5)
Moderate to marked	61 (23.4)	70 (27.2)
Severe to intolerable	11 (4.2)	10 (3.9)
Discontinuation due to intolerance — no. (%)¶	35 (12.5)	59 (20.6)‖
Serious adverse events — no.**	10 (3.6)	12 (4.2)
Death, nonsuicide	0	1
Medical event with hospitalization	8	5
Medical event without hospitalization	0	1
Psychiatric hospitalization for detoxification	1	0
Psychiatric hospitalization for suicidal ideation or attempt	1	3
Psychiatric hospitalization for worsening depression	1	1
Psychiatric hospitalization for other psychiatric condition	0	1
Suicidal ideation without hospitalization	0	1
Serious psychiatric adverse events — no. (%)	3 (1.1)	6 (2.1)

* Plus–minus values are means ±SD. HRSD-17 denotes the 17-item Hamilton Rating Scale for Depression (scores can range from 0 to 52; higher scores indicate increased severity of depressive symptoms), and QIDS-SR-16 the 16-item Quick Inventory of Depressive Symptomatology — Self-Rated (scores can range from 0 to 27; higher scores indicate increased severity of depressive 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.

† Outcome measures of depression were adjusted according to regional center, years with major depressive disorder, and treatment-acceptability strata.

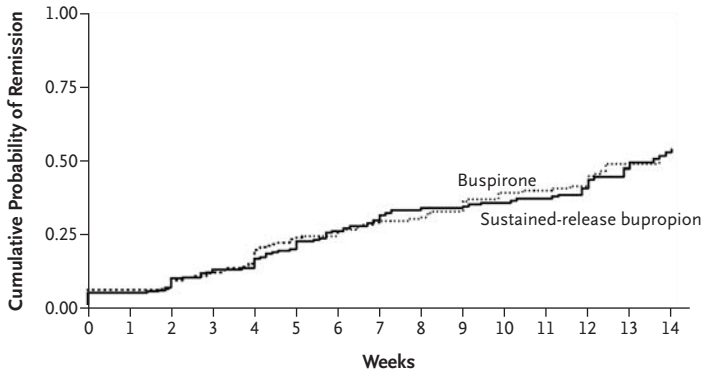
‡ Response is defined as a reduction of 50 percent or more from baseline in the QIDS-SR-16 score at the end of this study.

§ $P<0.03$.

¶ Discontinuation due to intolerance includes all study cessations before week 4, regardless of reason, and all cessations after week 4 if patients cited intolerable side effects as a reason for stopping medication.

‖ $P<0.0009$.

** Patients may have had more than one event.



No. of Patients							
Sustained-release bupropion	279	233	189	143	110	81	41
Buspirone	286	227	169	136	98	71	27
Total	565	460	358	279	208	152	68

Figure 1. Time to Remission with Medication.

bupropion or buspirone was associated with similar remission rates, as reflected by the primary outcome measure of HRSD-17 scores of 29.7 percent for sustained-release bupropion and 30.1 percent for buspirone. Remission rates were slightly higher according to QIDS-SR-16 scores, but these rates were not significantly different (39.0 percent for sustained-release bupropion and 32.9 percent for buspirone). The QIDS-SR-16 remission rates were slightly higher than the HRSD-17 remission rates, because patients for whom there was no HRSD-17 score at the end of this study (139 patients) were judged, according to the a priori study protocol, not to have had a remission; however, 31 of these patients (22.3 percent) had a remission at the end of this study according to the QIDS-SR-16 scores.

A significantly greater reduction from baseline in QIDS-SR-16 symptoms was found among patients receiving augmentation with sustained-release bupropion (25.3 percent) than with buspirone (17.1 percent), and the mean total QIDS-SR-16 scores at the end of this study were significantly lower with sustained-release bupropion (8.0) than with buspirone (9.1). Additional significant differences between the two groups included longer adherence to treatment with sustained-release bupropion (10.2 weeks) than with buspirone (9.2 weeks), lower rates of discontinuation owing to intolerance with sustained-release bupropion (12.5 percent) than with buspirone (20.6 percent), and a lower rate of treatment cessation before four weeks with sustained-release bupropion (14.0 percent) than with buspirone (21.0 percent, $P=0.03$). These secondary outcomes (which have traditionally been used as primary outcomes in efficacy studies) favored citalopram plus sustained-release bupropion over citalopram plus buspirone. There were no significant differences between the two groups in terms of the duration of treatment at the time of the final dose; overall attrition rates; proportion of serious adverse events; frequency, intensity, and global burden of side effects; or total number of treatment visits. Overall, these findings reveal a consistently more favorable outcome with sustained-release bupropion than with buspirone augmentation of citalopram.

This study might be considered a "real-world" trial of the augmentation of an SSRI — citalopram — with sustained-release bupropion or buspirone after a consistent, well-implemented trial of citalopram has been performed.[14] To our knowledge, there have been no randomized, controlled trials involving two or more augmentation medications in representative clinical-practice settings with which to compare our results. Remission rates in our trial were similar to those found in most previous uncontrolled trials of augmentation of SSRIs, which have typically been conducted in research clinics and have involved symptomatic volunteers with nonchronic depression and few general medical and psychiatric coexisting illnesses. Remission rates in our trial should be generalizable to most outpatients

with nonpsychotic major depressive disorder who are seen in both primary and psychiatric settings and who have not had adequate benefit with the use of an SSRI alone.

Limitations of the study include the lack of a pill placebo and unblinded delivery of treatment, although the data on the primary outcome measure were collected by evaluators who were unaware of patients' treatment assignments, and the HRSD-17 results were concordant with the QIDS-SR-16 results. Although the use of placebo in the second step of treatment could raise concern and may have limited the generalizability of results if patients with severe or chronic depression declined to participate, the lack of a placebo control does not allow us to exclude spontaneous remission, the nonspecific effects of treatment, or the extended use of citalopram alone as the likely explanation for the present findings.

Factors to be considered when selecting augmentation treatments include efficacy, tolerability, burden of side effects, interactions among drugs, dosing convenience, adherence, and cost. Sustained-release bupropion and buspirone, used to augment therapy with the SSRI citalopram, had similar remission rates on the basis of clinician and self-report ratings, but several important secondary measures favored citalopram plus sustained-release bupropion over citalopram plus buspirone. These findings show that augmentation of SSRIs with either agent will result in symptom remission, with some increased benefits with citalopram plus sustained-release bupropion. These results do raise the question of whether to use augmentation agents (or other treatment combinations) as first-line treatment in an attempt to achieve greater remission rates sooner in more patients than with SSRIs alone.

Supported by a contract (N01MH90003, to the University of Texas Southwestern Medical Center at Dallas) with the National Institute of Mental Health, National Institutes of Health.

Dr. Trivedi reports having received consulting fees from or having served on advisory boards for Bristol-Myers Squibb, Cyberonics, Eli Lilly, Forest Pharmaceuticals, Johnson and Johnson, Pfizer, Sepracor, and Wyeth-Ayerst Laboratories; lecture fees from Bristol-Myers Squibb, Cyberonics, Eli Lilly, Forest Pharmaceuticals, and Wyeth-Ayerst Laboratories; and research support from Bristol-Myers Squibb, Cephalon, Corcept Therapeutics, Eli Lilly, Janssen Pharmaceutica, Pfizer, Predix Pharmaceuticals, and Wyeth-Ayerst Laboratories. Dr. Fava reports having received research support from Abbott Laboratories, Lichtwer Pharma GmbH, and Lorex Pharmaceuticals; lecture fees from Bayer AG, Biovail, BrainCells, Compellis, Cypress Pharmaceuticals, DOV Pharmaceutical, Grünenthal GmbH, Janssen Pharmaceutica, Knoll Pharmaceutical, Lundbeck, Pan American Laboratories, Sepracor, and Somerset Pharmaceuticals; research support and honoraria from Aspect Medical Systems, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, Johnson & Johnson Pharmaceuticals, Novartis, Organon, Pharmavite, Pfizer, Roche, Sanofi–Synthelabo, Solvay Pharmaceuticals, and Wyeth-Ayerst Laboratories. Dr. Thase reports having received consulting fees from AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Novartis, Organon, Pfizer, and Wyeth-Ayerst Laboratories; and lecture fees from AstraZeneca, Eli Lilly, GlaxoSmithKline, Organon, and Wyeth-Ayerst Laboratories. Dr. Quitkin reports having received consulting fees from Bristol-Myers Squibb, McKinsey, Sepracor, and Sterne, Kessler, Goldstein, and Fox; and lecture fees from Almirall Prodesfarma (Spain), Eli Lilly, and Pfizer. Dr. Warden reports owning stock in Pfizer and having owned stock in Bristol-Myers Squibb. Dr. Nierenberg reports having received consulting fees from Eli Lilly, Genaissance Pharmaceuticals, GlaxoSmithKline, Innapharma, Sepracor, and Shire; research support from Bristol-Myers Squibb, Cederroth, Cyberonics, Forest Pharmaceuticals, Janssen Pharmaceutica, Lichtwer Pharma, and Pfizer; and research support and honoraria from Eli Lilly, GlaxoSmithKline, and Wyeth-Ayerst Laboratories. Dr. Biggs reports having received consulting fees from Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck, and Pfizer. Dr. Rush reports having received consulting fees from or having served on advisory boards for Advanced Neuronetic Systems, Bristol-Myers Squibb, Cyberonics, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, Health Technology Systems, Merck, Neuronetics, Organon, and Wyeth-Ayerst Laboratories; royalties from Guilford Press and Health Technology Systems; lecture fees from Cyberonics, Forest Pharmaceuticals, GlaxoSmithKline, and Merck; and owning stock in Pfizer. No other potential conflict of interest relevant to this article was reported.

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

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

We are indebted to Bristol-Myers Squibb, Forest Pharmaceuticals, GlaxoSmithKline, King Pharmaceuticals, Organon, Pfizer, and Wyeth-Ayerst Laboratories for providing medications at no cost for this trial.

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, La Jolla* — 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, 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.

REFERENCES

1. Depression Guideline Panel. Depression in primary care. Vol. 2. Treatment of major depression. Clinical practice guideline, number 5. Rockville, Md.: Agency for Health Care Policy and Research, April 1993. (AHCPR publication no. 93-0551.)

2. Greden JF. Recurrent depression — its overwhelming burden. In: Greden JF, ed. Treatment of recurrent depression. Review of psychiatry. Vol. 20. No. 5. Washington, D.C.: American Psychiatric Publishing, 2001:1-18.

3. Crismon ML, Trivedi M, Pigott TA, et al. The Texas Medication Algorithm Project: report of the Texas Consensus Conference Panel on Medication Treatment of Major Depressive Disorder. J Clin Psychiatry 1999;60:142-56.

4. Fava M, Rush AJ, Trivedi MH, et al. Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. Psychiatr Clin North Am 2003;26:457-94.

5. Fava M, Rush AJ. Current status of augmentation and combination treatments for major depressive disorder: a literature review and a proposal for a novel approach to improve practice. Psychother Psychosom (in press).

6. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control Clin Trials 2004;25:119-42.

7. Trivedi MH, Rush AJ, Crismon ML, et al. Clinical results for patients with major depressive disorder in the Texas Medication Algorithm Project. Arch Gen Psychiatry 2004;61:669-80.

8. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 2006;354:1231-42.

9. Rush AJ, Trivedi MH. Strategies and tactics in the treatment of depression. In: Evans DL, Charney DS, eds. The physician's guide to depression and bi-polar disorders. New York: McGraw-Hill, 2005:1-8.

10. Joffe RT, Singer W, Levitt AJ, MacDonald C. A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. Arch Gen Psychiatry 1993;50:387-93.

11. Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: fourth generation of progress. New York: Raven Press, 1995:1081-97.

12. Lavori PW, Rush AJ, Wisniewski SR, et al. Strengthening clinical effectiveness trials: equipoise-stratified randomization. Biol Psychiatry 2001;50:792-801.

13. Redrobe JP, Bourin M. Dose-dependent influence of buspirone on the activities of selective serotonin reuptake inhibitors in the mouse forced swimming test. Psychopharmacology (Berl) 1998;138:198-206.

14. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163:28-40.

15. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56-62.

16. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003;54:573-83. [Erratum, Biol Psychiatry 2003;54:585.]

17. Trivedi MH, Rush AJ, Ibrahim HM, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med 2004;34:73-82.

18. Fisher LD, Dixon DO, Herson J, Frankowski RF, Hearron MS, Peace KE. Intention-to-treat in clinical trials. In: Peace KE, ed. Statistical issues in drug research and development. New York: Marcel Dekker, 1990:331-50.

POSTING PRESENTATIONS AT MEDICAL MEETINGS ON THE INTERNET

Posting an audio recording of an oral presentation at a medical meeting on the Internet, with selected slides from the presentation, will not be considered prior publication. This will allow students and physicians who are unable to attend the meeting to hear the presentation and view the slides. If there are any questions about this policy, authors should feel free to call the *Journal*'s Editorial Offices.