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Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment
The VAST-D Randomized Clinical Trial

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IMPORTANCE Less than one-third of patients with major depressive disorder (MDD) achieve remission with their first antidepressant.

OBJECTIVE To determine the relative effectiveness and safety of 3 common alternate treatments for MDD.

DESIGN, SETTING, AND PARTICIPANTS From December 2012 to May 2015, 1522 patients at 35 US Veterans Health Administration medical centers who were diagnosed with nonpsychotic MDD, unresponsive to at least 1 antidepressant course meeting minimal standards for treatment dose and duration, participated in the study. Patients were randomly assigned (1:1:1) to 1 of 3 treatments and evaluated for up to 36 weeks.

INTERVENTIONS Switch to a different antidepressant, bupropion (switch group, n = 511); augment current treatment with bupropion (augment-bupropion group, n = 506); or augment with an atypical antipsychotic, aripiprazole (augment-aripiprazole group, n = 505) for 12 weeks (acute treatment phase) and up to 36 weeks for longer-term follow-up (continuation phase).

MAIN OUTCOMES AND MEASURES The primary outcome was remission during the acute treatment phase (16-item Quick Inventory of Depressive Symptomatology-Clinician Rated [QIDS-C_{16}] score ≤5 at 2 consecutive visits). Secondary outcomes included response (≥50% reduction in QIDS-C_{16} score or improvement on the Clinical Global Impression Improvement scale), relapse, and adverse effects.

RESULTS Among 1522 randomized patients (mean age, 54.4 years; men, 1296 [85.2%]), 1137 (74.7%) completed the acute treatment phase. Remission rates at 12 weeks were 22.3% (n = 114) for the switch group, 26.9% (n = 136)for the augment-bupropion group, and 28.9% (n = 146) for the augment-aripiprazole group. The augment-aripiprazole group exceeded the switch group in remission (relative risk [RR], 1.30 [95% CI, 1.05-1.60]; *P* = .02), but other remission comparisons were not significant. Response was greater for the augment-aripiprazole group (74.3%) than for either the switch group (62.4%; RR, 1.19 [95% CI, 1.09-1.29]) or the augment-bupropion group (65.6%; RR, 1.13 [95% CI, 1.04-1.23]). No significant treatment differences were observed for relapse. Anxiety was more frequent in the 2 bupropion groups (24.3% in the switch group [n = 124] vs 16.6% in the augment-aripiprazole group [n = 84]; and 22.5% in augment-bupropion group [n = 114]). Adverse effects more frequent in the augment-aripiprazole group included somnolence, akathisia, and weight gain.

CONCLUSIONS AND RELEVANCE Among a predominantly male population with major depressive disorder unresponsive to antidepressant treatment, augmentation with aripiprazole resulted in a statistically significant but only modestly increased likelihood of remission during 12 weeks of treatment compared with switching to bupropion monotherapy. Given the small effect size and adverse effects associated with aripiprazole, further analysis including cost-effectiveness is needed to understand the net utility of this approach.

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Supplemental content

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Authors/Group Information: The VAST-D Investigators appear at the end of this article. In addition, a complete list of collaborators for the VAST-D study is provided in the eAppendix in Supplement 3.

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Major depressive disorder (MDD) is a chronic, debilitating disorder[1] that affected an estimated 16.1 million adults in the United States in 2015.[2] Given that less than one-third of patients achieve remission with their first course of antidepressant pharmacotherapy,[3,4] an estimated 10.8 million US residents may benefit from an alternative treatment each year. For these patients, most treatment guidelines recommend either switching to another antidepressant or adjunctive use of another antidepressant or nonantidepressant agent.[5-7] Among the most commonly used of these treatment strategies are switching to bupropion, a norepinephrine-dopamine reuptake inhibitor, and adjunctive use of either bupropion or aripiprazole, a second-generation antipsychotic that is a partial dopamine agonist.[8]

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial showed that bupropion was at least as effective as other switching[9] and augmenting agents.[10] However, STAR*D was not powered to compare bupropion switching and augmentation strategies,[11] and atypical antipsychotics, frequently used as adjunctive agents for treatment-resistant MDD even prior to US Food and Drug Administration approval,[12] were not included. Several studies have shown efficacy of aripiprazole as an antidepressant augmentation strategy[13] and a recent study suggested aripiprazole augmentation is more beneficial than antidepressant switching and has comparable tolerability.[14] However, adequately powered and well-controlled clinical trials have yet to compare the effectiveness of these 2 treatments or compare them with augmentation with a second antidepressant.

The primary objective of this randomized clinical trial was to compare the effectiveness and adverse effect profiles of 3 commonly used alternative MDD treatment strategies: switch to the antidepressant bupropion sustained release; augment current treatment with bupropion sustained release; or augment current treatment with the antipsychotic aripiprazole.[15]

Key Points

Question Is there a difference among pharmacotherapeutic approaches for treating patients with depression unresponsive to an antidepressant course?

Findings In a 12-week follow-up of a randomized clinical trial of 1522 patients with major depressive disorder (85% men) unresponsive to previous antidepressant treatment, 29% achieved remission after augmenting their antidepressant with the antipsychotic aripiprazole vs 22% who switched to the antidepressant bupropion. Other remission comparisons were not significant.

Meaning Augmentation with aripiprazole resulted in a statistically significant, but only modestly increased, likelihood of remission during 12 weeks of treatment compared with switching to bupropion alone.

Methods

The Veterans Affairs (VA) Office of Research and Development and VA Central Institutional Review Board approved the study, the National Institutes of Health provided a certificate of confidentiality, the VA Central Institutional Review Board conducted annual continuing review, and a data and safety monitoring committee reviewed the study biannually. All patients provided written informed consent and privacy authorization. The full study protocol can be found in Supplement 1.

Study Design

VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) was a multisite randomized, single-blind, parallel-assignment trial including US Veterans Health Administration (VHA) patients whose condition was unresponsive to at least 1 course of antidepressant treatment meeting minimal standards for dose and duration.

Patient Selection

Participants were VHA patients, 18 years or older, with an MDD diagnosis, who were referred by their VA clinicians. Diagnostic eligibility was further established by research staff using criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*), supplemented with the 9-Item Patient Health Questionnaire (PHQ-9; range, 0-27; 0 indicates better health, 27 indicates worse health).[16] Study clinicians determined final diagnoses. Race and ethnicity were determined by self-report using open-ended questions and were recorded to document the level of inclusion of minority populations.

Patients with a suboptimal response to a treatment course with a selective-serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, or mirtazapine that met or exceeded minimal standards for dose and duration of treatment were eligible (Supplement 2).[15] Suboptimal response was defined as a score of 16 or more (indicating severe depression) on the 16-Item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C_{16}) questionnaire[17] after at least 6 weeks of treatment or a score of 11 or more (indicating moderately severe depression) after at least 8 weeks of treatment with the 3 most recent weeks at a stable "optimal" dose (Supplement 2).

Patients were excluded if they were receiving current treatment with bupropion or any antipsychotic; had a lifetime history of bipolar disorder, schizophrenia, schizoaffective disorder, or other psychosis; had current dementia, an eating disorder, or a seizure disorder; suicidal ideation requiring inpatient treatment; had an unstable medical condition; had need of immediate psychiatric hospitalization; had substance dependence requiring detoxification in the past 30 days; were pregnant, lactating, or planning to become pregnant; or were unable or unwilling to provide informed consent or declined to participate prior to randomization.

Randomization

Patients at 35 VA medical centers were randomized to 1 of 3 treatments: switch to another antidepressant, bupropion sustained release (switch group); augment current treatment

with bupropion sustained release (augment-bupropion group); or augment current treatment with an antipsychotic, aripiprazole (augment-aripiprazole group) (**Figure 1**). They were randomized using a stratified randomization scheme balanced (1:1:1) within each medical center using a random permuted-block scheme with variable block sizes (3 or 6) and random number generation in SAS Proc Plan (SAS Institute) prepared by VA Cooperative Studies Program Coordinating Center. After patient eligibility was confirmed, randomization was completed by site personnel using a web-based application. Outcomes were assessed by independent evaluators blind to treatment assignment.

Interventions

Treatments included titration (cross-titration for the switch group) from standard starting doses of 150 mg of bupropion sustained release to 300 mg or 400 mg daily; or from 2 mg of aripiprazole with titration to 5, 10, or 15 mg daily, until depressive symptoms remitted or adverse effects were intolerable. Dose adjustments were guided by "measurement-based care"[18] using a patient-rated symptom measure (PHQ-9)[16] and a global adverse effects measure (Frequency, Intensity, and Burden of Side Effects Rating [FIBSER]; range 0-18, 0 indicates no adverse effects, 18 indicates severe adverse effects; scores >8 suggest doses should not be increased due to adverse effects.)[19] at each visit. Acute treatment visits occurred at baseline and at weeks 1, 2, 4, 6, 8, 10, and 12. The acute treatment phase was up to 12 weeks and up to 36 weeks for longer-term follow-up.

Patients who tolerated acute treatment and achieved adequate benefit were eligible to enter a 24-week continuation phase to evaluate relapse and other outcomes. Adequate benefit was defined as either QIDS-C_{16} score of 8 or less at 12 weeks or QIDS-C_{16} score of 9 or 10 with clinician judgment of adequate benefit. This article addresses relapse among those who achieved remission during the acute treatment phase with follow-up for relapse of symptoms for up to 36 weeks. Assigned treatment was sustained after 12 weeks and follow-up visits occurred every 4 weeks.

Outcome Measures

The primary outcome was remission (close to asymptomatic status), defined as a QIDS-C_{16} score (range, 0-27 with higher scores indicating more severe symptoms) of 5 or less at 2 consecutive scheduled follow-up visits during the acute treatment phase. The QIDS-C_{16} questionnaire was administered every visit. Secondary outcomes included 2 measures of response: reduction in QIDS-C_{16} score from baseline by 50% or more[20] and a Clinical Global Impression (CGI)[21] Improvement scale rating (range, 0-7; 0 indicates not assessed, 1 indicates very much improved since the initiation of treatment, 7 indicates very much worse since the initiation of treatment) of 2 (much improved) or 1 (very much improved) at any scheduled visit through week 12; and 1 measure of relapse: QIDS-C_{16} score of 11 or more during the continuation phase after achieving remission in the acute treatment phase.

Other secondary measures that were assessed but not reported in this article include suicidal ideation and behaviors, anxiety, global improvement, quality of life, health-related costs and cost-effectiveness, and medication adherence and satisfaction.

At each visit, treatment-emergent adverse effects were queried with a checklist based on the Systematic Assessment for Treatment of Emergent Events–Specific Inquiry (SAFETEE-SI)[22] and vital signs were obtained. A 7% weight gain was considered clinically important.[23] Every 12 weeks, laboratory assessments and metabolic indicators were obtained for safety monitoring. Serious adverse events, reported to the sponsor as required, were tabulated for 30 days after withdrawal from the study.

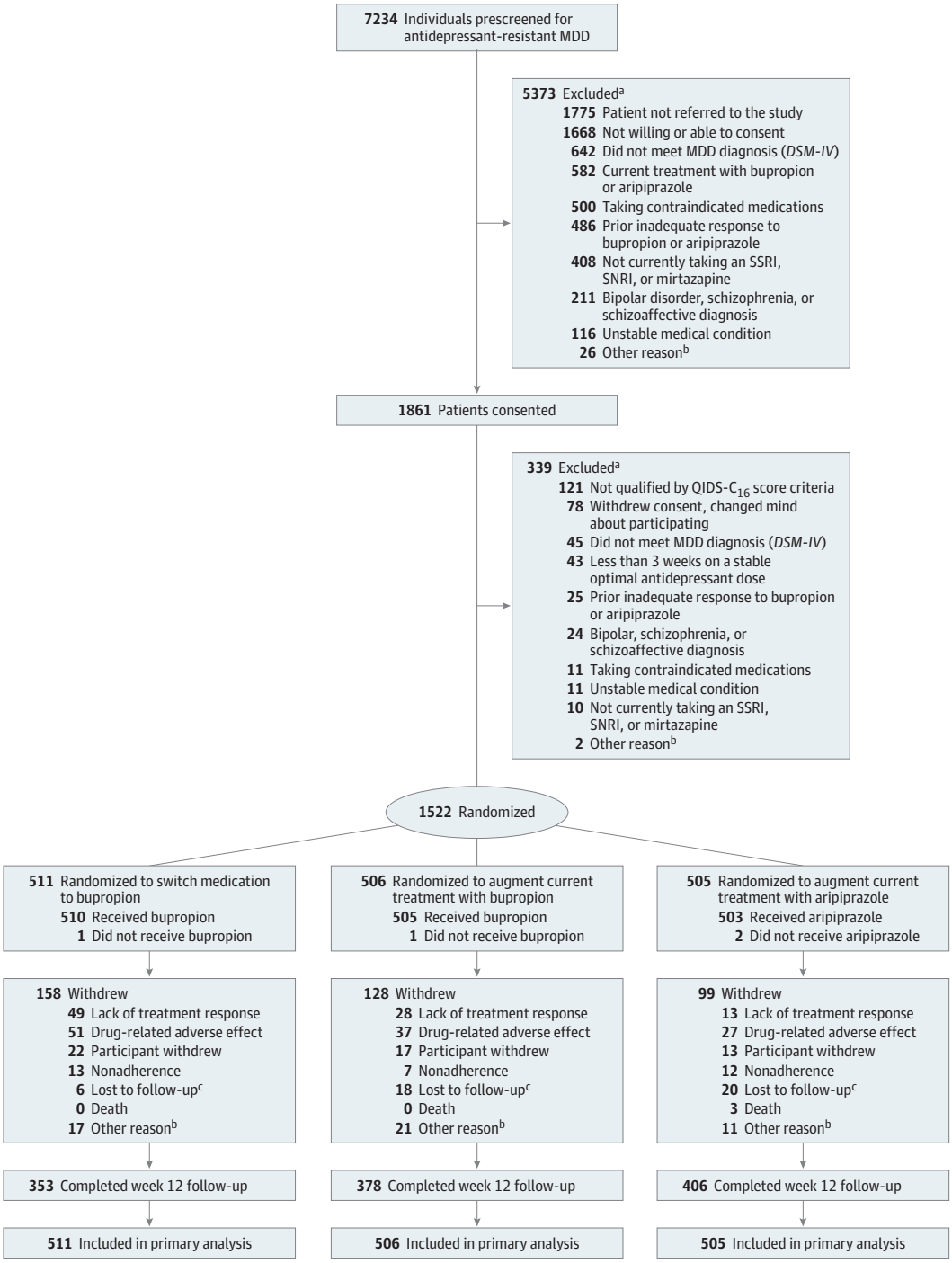
Statistical Methods

A clinically significant difference in remission of 10% was chosen for estimating sample size and power based on results of previous trials.[9,10] A target sample size of 1518 patients (506 per treatment group) was chosen to give 90% power to detect a 10% increase in remission for an augmentation group compared with the switch group (hypothetically 35% vs 25% remission, odds ratio [OR], 1.62) at a *P* value of less than .05, and 84% power to detect a 10% increase in remission for the other co-primary hypothesis at a *P* value of less than .025. The secondary hypothesis comparing the augment-aripiprazole group and augment-bupropion groups would then have 80% power to detect a 9% absolute difference (30% vs 39%; OR, 1.49) in remission at a *P* value of less than .05.

To compare the proportion of patients achieving remission in each augmentation group relative to the proportion of patients achieving remission in the switch group, the intention-to-treat analysis for these co-primary hypotheses used logistic regression models stratified by participating medical center. The 2 co-primary hypotheses were tested using the Wald test statistic and the sequentially rejective procedure of Hochberg[24] with a familywise type I error rate of .05 (2-sided) for the largest *P* value, and, if not significant, a test at the .025 level (2-sided) for the smallest *P* value. Using a gatekeeping approach, the treatment effect for the augment-aripiprazole group vs augment-bupropion group was evaluated at .05 as the second family of comparisons only if at least 1 of the co-primary hypotheses tests were statistically significant. To correct for overestimation of the risk ratio by the odds ratio, log-binomial regression was used for analysis of remission and the analysis of the secondary response outcomes; relative risk (RR) ratios with 95% CIs are reported (SAS PROC GENMOD [SAS Institute]). A supportive mixed-model analysis including participating medical centers as random effects was also conducted (SAS PROC GLIMMIX [SAS Institute]).

Time-to-event analysis of relapse among patients achieving remission in the acute treatment phase was based on time from remission to relapse within the 36-week study period. The Kaplan-Meier method was used to calculate cumulative time-to-event curves for remission, response, and relapse. Treatment differences were tested using the Cox proportional-hazards regression models stratified by site. For relapse, treatment comparisons yielding a *P* value of less than .025 were considered significant,

Figure 1. Flow of Patients Through the VAST-D Trial of Antidepressant Switching vs Augmentation



DSM-IV indicates *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; MDD, major depressive disorder; QIDS-C_{16}, 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Patients followed up to week 12 completed the acute treatment phase. All 1522 patients were included in the primary analysis, following the intention-to-treat principle.

[a] Only the most frequent reasons for not enrolling screened individuals are shown. Individuals could have more than 1 reason for exclusion.

[b] Other includes patients who moved away or withdrew for other illness.

[c] Lost to follow-up includes patients who did not return to the clinic and could not be located for contact.

except for the augment-aripiprazole group vs augment-bupropion group for which a *P* value of less than .05 was considered significant.

Results for the primary outcome, remission in the acute phase, and secondary outcomes including response and relapse among those who achieved remission in the acute treatment phase as well as adverse events occurring throughout follow-up are presented in this article. Missing data due to missed assessments were treated as missing and were not imputed in the primary analysis. Overall, 178 scheduled visits (1.7%) in the acute treatment phase were missed (eTable 1 in Supplement 2). For data missing due to withdrawal before week 12, the status of the patient at the last completed assessment was retained. There was no imputation of QIDS-C_{16} scores for missing assessments.

Multiple imputation methods (SAS Procedures MI and MIANALYZE [both from SAS Institute]) were used in sensitivity analyses to impute values (0 or 1) for protocol remission and protocol response for patients who withdrew prior to week 12. Patients who withdrew due to lack of treatment effect were considered to be unresponsive to treatment. Baseline QIDS-C_{16} score, age, sex, days of participation, and treatment group were used to impute missing values for 19.4% of the patients.

The proportions of patients who developed adverse effects were compared across treatment groups using χ^2 tests for the difference in proportions at the .05 significance level, and subgroupings of serious adverse events (SAEs) or nonserious adverse events at the .01 significance level. Pairwise comparisons were performed for the composite akathisia symptom and extrapyramidal adverse effects count, and a *P* value of less than .025 was considered significant, except for the augment-aripiprazole group vs augment-bupropion group for which a *P* value of less than .05 was considered significant.

For other secondary (supportive) analyses, a *P* value of less than .025 was considered significant, except for the augment-aripiprazole group vs augment-bupropion group for which a *P* value of less than .05 was considered significant.

SAS software (SAS Institute), version 9.3, was used to complete these analyses.

One interim analysis using conditional power calculations was conducted for futility (conditional power lower boundary of 25%) or sample size reestimation (25% < conditional power < 80%) after approximately 50% enrollment. No sample size increase was indicated and the study was continued.

Results

Study Population

Of the 7234 VHA patients screened, 1861 patients (25.7%) consented to participate and, of these, 1522 (81.8%) were randomly assigned to the switch group (n = 511), augment-bupropion group (n = 506), and augment-aripiprazole group (n = 505) (Figure 1). Baseline characteristics, described previously,[25] were similar across treatment groups (**Table 1**).

Treatment and Retention

Index antidepressants are presented in Table 1; the bupropion or aripiprazole dose prescribed at each visit is presented in eTable 1 in Supplement 2. In the switch group, the modal dose of bupropion reached a maximum of 200 mg twice daily by 6 weeks and remained at that level through 12 weeks. The augment-bupropion group also reached the maximum modal dose by 6 weeks. In the augment-aripiprazole group, the modal dose was 5 mg daily from weeks 2 through 10 and reached 10 mg daily at week 12. Doses of study medications were initiated at randomization per protocol for all but 3 patients.

Retention of patients through the 12-week acute treatment phase was greatest for the augment-aripiprazole group (80.4%), lower for the augment-bupropion group (74.7%) and lowest for the switch group (69.1%) (Figure 1). Withdrawal for lack of response was lowest for the augment-aripiprazole group (2.6%), followed by the augment-bupropion group (5.5%) and the switch group (9.6%). Withdrawal for medication adverse effects was also lower for the augment-aripiprazole group (5.3%) than either the augment-bupropion group (7.3%) or switch group (10.0%) (Figure 1). The major reason for withdrawal at week 12 was lack of response per protocol (Figure 1). Those who achieved remission (n = 396) were followed up for relapse for up to 36 weeks after randomization.

Outcomes

The primary outcome of remission occurring through week 12 was significantly, albeit modestly, higher for the augment-aripiprazole group (28.9%) compared with the switch group (22.3%; RR, 1.30 [95% CI, 1.05-1.60]; *P* = .02) but not compared with the augment-bupropion group (26.9%; RR, 1.08 [95% CI, 0.88-1.31]; *P* = .47) (**Table 2** and **Table 3**). Remission with the augment-bupropion group was not significantly different than the switch group (RR, 1.20 [95% CI, 0.97-1.50]; *P* = .09). Cox regression analysis of time to remission showed no significant differences in cumulative remission for the augment-aripiprazole group vs the switch group (hazard ratio [HR], 1.28 [95% CI, 1.00-1.64]; *P* = .05), the augment-bupropion group vs the switch group (HR, 1.15 [95% CI, 0.89-1.48]; *P* = .27), or the augment-aripiprazole group vs the augment-bupropion group (HR, 1.06 [95% CI, 0.84-1.35]; *P* = .61) (**Figure 2**A). The supportive mixed-model analysis including participating medical centers as random effects showed essentially the same results as the stratified primary analysis (Supplement 2).

Response, a secondary outcome based on 50% reduction in QIDS-C_{16} score, was significantly higher for the augment-aripiprazole group (74.3%) than for both the switch group (62.4%; RR, 1.19 [95% CI, 1.09-1.29]; *P* < .001) and the augment-bupropion group (65.6%; RR, 1.13 [95% CI, 1.04-1.23]; *P* = .003), with no significant difference between the augment-bupropion group and the switch group (RR, 1.05 [95% CI, 0.96-1.15]; *P* = .29) (Table 2 and Table 3). Response measured by CGI improvement similarly favored the augment-aripiprazole group (79%) compared with both the switch group (70%; RR, 1.14 [95% CI, 1.06-1.22]; *P* < .001) and

Table 1. Baseline Characteristics of Randomized Patients With Antidepressant-Resistant Major Depressive Disorder by Treatment Group[a]

	Switch Group (n = 511)	Augment-Bupropion (n = 506)	Augment-Aripiprazole (n = 505)
Age, mean (SD), y	54.5 (12.2)	54.4 (12.2)	54.2 (12.3)
Sex, No. (%)			
Men	443 (86.7)	425 (84.0)	428 (84.8)
Women	68 (13.3)	81 (16.0)	77 (15.2)
Race/ethnicity, No. (%)[b]			
White	349 (68.3)	358 (70.8)	346 (68.5)
African American or black	133 (26.0)	124 (24.5)	133 (26.3)
Hispanic	57 (11.2)	55 (10.9)	45 (9.0)
Other	46 (9.0)	46 (9.1)	47 (9.3)
Education, No. (%)			
< High school diploma	31 (6.1)	15 (3.0)	16 (3.2)
High school diploma or equivalent	129 (25.2)	124 (24.5)	114 (22.6)
Some college credit, but no degree	188 (36.8)	199 (39.3)	199 (39.4)
College degree (associates or greater)	163 (31.9)	168 (33.2)	176 (34.9)
Current marital status, No. (%)			
Married	213 (41.7)	218 (43.1)	217 (43.0)
Divorced or separated	195 (38.2)	189 (37.4)	183 (36.2)
Never married	72 (14.1)	67 (13.2)	69 (13.7)
Other[c]	31 (6.1)	32 (6.3)	36 (7.1)
Smoking history, No. (%)			
No, never smoked	133 (26.0)	164 (32.4)	166 (32.9)
Yes, smoked in the past (quit)	222 (43.4)	195 (38.5)	182 (36.0)
Yes, currently smoke	156 (30.5)	147 (29.1)	157 (31.1)
Average packs cigarettes per day, No. (%)			
<1	207 (54.8)	198 (57.9)	185 (54.6)
1-2	146 (38.6)	113 (33.0)	126 (37.2)
>2	23 (6.1)	30 (8.8)	27 (8.0)
Lifetime episodes of depression, median (IQR)	3 (1-10)	3 (1-8)	3 (1-7)
No. of psychotherapy treatment trials in lifetime			
Mean (SD)	2.74 (9.13)	2.1 (5.91)	2.38 (7.46)
Median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)
Patient currently receiving psychotherapy, No. (%)	330 (64.6)	310 (61.3)	307 (60.8)
Duration of current episode of MDD, mo			
Mean (SD)	85.0 (130.5)	86.1 (127.6)	89.9 (138.0)
Median (IQR)	36 (12-96)	36 (12-99)	28 (11-96)
Age at onset of first diagnosis of MDD, y			
Mean (SD)	38.1 (15.6)	37.2 (15.2)	36.3 (15.9)
Median (IQR)	38 (25-51)	36 (24-50)	35 (23-50)
Vital signs, mean (SD)			
Systolic blood pressure, mm Hg	130.0 (17.3)	129.9 (16.3)	131.4 (16.0)
Diastolic blood pressure, mm Hg	79.3 (10.5)	79.4 (10.5)	80.2 (10.6)
Weight, kg	97.7 (22.1)	98.0 (22.5)	97.4 (22.5)
BMI	31.5 (6.5)	32.0 (7.6)	31.7 (7.2)
Medication Use			
No. of previous antidepressant courses			
Mean (SD)	2.3 (1.6)	2.5 (1.7)	2.4 (1.7)
Median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)
Medication history, No. (%)			
Bupropion use	82 (16.0)	94 (18.6)	92 (18.2)
Aripiprazole use	11 (2.2)	11 (2.2)	16 (3.2)
Any antipsychotic use	76 (14.9)	72 (14.2)	72 (14.3)

(continued)

Table 1. Baseline Characteristics of Randomized Patients With Antidepressant-Resistant Major Depressive Disorder by Treatment Group[a] (continued)

	Switch Group (n = 511)	Augment-Bupropion (n = 506)	Augment-Aripiprazole (n = 505)
Prescribed antidepressant prior to study, No. (%)			
Citalopram	128 (25.0)	126 (24.9)	129 (25.5)
Duloxetine	25 (4.9)	25 (4.9)	28 (5.5)
Escitalopram	8 (1.6)	12 (2.4)	7 (1.4)
Fluoxetine	100 (19.6)	91 (18.0)	91 (18.0)
Mirtazapine	16 (3.1)	14 (2.8)	17 (3.4)
Paroxetine	36 (7.0)	34 (6.7)	37 (7.3)
Sertraline	136 (26.6)	138 (27.3)	122 (24.2)
Venlafaxine	62 (12.1)	66 (13.0)	74 (14.7)
Psychopathology Assessments[d]			
CIRS Illness Severity Index score			
Mean (SD)	11.4 (5.5)	11.1 (4.9)	11.0 (5.1)
Median (IQR)	11 (7-15)	11 (7-14)	10 (7-14)
CIRS Comorbidity Index			
Mean (SD)	1.83 (0.36)	1.82 (0.37)	1.83 (0.38)
Median (IQR)	2 (2-2)	2 (2-2)	2 (2-2)
Depression symptom and other features			
QIDS-C_{16}	16.6 (3.3)	16.6 (3.2)	16.9 (3.3)
Patient Health Questionnaire-9	15.9 (5.2)	16.3 (5.2)	16.3 (5.2)
Clinical Global Impression-Severity	4.5 (1.0)	4.6 (0.9)	4.6 (1.0)
Beck Anxiety Inventory	18.6 (11.1)	19.0 (11.4)	19.7 (11.3)
Adverse Child Experience questionnaire	3.1 (2.5)	3.2 (2.6)	3.1 (2.5)
Posttraumatic stress disorder, No. (%)[e]	248 (48.5)	244 (48.2)	225 (44.6)
Adverse Effect Assessments[d]			
FIBSER scale, No. (%)			
Moderate to marked impairment	42 (8.2)	32 (6.3)	39 (7.7)
Severe impairment	9 (1.8)	11 (2.2)	7 (1.4)
Barnes Akathisia score of mild, moderate, or severe, No. (%)	32 (6.3)	43 (8.5)	49 (9.7)
Arizona Sexual Experiences scale (female)			
Mean (SD)	4.2 (1.1)	4.2 (1.1)	4.2 (1.2)
Median (IQR)	4 (4-5)	4 (3-5)	4 (3-5)
Arizona Sexual Experiences scale (male)			
Mean (SD)	4.1 (1.1)	4.1 (1.1)	4.1 (1.2)
Median (IQR)	4 (3-5)	4 (3-5)	4 (3-5)
Quality-of-Life Assessments[d]			
EuroQol Health State Score			
Mean (SD)	54.7 (20.5)	52.7 (19.8)	54.0 (20.8)
Median (IQR)	55 (40-70)	50 (40-70)	55 (40-70)
Quality of Life Enjoyment and Satisfaction score			
Mean (SD)	41.4 (13.8)	40.3 (14.8)	40.1 (14.8)
Median (IQR)	41 (32-50)	41 (32-48)	41 (30-50)
Alcohol dependence, No. (%)[e]	39 (7.6)	42 (8.3)	43 (8.5)
Substance dependence (nonalcohol), No. (%)[e]	18 (3.5)	12 (2.4)	12 (2.4)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CIRS, Cumulative Illness Rating Scale; FIBSER, Frequency, Intensity, and Burden of Side Effects Rating; IQR, interquartile range; MDD, major depressive disorder; QIDS-C_{16}, 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated.

[a] The 3 treatment groups: switch to another antidepressant, bupropion sustained release (switch group); augment current treatment with bupropion sustained release (augment-bupropion group); or augment current treatment with an antipsychotic, aripiprazole (augment-aripiprazole group.

[b] Participants could choose more than 1 race or ethnic group.

[c] Other includes widowed, cohabitating, or civil commitment.

[d] Range of scores for standard instruments: Beck Anxiety Inventory (range, 0-63; 0-9 indicates minimal anxiety, 30-63 indicates severe anxiety); Adverse Child Experience questionnaire (range, 0-10; 0 indicates no experiences endorsed, 10 indicates all experiences endorsed); Arizona Sexual Experiences Scale (female or male) (range, 5-30; 5 indicates better experience, 30 indicates worse experience); EuroQol Health State Score (range, 0-100; 0 indicates worst imaginable health, 100 indicates best imaginable health); Barnes Akathisia Scale (range, 0-5; 0 indicates absent, 5 indicates severe akathisia); Quality of Life Enjoyment and Satisfaction questionnaire score (range, 14-70; 14 indicates worst quality, 70 indicates best quality); CIRS Illness Severity Index score (range, 0-56; 0 indicates best, 56 indicates worst) and CIRS Comorbidity Index (range, 1-4; 1 indicates best, 4 indicates worst); for other ranges, see Methods.

[e] Determined from a Mini-International Neuropsychiatric Interview prior to randomization: current diagnosis of posttraumatic stress disorder or alcohol or substance dependence in the last 12 months.

Table 2. Patients With Antidepressant-Resistant Major Depressive Disorder Achieving Cumulative Remission and Response, Acute Treatment Phase

	Switch Group[a] (n = 511)	Augment-Bupropion[a] (n = 506)	Augment-Aripiprazole[a] (n = 505)
Remission (Primary Outcome), No. (%)[b]			
Week 2	22 (4.3)	21 (4.2)	19 (3.8)
Week 4	39 (7.6)	45 (8.9)	51 (10.1)
Week 6	63 (12.3)	67 (13.2)	83 (16.4)
Week 8	81 (15.9)	92 (18.2)	106 (21)
Week 10	96 (18.8)	113 (22.3)	128 (25.3)
Week 12	114 (22.3)	136 (26.9)	146 (28.9)
Response (Secondary Outcome), No. (%)[c]			
≥50% Reduction in QIDS-C_{16} score			
Week 1	77 (15.1)	82 (16.2)	98 (19.4)
Week 2	147 (28.8)	156 (30.8)	184 (36.4)
Week 4	204 (39.9)	213 (42.1)	249 (49.3)
Week 6	245 (47.9)	257 (50.8)	296 (58.6)
Week 8	270 (52.8)	296 (58.5)	325 (64.4)
Week 10	297 (58.1)	316 (62.5)	352 (69.7)
Week 12	319 (62.4)	332 (65.6)	375 (74.3)
CGI Improvement score			
Week 12	356 (69.7)	376 (74.3)	400 (79.2)

Abbreviations: CGI, Clinical Global Impression; QIDS-C_{16}, 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated.

[a] The 3 treatment groups: switch to another antidepressant, bupropion sustained release (switch group); augment current treatment with bupropion sustained release (augment-bupropion group); or augment current treatment with an antipsychotic, aripiprazole (augment-aripiprazole group).

[b] Remission was defined as a QIDS-C_{16} score (range, 0-27; 0 indicates better symptoms, 27 indicates worse symptoms) of 5 or less for 2 consecutive weeks after baseline during the acute treatment phase.

[c] Response was defined as reduction in QIDS-C_{16} score of 50% or more from baseline at any scheduled visit after baseline through week 12 or improvement in CGI Improvement score (range, 1-7) of 2 (much improved) or 1 (very much improved) at any scheduled visit after baseline through week 12.

Table 3. Treatment Comparisons for Remission and Response at Week 12 Among Patients With Antidepressant-Resistant Major Depressive Disorder, Acute Treatment Phase[a]

	Difference (95% CI), %[b]	Relative Risk (95% CI)	*P* Value
Remission (Primary Outcome)[c]			
Augment-bupropion vs switch group	4.6 (−0.1 to 9.9)	1.20 (0.97 to 1.50)	.09
Augment-aripiprazole vs switch group	6.6 (1.3 to 12.0)	1.30 (1.05 to 1.60)	.02[d]
Augment-aripiprazole vs augment-bupropion	2.0 (−3.5 to 7.6)	1.08 (0.88 to 1.31)	.47
Response (Secondary Outcome)[e]			
50% Reduction in QIDS-C_{16} score			
Augment-bupropion vs switch group	3.2 (−2.7 to 9.1)	1.05 (0.96 to 1.15)	.29
Augment-aripiprazole vs switch group	11.8 (6.2 to 17.5)	1.19 (1.09 to 1.29)	<.001
Augment-aripiprazole vs augment-bupropion	8.6 (3.0 to 14.3)	1.13 (1.04 to 1.23)	.003
Improvement in CGI Improvement score			
Augment-bupropion vs switch group	4.6 (−0.9 to 10.2)	1.07 (0.99 to 1.15)	.10
Augment-aripiprazole vs switch group	9.5 (4.2 to 14.9)	1.14 (1.06 to 1.22)	<.001
Augment-aripiprazole vs augment-bupropion	4.9 (−0.3 to 10.1)	1.07 (1.00 to 1.14)	.07

Abbreviations: CGI, Clinical Global Impression; QIDS-C_{16}; 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated.

[a] Treatment comparisons were determined by relative risk ratio from log-binomial regression models stratified by site. The 3 treatment groups: switch to another antidepressant, bupropion sustained release (switch group); augment current treatment with bupropion sustained release (augment-bupropion group); or augment current treatment with an antipsychotic, aripiprazole (augment-aripiprazole group).

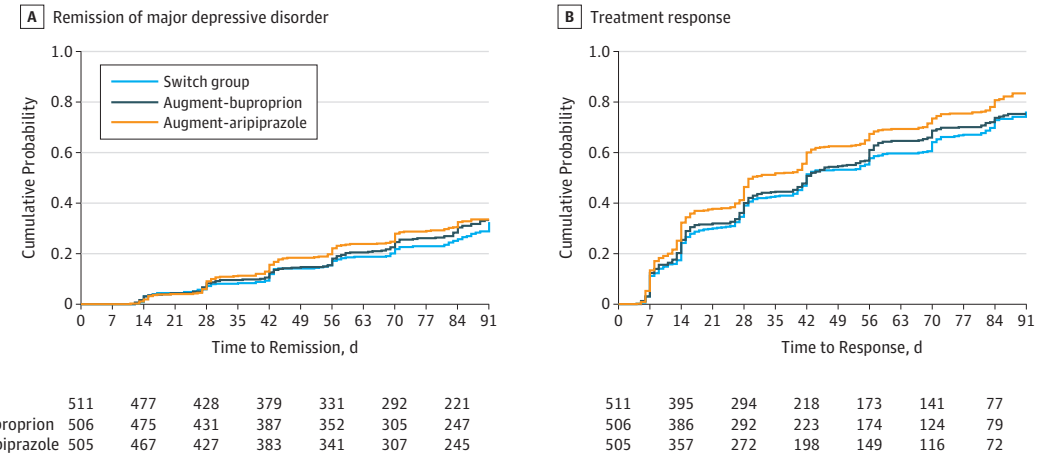
[b] Absolute difference in percentage of patients with events between treatments.

[c] Remission was defined as a QIDS-C_{16} score (range, 0-27; 0 indicates better symptoms, 27 indicates worse symptoms) of 5 or less for 2 consecutive weeks after baseline during the acute treatment phase.

[d] *P* value less than .025 for second familywise test of co-primary hypothesis.

[e] Response was defined as reduction in QIDS-C_{16} score of 50% or more from baseline at any scheduled visit after baseline through week 12 or improvement in CGI Improvement score (range, 1-7) of 2 (much improved) or 1 (very much improved) at any scheduled visit after baseline through week 12.

Figure 2. Cumulative Probability of Remission and Response Among Patients With Antidepressant-Resistant Major Depressive Disorder, Acute Treatment Phase



No. at risk

Switch group	511	477	428	379	331	292	221
Augment-buproprion	506	475	431	387	352	305	247
Augment-aripiprazole	505	467	427	383	341	307	245

Switch group	511	395	294	218	173	141	77
Augment-buproprion	506	386	292	223	174	124	79
Augment-aripiprazole	505	357	272	198	149	116	72

HR, hazard ratio. Remission was defined as a 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C_{16}) score (range, 0-27; 0 indicates better symptoms, 27 indicates worse symptoms) of 5 or less for 2 consecutive weeks after baseline during the acute treatment phase. Response was defined as reduction in QIDS-C_{16} score of 50% or more from baseline at any scheduled visit after baseline through week 12 or improvement in Clinical Global Impression Severity score (range, 1-7; 1 indicates less severe, 7 indicates more severe) of "much improved" or "very much improved" at any scheduled visit after baseline through week 12. Time to first remission or first response was determined by 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C_{16}) assessments at scheduled visits. In this analysis, follow-up was censored if the patient withdrew from the study. A, HRs from stratified life-table regressions: augment-aripiprazole group vs switch group, 1.28 (95% CI, 1.00-1.64); augment-bupropion group vs switch group, 1.15 (95% CI, 0.89-1.48); augment-aripiprazole group vs augment-bupropion group, 1.06 (95% CI, 0.84-1.35). Median follow-up time to remission or censoring was 81 days (interquartile range [IQR], 41-90) for the switch group, 83 days (IQR, 42-90) for both the augment-bupropion group and augment-aripiprazole group. Plot is truncated at 91 days; 32 observations for week 12 occurred after 91 days. B, HRs from stratified life-table regressions: augment-aripiprazole group vs switch group, 1.32 (95% CI, 1.13-1.54); augment-bupropion group vs switch group, 1.05 (95% CI, 0.89-1.23); augment-aripiprazole group vs augment-bupropion group, 1.23 (95% CI, 1.05-1.43). Median follow-up time to response or censoring was 30 days (IQR, 14-70) for the switch group, 30 days (IQR, 14-69) for the augment-bupropion group and 28 days (IQR, 12-65) for the augment-aripiprazole group. Plot is truncated at 91 days; 25 observations for week 12 occurred after 91 days.

the augment-bupropion group (74%; RR, 1.07 [95% CI, 1.00-1.14]; P = .07) (Table 2 and Table 3).

In the Cox regression analysis of response based on the QIDS-C_{16} score, cumulative response for the augment-aripiprazole group was greater than both the switch group (HR, 1.32 [95% CI, 1.13-1.54]; P < .001) and augment-bupropion group (HR, 1.23 [95% CI, 1.05-1.43]; P = .007) (Figure 2B). Cumulative response did not differ significantly between the augment-bupropion group and switch group (HR, 1.05 [95% CI, 0.89-1.23]; P = .56).

The results of the multiple-imputation sensitivity analysis for protocol remission at week 12 showed comparison of the augment-aripiprazole group vs the switch group to be statistically significant (RR, 1.33 [95% CI, 1.07-1.66]; P = .01), but not the augment-bupropion group vs the switch group (RR, 1.16 [95% CI, 0.93-1.46]; P = .19). For response as defined by the protocol, there was a statistically significant effect for the augment-aripiprazole group vs the switch group (RR, 1.26 [95% CI, 1.13-1.39]; P < .001) but not for the augment-bupropion group vs the switch group (RR, 1.10 [95% CI, 0.99-1.23]; P = .08).

Among the 396 patients achieving remission in the acute treatment phase, there were no significant differences in the secondary outcome of cumulative relapse: augment-bupropion group vs switch group (HR, 1.36 [95% CI, 0.78-2.39]; P = .70); augment-aripiprazole group vs switch group (HR, 1.12 [95% CI, 0.65-1.94]; P = .68); or augment-bupropion group vs augment-aripiprazole group (HR, 0.96 [95% CI, 0.58-1.59]; P = .87) (**Figure 3**).

Adverse Events

Among 165 patients (10.8%), a total of 207 SAEs occurred (**Table 4**). Eight deaths occurred among study patients during the safety reporting period: 3 during follow-up; and 5 in the 30 days after withdrawal or completion of follow-up, with 1 completed suicide. Causes of death included completed suicide, sudden unexpected death, chronic obstructive pulmonary disease, bilateral pulmonary embolisms, arteriosclerosis, acute myocardial infarction, lung cancer, and rhabdomyolysis. The investigators and the data and safety monitoring committee agreed that the deaths were not related to study medication.

There were 4356 nonserious adverse events recorded (eTable 2 in Supplement 2). Specific nonserious adverse events occurred in a greater proportion of patients in the switch group than in the other groups and included nausea, irritability, and hypomania (Table 4). Nonserious adverse events occurring in greater proportions of both the switch and augment-bupropion groups than among patients in the augment-aripiprazole group included anxiety, decreased appetite, dry mouth, and increased blood pressure. Nonserious adverse events occurring in a greater proportion of

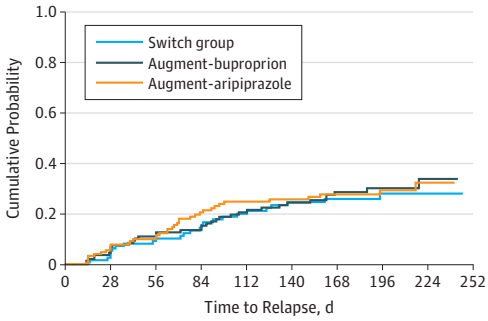
patients in the augment-aripiprazole group compared with the other 2 groups included fatigue, increased appetite, increased weight, akathisia, somnolence, and abnormal values for several laboratory tests. At week 12, weight gain of 7% or greater was more frequent for the augment-aripiprazole group (38 of 399 patients [9.5%]) compared with the switch group (8 of 347 patients [2.3%]) and the augment-bupropion group (7 of 369 patients [1.9%]). For the subset of patients continuing through week 36, the proportion with weight gain 7% or greater was also greater for the augment-aripiprazole group (53 of 210 patients [25.2%]) compared with the augment-bupropion group (10 of 193 patients [5.2%]) and the switch group (8 of 153 patients [5.2%]) (Table 4).

Discussion

In this randomized clinical trial in a predominantly male population with MDD who were unresponsive to antidepressant treatment, augmentation with aripiprazole resulted in a statistically significant but only modestly increased likelihood of remission during 12 weeks of treatment compared with switching to bupropion monotherapy. On 2 measures of response, the secondary outcome, the augment-aripiprazole group exceeded both the switch group and the augment-bupropion group. The lowest discontinuation rates were also observed for the augment-aripiprazole group. There were no significant differences in relapse rates between treatment groups among acute treatment phase remitters during the continuation phase. On adverse effects, the results were mixed with treatment-emergent anxiety favoring the augment-aripiprazole group and akathisia, somnolence, and weight gain favoring the switch group and the augment-bupropion group.

The most clinically meaningful adverse event occurring in at least 5% of patients in the switch and augment-bupropion groups was increased anxiety (which also included reports of nervousness). Anxiety is known to be a negative prognostic factor in patients with MDD associated with poor response, increased relapse and recurrence, and suicide risk.[26] On the other hand, the augment-aripiprazole group reported more somnolence, extrapyramidal effects (including akathisia), and weight gain than the 2 bupropion groups. Although each of these adverse effects has been associated with dropping out of treatment,[27] dropout rates in this study were smallest for the augment-aripiprazole group, suggesting limited effect of these adverse effects on treatment adherence. Although weight gain did not lead to medication discontinuation, it is related to metabolic syndrome and could lead to serious health concerns in the long-term. There is a need to further investigate the benefit-risk ratio of long-term risks of weight gain and other adverse effects compared with the benefit of modestly reducing depression. A major asset of the VAST-D study is the comparative evaluation of the longer-term benefits and risks of this second-generation antipsychotic, the first approved for this indication.

Figure 3. Cumulative Probability of Relapse After Remission Among Patients With Antidepressant-Resistant Major Depressive Disorder, Acute Treatment Phase



No. at risk

Switch group	114	105	90	78	70	64	53	32	16
Augment-buproprion	136	119	106	100	85	78	63	35	13
Augment-aripiprazole	146	129	117	94	86	80	68	41	19

HR, hazard ratio. Time to first relapse was determined by first occurrence of QIDS-C_{16} score of 11 or more after remission in the acute treatment phase through the week 36 visit. Follow-up time 0 indicates the day that remission was determined. The proportions relapsing within each treatment group were 26 of 114 patients (22.8%) for the switch group, 35 of 136 patients (25.7%) for the augment-bupropion group, and 37 of 146 patients (25.3%) for the augment-aripiprazole group. Follow-up time was censored in this analysis if the patient withdrew from the study. HRs for stratified life-table regressions for relapse: augment-bupropion group vs switch group, 1.36 (95% CI, 0.78-2.39); augment-aripiprazole group vs switch group, 1.12 (95% CI, 0.65-1.94); augment-aripiprazole group vs augment-bupropion group, 0.96 (95% CI, 0.58-1.59). Median follow-up time to relapse or censoring was 163 days (interquartile range [IQR], 70-201) for the switch group, 163 days (IQR, 68.5-197) for the augment-bupropion group and 160.5 days (IQR, 59-203) for the augment-aripiprazole group. Maximum follow-up time was 245 days.

Although use of the augment-aripiprazole strategy as an alternative treatment may offer an increased likelihood of remission, patients should be alerted to the risk of weight gain in a process of shared decision making[28] and baseline screening and follow-up monitoring of metabolic indicators should be provided.[29]

Limitations

This study had several limitations. First, only 1 antidepressant (bupropion sustained release) and 1 antipsychotic (aripiprazole) were evaluated, and the generalizability of the results to other medications is unknown.

Second, only 1137 patients (74.7%) completed the 12-week acute treatment phase and differences in outcomes between groups were small in magnitude. Multiple imputation was used to address missing data due to withdrawals, and the results of imputing 12-week outcomes were consistent with the direction and magnitude of effects reported in the primary analysis of protocol defined remission and response. A limitation of the imputation analysis was that withdrawals may be associated with outcome or treatment assignment so that missing data could not be assumed to be missing at random.

Third, it is possible that discontinuation in the switch group was increased by withdrawal symptoms from their previous treatment. Fourth, the study was conducted with

Table 4. Adverse Events and Serious Adverse Events Reported by Treatment Group Among Patients With Antidepressant-Resistant Major Depressive Disorder, Acute Treatment and Continuation Phases

	Switch Group[a]	Augment-Bupropion[a]	Augment-Aripiprazole[a]	*P* Value[b]
Patients, No.	511	506	505	
Adverse events (nonserious), No.	1496	1458	1405	
Patient adverse events (unique diagnosis), No.	1375	1310	1289	
Patients with ≥1 adverse event, No. (%)	383 (75.0)	369 (72.9)	374 (74.1)	.76
Serious adverse events, No.	63	71	73	
Patients with serious adverse events, No. (%)	52 (10.2)	57 (11.3)	56 (11.1)	.84
Serious adverse events per patient, No. (%)				
1	43 (82.7)	47 (82.5)	46 (82.1)	
2	9 (17.3)	9 (15.8)	5 (8.9)	
3	0	0	5 (8.9)	
≥4	0	1 (1.8)	0	
Serious adverse events possibly related to treatment, No. (%)	4 (6.3)	5 (7.0)	9 (12.3)	.39
Adverse Events (System Organ Class-Preferred Term)	**No. of Adverse Events/ No. of Patients (%)[c]**	**No. of Adverse Events/ No. of Patients (%)[c]**	**No. of Adverse Events/ No. of Patients (%)[c]**	***P* Value[b]**
Serious adverse events				
Psychiatric disorder, No.	15/15 (2.9)	17/14 (2.8)	16/13 (2.6)	.98
Suicidal ideation	8/8 (1.6)	11/10 (2.0)	6/6 (1.2)	.59
Suicide attempt	3/3 (0.6)	1/1 (0.2)	3/3 (0.6)	.65
Completed suicide	1/1 (0.2)	0	0	>.99
Other psychiatric disorders	3/3 (0.6)	5/5 (1.0)	7/6 (1.2)	.53
Deaths[d]	3 (0.6)	1 (0.2)	4 (0.8)	.42
Adverse events[e]				
Psychiatric disorders	393/224 (43.8)	349/200 (39.5)	270/176 (34.9)	.01
Nervousness (anxiety)[f]	143/124 (24.3)	128/114 (22.5)	91/84 (16.6)	.007[g]
Insomnia[f]	115/105 (20.6)	107/92 (18.2)	100/88 (17.4)	.41
Libido decreased[f]	20/20 (3.9)	36/33 (6.5)	26/25 (5.0)	.17
Irritability	32/32 (6.3)	15/14 (2.8)	8/7 (1.4)	<.001[g]
Libido increased[f]	15/15 (2.9)	13/13 (2.6)	10/10 (2.0)	.63
Hypomania[f]	14/12 (2.4)	3/3 (0.6)	3/3 (0.6)	.02
Agitation	7/6 (1.2)	4/4 (0.8)	4/4 (0.8)	.84
Restlessness	1/1 (0.2)	10/9 (1.8)	4/4 (0.8)	.02
Anger	7/6 (1.2)	4/4 (0.8)	2/2 (0.4)	.42
Abnormal dreams	6/6 (1.2)	1/1 (0.2)	4/3 (0.6)	.16
Nervous system disorders	383/218 (42.7)	426/235 (46.4)	433/239 (47.3)	.29
Headache[f]	116/102 (20.0)	125/107 (21.2)	99/86 (17.0)	.23
Dizziness[f]	102/89 (17.4)	101/93 (18.4)	82/72 (14.3)	.18
Somnolence[f]	38/37 (7.2)	47/40 (7.9%)	82/73 (14.5)	<.001[g]
Akathisia[f]	24/22 (4.3)	32/27 (5.3)	82/75 (14.9)	<.001[g]
Tremor	31/31 (6.1)	62/52 (10.3)	19/19 (3.8)	<.001[g]
Parkinsonism[f]	25/22 (4.3)	24/21 (4.2)	26/23 (4.6)	.95
Dystonia[f]	4/4 (0.8)	1/1 (0.2)	6/6 (1.2)	.17
Dizziness postural	0	4/4 (0.8)	0	.02
Tardive dyskinesia[f]	1/1 (0.2)	0	2/2 (0.4)	.44
Extrapyramidal symptoms[h]	54/42 (8.2)	57/46 (9.1)	116/97 (19.2)	<.001[g]

(continued)

Table 4. Adverse Events and Serious Adverse Events Reported by Treatment Group Among Patients With Antidepressant-Resistant Major Depressive Disorder, Acute Treatment and Continuation Phases (continued)

	Switch Group[a]	Augment-Bupropion[a]	Augment-Aripiprazole[a]	*P* Value[b]
Other diagnoses				
Nausea[f]	98/89 (17.4)	66/60 (11.9)	70/64 (12.7)	.02
Diarrhea[f]	53/45 (8.8)	71/58 (11.5)	59/51 (10.1)	.38
Abdominal pain[f]	37/33 (6.5)	46/42 (8.3)	33/31 (6.1)	.36
Dry mouth	52/51 (10.0)	38/36 (7.1)	14/14 (2.8)	<.001[g]
Vomiting[f]	28/26 (5.1)	30/26 (5.1)	23/23 (4.6)	.91
Constipation	28/25 (4.9)	22/22 (4.4)	13/13 (2.6)	.13
Fatigue[f]	77/69 (13.5)	84/66 (13.0)	97/89 (17.6)	.08
Laboratory test abnormal	14/14 (2.7)	21/19 (3.8)	47/44 (8.7)	<.001[g]
Blood glucose increased	0	0	3/3 (0.6)	.04
Decreased appetite[f]	86/79 (15.5)	65/60 (11.9)	46/40 (7.9)	.001[g]
Increased appetite[f]	44/38 (7.4)	46/44 (8.7)	93/81 (16.0)	<.001[g]
Pruritus (itching)[f]	25/24 (4.7)	24/22 (4.4)	14/14 (2.8)	.23
Rash[f]	21/20 (3.9)	22/21 (4.2)	19/19 (3.8)	.96
Weight increased from baseline[i]	2/2 (0.4)	3/3 (0.6)	30/29 (5.7)	<.001[g]
≥7% Weight gain				
At week 12	8 (2.3)	7 (1.9)	38 (9.5)	<.001[g]
At week 36	8 (5.2)	10 (5.2)	53 (25.2)	<.001[g]
Weight decreased from baseline[i]	0	3/3 (0.6)	0	.07
≥7% Weight loss				
At Week 12	15 (4.3)	19 (5.1)	7 (1.8)	.06
At Week 36	20 (13.1)	23 (11.9)	10 (4.8)	.02
Blood pressure increased	6/6 (1.2)	6/6 (1.2)	0	.03
Tinnitus	4/4 (0.8)	11/10 (2.0)	1/1 (0.2)	.02
Muscle spasms	0	1/1 (0.2)	7/7 (1.4)	.002[g]
Dyspnea	1/1 (0.2)	0	6/5 (1.0)	.03
Erectile dysfunction (men)	0	6/6 (1.4)	1/1 (0.2)	.004
Menstruation irregular (women)[f]	0	1/1 (1.2)	4/4 (5.2)	.08

[a] The 3 treatment groups: switch to another antidepressant, bupropion sustained release (switch group); augment current treatment with bupropion sustained release (augment-bupropion group); or augment current treatment with an antipsychotic, aripiprazole (augment-aripiprazole group).

[b] *P* values are from the results of exact χ^2 tests for differences in proportions of patients with an adverse events or serious adverse events between treatments.

[c] Percentage indicates the percentage of patients with the adverse event divided by the No. of patients at risk in the treatment group.

[d] Eight deaths occurred during follow-up or within 30 days after withdrawal and were not attributed to the study (reviewed by data and safety monitoring committee and the VA Central institutional review board). Causes of death include completed suicide, sudden unexpected death, due to chronic obstructive pulmonary disease, due to bilateral pulmonary embolisms, due to arteriosclerosis, acute myocardial infarction, due to lung cancer, and due to rhabdomyolysis.

[e] This is a partial listing of all nonserious adverse effects; shows only adverse effects reviewed at each clinic visit, that occurred at a frequency in more than 2% of the population, or had a significant difference (*P* < .05) for any other adverse effects.

[f] On the possible adverse effect checklist prompted at each follow-up visit.

[g] *P* value less than .01; protocol-specified significance level for comparing proportions with adverse effects between treatment groups.

[h] Extrapyramidal symptoms—composite outcome was defined as occurrence of Parkinsonism, tardive dyskinesia, akathisia, or dystonia. Pairwise comparisons between the augment-aripiprazole group vs the switch group and between the augment-aripiprazole vs augment-bupropion groups were statistically significant (*P* < .001)

[i] Not all these occurrences were reported as adverse events possibly related to the intervention.

VA patients with many exclusion criteria. As a result, the generalizability of results from this older, predominantly male population is also unknown. However, with a mean QIDS-C_{16} score of 16.6 to 16.9 across groups (SD, 3.2-3.3), this sample was in the severe depression range (score, 16-20),[17] similar to the STAR*D study (mean score, 16.2 [SD, 4.1]) although the duration of the current episode in the VAST*D study was a mean of 87 months, which is considerably longer, and suggests less potential for treatment responsiveness than the mean of 28 months in the second step of the STAR*D study.[30] Other important secondary outcomes, including cost-effectiveness, quality of life, and suicidal ideation that may clarify the balance between clinical benefits and adverse effects still need to be addressed.

Conclusions

Among a predominantly male population with major depressive disorder unresponsive to antidepressant treatment, augmentation with aripiprazole resulted in a statistically significant but only modestly increased likelihood of remission during 12 weeks of treatment compared with switching to bupropion monotherapy. Given the small effect size and adverse effects associated with aripiprazole, further analysis including cost-effectiveness is needed to understand the net utility of this approach.

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