Comparing Cost-Effectiveness of Aripiprazole Augmentation With Other "Next-Step" Depression Treatment Strategies:
A Randomized Clinical Trial

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ABSTRACT

Objective: To compare the cost-effectiveness of 3 common alternate treatments for depression.

Methods: The cost-effectiveness analysis was conducted as part of a randomized clinical trial, the Veterans Affairs Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) trial, in which patients were randomized from December 2012 to May 2015 and followed for 12 weeks in 35 Veterans Affairs medical centers. Depression diagnosis was based on *ICD-9* codes. Patients were randomized to standard antidepressant therapy augmented with aripiprazole, standard antidepressant therapy augmented with bupropion, or switch to bupropion. Remission was measured using the 16-item Quick Inventory of Depressive Symptomatology–Clinican Rated. Outcomes included the incremental cost-effectiveness ratio (ICER) comparing costs per remission and costs per quality-adjusted life-year (QALY) with 12 weeks as the time horizon using the health care sector perspective.

Results: The mean age of participants enrolled in the trial (N = 1,522) was 54 years, and participants were predominantly male. The rate of remission at 12 weeks was highest for the aripiprazole augmentation arm (29%), followed by bupropion augmentation (27%), and lowest for switching to bupropion (22%). Switching to bupropion was strongly dominated by bupropion augmentation at an ICER of –$640/remission (95% CI, –$5,770 to $3,008). The ICER for the aripiprazole augmentation versus switching to bupropion was $1,074/remission (95% CI, $47 to $5,022), and the ICER for aripiprazole augmentation versus bupropion augmentation was $5,094/remission (95% CI, –$34,027 to $32,774). There were no significant differences in QALYs, mental health care costs, employment, or other work and social adjustment outcomes between treatment groups.

Conclusions: In treatment of depression with less than optimal response, augmentation with either aripiprazole or bupropion was cost-effective relative to switching to bupropion.

Trial Registration: ClinicalTrials.gov identifier: NCT01421342

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The morbidity and costs due to major depressive disorder (MDD) are considerable, with an estimated 7% of the population affected by MDD and $28 billion spent annually on direct treatment.[1,2] While many nonpharmacologic treatments are effective and may be preferred by some patients to treat MDD,[3,4] most patients receive pharmacologic treatment.[5] About 30% of patients with MDD do not respond to initial pharmacologic treatment,[6] leading to societal costs of $29–$48 billion a year for health care, loss of productivity, and reductions in well-being.[7] Newer, atypical antipsychotic drugs are frequently prescribed as a second-line therapy to augment antidepressant use despite little evidence regarding their long-term safety or cost-effectiveness compared to other "next-step" treatments.[8,9] Generic equivalents have substantially narrowed price differentials between atypical antipsychotics and older antidepressant drugs in recent years.

Aripiprazole is one of the most commonly prescribed atypical antipsychotics for MDD[10] and was recently found, during a 12-week acute treatment phase, to be more effective at producing remission and reducing depression symptoms than other next-step pharmacotherapies for MDD.[11] It may also be more cost-effective given that it is only slightly more expensive than standard antidepressants. However, aripiprazole has been associated with side effects such as weight gain, metabolic disorders, akathisia, headache, and fatigue,[12,13] all of which may impact quality of life. Additionally, impacts on other health care costs are unclear since higher remission from aripiprazole may lead to less care, but greater side effects can lead to higher costs for treating side effects. Limited research has examined cost-effectiveness of antipsychotics such as aripiprazole in MDD,[14–16] and no study was based on randomized trial data.

We used data from a randomized trial to compare the cost-effectiveness of (1)

Clinical Points

- Augmentation with either aripiprazole or bupropion was cost-effective compared to switching to bupropion in patients with treatment-resistant depression.
- Physicians should discuss cost and benefits, including side effects, of treatment strategies for nonresponsive depression with patients.

augmenting antidepressant therapy with aripiprazole compared to (2) augmenting antidepressant therapy with bupropion, a widely prescribed norepinephrine-dopamine reuptake inhibitor, and (3) switching to bupropion over a 12-week acute treatment phase. We also compared the effects on employment and work and social adjustment.

METHODS

Study Design

This cost-effectiveness analysis (CEA) was conducted as part of the Veterans Affairs (VA) Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) trial. The multisite randomized, single-blind, parallel-assignment trial was designed to study effectiveness and cost-effectiveness of augmentation of original antidepressant therapy with a major second-generation antipsychotic, aripiprazole; augmentation with a widely used antidepressant, bupropion; and switching from original antidepressant therapy to bupropion in treatment-resistant patients with MDD.[17] Participants were 1,522 veterans, aged 18 years or older, who remained at least moderately depressed after meeting minimal standards of treatment for nonpsychotic MDD and were enrolled in 35 participating VA medical centers. Participants were randomized from December 2012 to May 2015 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 the coordinating center in West Haven, Connecticut.

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. Patients were allowed to use other non-pharmacologic treatments for depression (eg, psychotherapy, peer support, meditation) throughout the trial if they were initiated prior to randomization. Acute treatment visits occurred at baseline and at weeks 1, 2, 4, 6, 8, 10, and 12.

Patients were withdrawn from the study during follow-up if they had worsening symptoms, experienced side effects, were noncompliant, or had other reasons for withdrawal. Our analysis was conducted by intention-to-treat and included all randomized patients.[17] A clinically significant difference in remission of 10% for a target sample size of 1,518 was chosen for estimating sample size and power. Outcomes were assessed by independent evaluators blinded to treatment assignment.

Our time horizon for this study was 12 weeks. Many patients are treated with pharmacotherapy long-term for recurrent or chronic depression,[18–20] so we expected that costs and benefits similar to those that accrued over the study period would persist over the longer term. The CEA of the trial was approved by both the Stanford University institutional review board (IRB) and the VA Central IRB. The trial was registered in Clinicaltrials.gov (identifier: NCT01421342). All patients provided written informed consent and privacy authorization.

Data Sources

The main effects of remission from depression, quality-adjusted life-years (QALYs), costs, and other outcomes were estimated from trial and administrative data collected at baseline and 12 weeks after randomization. VA health care costs were obtained from the VA Managerial Cost Accounting (MCA) files. Study drug costs were obtained from Federal Supply Schedule (FSS). VA utilization was obtained from the VA Patient Treatment File for inpatient care, the National Patient Care Database for outpatient care, and the MCA Pharmacy File for prescription records.

Outcome Measures

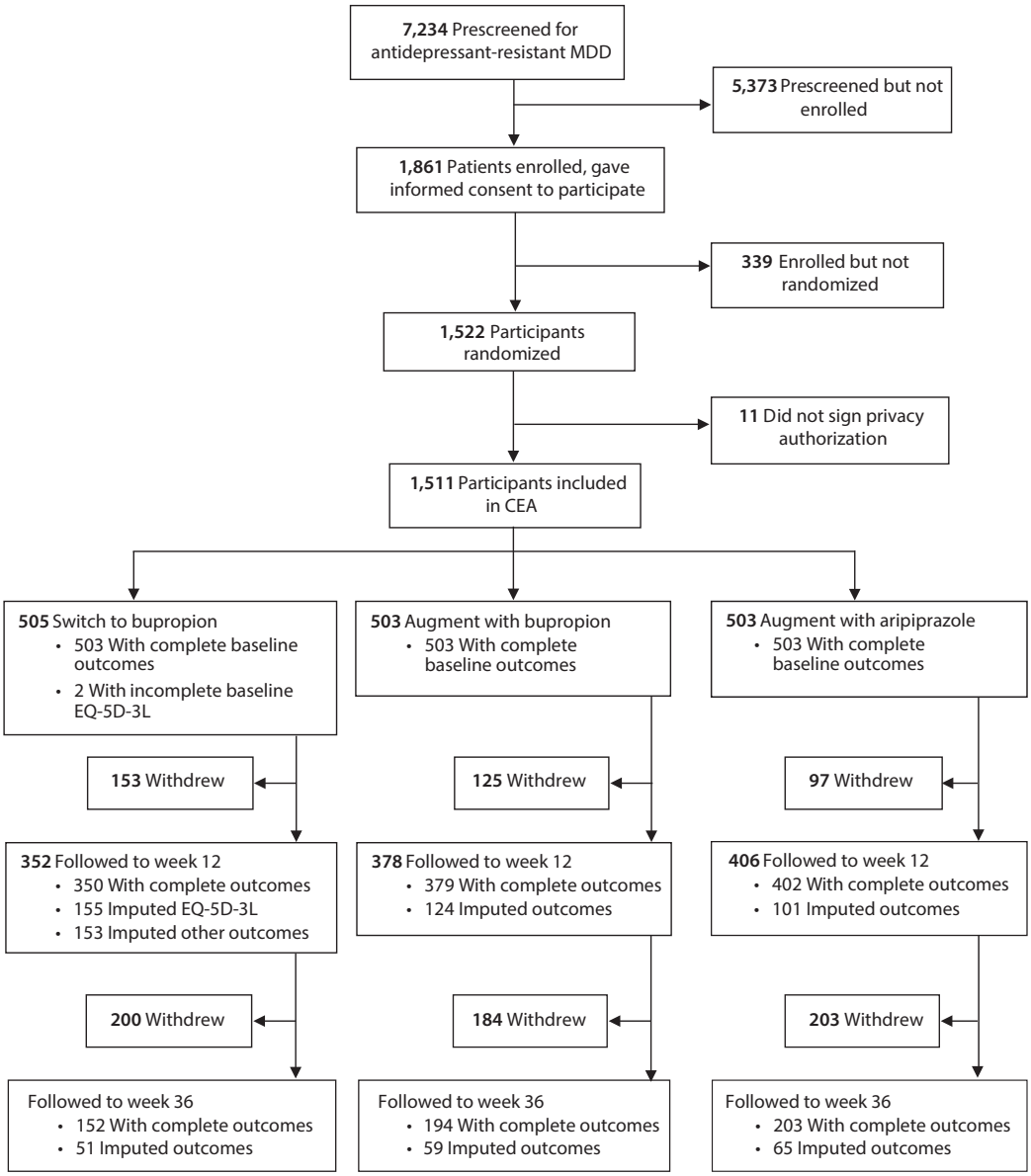
Our primary CEA outcome was based on remission of depression. Remission was indicated if a patient had 2 consecutive follow-up visits with a 16-item Quick Inventory of Depressive Symptomatology–Clinician Rated (QIDS-C_{16})[21] score of ≤ 5. As a secondary outcome, we estimated QALYs, the recommended CEA outcome.[22] To measure patients' QALYs, we administered the 3-level EuroQol 5-dimensional index (EQ-5D-3L),[23] a survey assessing health-related quality of life in 5 domains. Gains in QALYs were obtained by summing the area under the curve for health utilities measured by the EQ-5D-3L, and deaths were assigned a value of 0 for the remaining period.

Costs and Utilization Measures

We measured mental health care utilization, including outpatient visits to mental health providers and inpatient stays for psychiatric care and all other health care utilization, separately. MCA data use an activity-based cost allocation system to estimate costs, and these costs were adjusted using a geographic wage index. VA-sponsored health care costs were obtained from the Fee Basis files using payments to non-VA providers. Other non-VA care costs were estimated from patients' self-reports for non-VA inpatient stays and the median cost of VA inpatient stays.

Cost of bupropion, aripiprazole, and patients' original antidepressants were measured based on the 2016 FSS generic price as recommended for conducting CEA.[24] The FSS price of a 12-week supply of aripiprazole was $30 compared to $12 for bupropion sustained release (SR). Cost of patients' original antidepressants were obtained by estimating a weighted average price of generic versions of

Figure 1. Study Cohort



Abbreviations: ARI = aripiprazole, BUP = bupropion, CEA = cost-effectiveness analysis, EQ-5D-3L = 3-level EuroQol 5-dimensional index, MDD = major depressive disorder.

citalopram, fluoxetine, sertraline, and venlafaxine, which constituted 80% of all antidepressant fills; the mean price of these drugs for a 12-week supply was $22. Costs of all other VA prescription drugs were obtained from MCA data and included in all other health care costs.

Other Costs

We adopted a health sector perspective for the primary CEA and included all mental health care costs (study drugs, outpatient mental health, and inpatient psychiatric care) since the VA directly provides this care and must implicitly justify this spending in annual budget projections. In additional analyses, we used a societal perspective and accounted for all other health care costs and costs borne by patients, including costs of accessing medical care such as travel expenses. We calculated travel expenses based on the distance from a patient's zip code to the nearest VA provider and the tax-deductible per-mile travel expense.[25]

We estimated time spent obtaining health care using a count of visits and hospital days and valued patients' time based on their self-reported wage rates or else the mean of national wage rates in the US Bureau of Labor Statistics.[26] Costs were adjusted for inflation using the Consumer Price Index for all goods.

Secondary Outcome Measures

We used an alternate measure of quality of life with the Quality of Life Enjoyment and Satisfaction Questionnaire

Table 1. Baseline Characteristics of Randomized Participants by Treatment Group[a]

Characteristic	Switch-BUP (n = 505)	Augment-BUP (n = 503)	Augment-ARI (n = 503)
Age, mean ± SD, y	54.4 ± 12.2	54.4 ± 12.2	54.2 ± 12.3
Sex			
Male	437 (86.5)	422 (83.9)	427 (84.9)
Female	68 (13.5)	81 (16.1)	76 (15.1)
Race			
White	331 (65.8)	340 (67.6)	336 (66.9)
African American or black	129 (25.6)	114 (22.7)	124 (24.7)
Other race	43 (8.6)	49 (9.7)	42 (8.4)
Hispanic ethnicity	57 (11.3)	55 (10.9)	44 (8.8)
Education			
Less than high school diploma	29 (5.7)	15 (3.0)	16 (3.2)
High school diploma/GED	128 (25.4)	124 (24.7)	114 (22.7)
Some college credit/but no degree	188 (37.2)	197 (39.2)	197 (39.2)
College degree (associates or greater)	160 (31.7)	167 (33.2)	176 (35.0)
Current marital status			
Married	212 (42.1)	221 (43.9)	216 (42.9)
Divorced or separated	194 (38.4)	187 (37.2)	183 (36.4)
Never married	71 (14.1)	67 (13.3)	69 (13.7)
Other	28 (5.5)	28 (5.6)	35 (7.0)
Lifetime episodes of depression, median	3	3	3
Duration of current episode of MDD, mean ± SD, mo	85.5 ± 131.1	84.9 ± 125.8	90.2 ± 138.2
CIRS Comorbidity index score, mean ± SD	1.83 ± 0.36	1.82 ± 0.37	1.83 ± 0.38
Depression symptom and other features, mean ± SD			
QIDS-C_{16} score	16.6 ± 3.3	16.6 ± 3.2	16.9 ± 3.3
PHQ-9 score	15.9 ± 5.2	16.3 ± 5.2	16.3 ± 5.2
CGI-S score	4.6 ± 1.0	4.6 ± 0.9	4.7 ± 1.0

[a]Values shown as n (%) unless otherwise noted.
Abbreviations: ARI = aripiprazole, BUP = bupropion, CGI-S = Clinical Global Impressions–Severity of Illness scale, CIRS = Cumulative Illness Rating Scale, GED = General Equivalence Development certificate, MDD = major depressive disorder, PHQ-9 = 9-item Patient Health Questionnaire, QIDS-C_{16} = 16-item Quick Inventory of Depressive Symptomatology–Clinician Rated.

(Q-LES-Q).[27,28] We also measured hours worked and participation in social activities. We collected self-reported data about patients' employment status and wages earned. We also collected measures of work and social impairment using the Work Productivity and Activity Impairment (WPAI) tool[29] and the Work and Social Adjustment Scale (WSAS)[30] at baseline and 12-week follow-up.

Other Study Measures

Data collected by the trial included patients' age, sex, marital status, race (self-reported in investigator-specified categories to understand study generalizability), and education; a comorbidity measure, the Cumulative Illness Rating Scale (CIRS) severity index[31]; the 9-item Patient Health Questionnaire[32]; and the Clinical Global Impressions–Severity of Illness scale.[33]

Analysis

Baseline characteristics were compared using χ^2 tests and analysis of variance. Our primary outcome was the incremental cost-effectiveness ratio (ICER) for costs per remission, defined as the difference in costs between each treatment strategy versus the other divided by the differences in remission rates. We calculated 95% confidence intervals (CIs) and regions around the ICERs using bootstrap methods.[34] As a ratio, the statistical uncertainty for an ICER is best represented by a confidence ellipsoid plotted in 2-dimensional space, with cost plotted on the y-axis and effectiveness plotted on the x-axis. On the basis of bootstrapped samples, we estimated cost acceptability curves to indicate the probability that the treatment was cost-effective compared with the alternative for a range of willingness-to-pay values. For our secondary outcome, we estimated the ICERs for the cost per QALY with estimated 95% CIs and regions. An ICER below willingness-to-pay thresholds per QALY (typically $50,000–$100,000) leads to recommendation of treatment.[35]

To compare outcomes between the 3 treatment strategies, we used linear mixed models adjusted for baseline measures and treatment group. We tested differences in mean outcome for each group against the other 2 groups with a significance level of $P < .05$ with 2-sided hypothesis tests. Since some patients withdrew before the end of the 12-week assessment period (n = 375, 25%) (Figure 1), for QIDS-C_{16} data missing due to withdrawal, the QIDS-C_{16} score of the patient at the last completed assessment was retained to measure remission. For EQ-5D-3L data missing due to withdrawal or incomplete assessments, we imputed EQ-5D-3L values using data from patients who remained in the trial for the 12-week period and did not remit to provide a conservative estimate. We conducted multiple imputations based on a multivariate normal distribution with 10 imputations using age, sex, marital status, education, and treatment group using PROC MI in SAS.[36,37] Costs were not imputed for any analysis since they were obtained from administrative data sources for all enrolled patients.

In sensitivity analyses, we accounted for any response bias in the EQ-5D-3L due to differences between the patients who withdrew before end of follow-up and patients who did not by including attrition weights in regression models.[38,39] Attrition weights were used to weight responses by the likelihood of withdrawal and adjusted for treatment group, age, sex, marital status, race, education, and baseline CIRS, EQ-5D-3L, and QIDS-C_{16} scores. SAS 9.4 (SAS Institute Inc, Cary, North Carolina) was used for all analyses.

RESULTS

A total of 1,522 adults were enrolled in the trial. There were no significant differences in sociodemographic characteristics between treatment groups. The mean age of participants enrolled in the trial was 54 years, participants were predominantly male (84%–87%), and all groups had similar depression characteristics (Table 1).

Mean mental health care costs were similar across treatment groups but nonsignificantly higher for the aripiprazole group at $2,273 per patient (95% CI, $1,696 to $2,850) (Table 2). The

Table 2. Mean Mental Health Care Costs by Treatment Group for 12-Week Follow-Up[a]

Cost Category	Adjusted Cost, Mean (95% CI), $		
	Switch-BUP	Augment-BUP	Augment-ARI
Antidepressant drugs plus augmentation therapies	53 (35 to 71)	73 (55 to 90)	88 (70 to 106)
Outpatient mental health visits	1,931 (1,503 to 2,359)	1,913 (1,492 to 2,334)	1,970 (1,547 to 2,393)
Inpatient psychiatric stays	218 (–147 to 582)	186 (173 to 545)	215 (–146 to 575)
Total mental health costs	2,201 (1,617 to 2,785)	2,171 (1,597 to 2,746)	2,273 (1,696 to 2,850)

[a]Mean costs were obtained from regression models adjusting for baseline costs and sociodemographics.
Abbreviations: ARI = aripiprazole, BUP = bupropion.

Table 3. Cost per Remission by Treatment Group

Treatment Group	Mental Health Services and Medication Cost, Mean (95% CI), $[a]	Remission From Depression, Rate	Cost Per Remission, ICER (95% CI[b]), $
Switch-BUP (n = 505)	2,201 (1,617 to 2,785)	0.22	
Augment-BUP (n = 503)	2,171 (1,597 to 2,746)	0.27	
Augment-ARI (n = 503)	2,273 (1,696 to 2,850)	0.29	
Augment-BUP vs Switch-BUP	–30 (–39 to –20)	0.047	–640 (–5,770 to 3,008)
Augment-ARI vs Switch-BUP	71 (65 to 79)	0.066	1,074 (47 to 5,022)
Augment-ARI vs Augment-BUP	101 (99 to 104)	0.02	5,094 (–34,027 to 32,774)

[a]Costs include outpatient mental health visits, inpatient psychiatric stays, and antidepressants and study drugs. Mean costs were estimated from adjusted models (adjusted for baseline costs and sociodemographics).
[b]95% CIs were obtained from bootstrapping methods.
Abbreviations: ARI = aripiprazole, BUP = bupropion, ICER = incremental cost-effectiveness ratio.

rate of remission at 12 weeks was highest for aripiprazole augmentation (29%), followed by bupropion augmentation (27%), and lowest for bupropion switching (22%) (Table 3).

The ICER for incremental costs divided by incremental remission rate for aripiprazole augmentation versus bupropion switching group was $1,074, and bootstrap analyses showed that 97.9% of observations were in the upper right quadrant, indicating greater costs and benefits associated with aripiprazole (Supplementary Figure 1). The ICER for aripiprazole augmentation versus bupropion augmentation was $5,094, and bootstrap analyses showed 75.6% of observations in the upper right quadrant (Supplementary Figure 2). Bupropion augmentation strongly dominated bupropion switching, as the ICER was –$640, with 79.0% of observations in the lower right quadrant, showing lower costs and greater benefit for bupropion augmentation (Supplementary Figure 3).

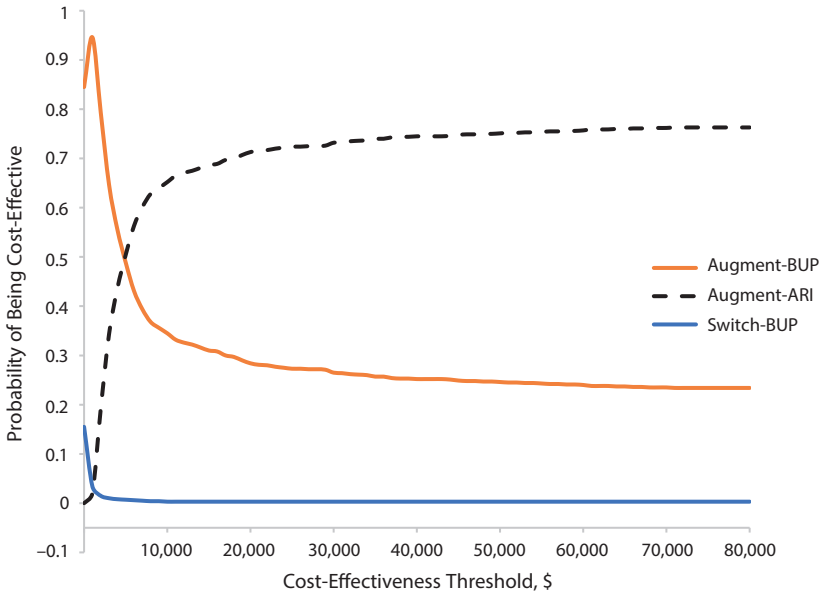
Comparing cost-effectiveness of the treatments across a range of willingness-to-pay values for remission, we found that at remission values less than $10,000, bupropion augmentation had a higher probability of being more cost-effective than the other 2 strategies (Figure 2). At remission values greater than $10,000, aripiprazole augmentation had a 76% probability of being more cost-effective and bupropion augmentation had a 23% probability of being more cost-effective than the other strategies.

We conducted CEA using QALYs, and mean QALYs were not significantly different across treatment groups (Supplementary Table 1). The ICER for costs per QALY for aripiprazole augmentation versus bupropion switching was $468,126, as aripiprazole augmentation was negligibly more effective but more expensive and substantially above traditional cost-effectiveness thresholds. The ICER for the aripiprazole augmentation versus bupropion augmentation was $85,817, while the ICER for bupropion augmentation versus bupropion switching was $29,039.

We compared quality of life using the Q-LES-Q, employment, work impairment, and work and social adjustment and found that all measures improved from baseline to 12-week follow-up (Supplementary Table 2). However, none of the comparisons between treatment groups was statistically significant.

We conducted analyses from a societal perspective comparing cost per remission using all inpatient, outpatient, and prescription drug costs in addition to patients' time, travel, and productivity costs (Supplementary Tables 3–5). These results were similar to results from the health sector perspective since both augmentation groups were cost-effective relative to switching and aripiprazole augmentation was more cost-effective than bupropion augmentation. Since our cost-per-QALY results were affected by withdrawal during follow-up, we conducted sensitivity analysis in which we used attrition weights to account for differential attrition by treatment group (Supplementary Table 6). Results showed that only bupropion augmentation was more cost-effective than switching.

Figure 2. 12-Week Cost-Effectiveness Acceptability Curves



Abbreviations: ARI = aripiprazole, BUP = bupropion.

DISCUSSION

During a 12-week acute treatment phase, we found that both augmentation strategies were cost-effective relative to bupropion switching in comparing the cost per remission, and this result was consistent over a range of willingness-to-pay thresholds. Moreover, bupropion switching was strongly dominated by bupropion augmentation since remission was higher and costs were lower in the augmentation group. We found that bupropion augmentation was more cost-effective than aripiprazole augmentation only at low values for remission less than $10,000 per remission, so aripiprazole augmentation was more cost-effective than the other strategies for all higher willingness-to-pay values.

While we observed significant improvements in QALYs from baseline to follow-up for all treatment groups, there were only small differences between groups. When the cost per QALYs between groups is compared, augmentation with bupropion relative to bupropion switching had the lowest ICER while aripiprazole augmentation had less favorable cost-effectiveness ratios relative to the other groups. The differences in our results between cost per remission and cost per QALY is partly explained by the lack of treatment differences in QALYs. Since our study population was predominantly older men, they had greater comorbidity and worse overall health status than other patients, which may partly explain the limited ability of the EQ-5D-3L to pick up on improvements in quality of life associated with depression remission. The primary report[11] previously found that the aripiprazole group had higher rates of adverse effects for fatigue, increased appetite, increased weight, akathisia, and somnolence and abnormal values for several laboratory tests. Therefore, it is plausible that higher QALYs that would have resulted from greater remission from aripiprazole augmentation were negated by lower QALYs from side effects of the drug.

It is also unclear why we found higher remission rates with aripiprazole but not greater improvements in other outcome measures such as employment, work, and social adjustment. Further exploration of side effects from aripiprazole may be warranted.[40,41]

Our results make a new contribution to the literature, as no prior studies used randomized trial data to compare cost-effectiveness of aripiprazole with other strategies for treatment-nonresponsive depression. One cost-effectiveness analysis[14] was based on information compiled from other studies and estimated that costs per additional responder (measured as depression symptoms) were lower for aripiprazole compared to standard antidepressants and other antipsychotic drugs. Observational studies[15,16] found mixed results regarding whether aripiprazole as an augmentation therapy was associated with lower or higher utilization and costs compared to other antidepressants.

Limitations

In this study, all costs and benefits from treatment were limited to the initial 12-week treatment period. If this time horizon was not long enough to fully measure impacts on employment outcomes and health care utilization, then our estimates are conservative. However, we examined costs over a 36-week continuation phase and found similar cost differences between treatment groups (J.Y., S.Z., A.P., et al, unpublished data, 2018), so extending the time horizon through several months did not appear to affect cost findings. All treatment groups were followed in outpatient care using the same protocol, which may have limited our ability to identify differences in patients' outpatient visit costs that may otherwise have occurred by treatment group.

Some patients received non-pharmacologic treatments for MDD such as psychotherapy, and we were unable to examine the interaction of these treatments with the study drugs as patients may have experienced greater improvements in depression symptoms when combining pharmacotherapy and nonpharmacologic care. The measures of quality of life that we used may not have been sensitive enough to pick up differences between treatment groups in depression symptoms; however, prior studies[27,42,43] have found that the EQ-5D-3L and the Q-LES-Q measures were associated with small differences in depression symptoms. The trial had high rates of withdrawal during follow-up, although we did conduct analyses with attrition weighting to account for this. The lack of a placebo group is another limitation. Finally, our findings may not be generalizable to the general population.

CONCLUSION

Many patients with major depressive disorder who do not receive optimal benefit from their initial or subsequent treatment trial may benefit from augmentation therapy with aripiprazole or bupropion, and these treatments are cost-effective relative to switching to a commonly prescribed antidepressant. Additional considerations should be given to side effects in selecting an augmentation therapy for nonresponsive depression.

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Additional information: VA health care costs were obtained from the VA Managerial Cost Accounting (MCA) files. Study drug costs were obtained from Federal Supply Schedule (FSS). VA utilization was obtained from the VA Patient Treatment File for inpatient care, the National Patient Care Database for outpatient care, and the MCA Pharmacy File for prescription records. Researchers can request access to these data sources if they have a research protocol approved by a VA Research and Development (R&D) Committee and reviewed by an institutional review board. For access, contact VINCI@va.gov.

Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Comparing Cost Effectiveness of Aripiprazole Augmentation With Other "Next-Step" Depression Treatment Strategies: A Randomized Clinical Trial

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Supplementary Table 1. Cost per Quality Adjusted Life Year (QALY)

Comparison	Mental health cost difference	Utility difference†	ICER Cost per Utility (95% Confidence Intervals‡)
Aug-BUP Vs. BUP	-$30	-0.0010	$29,039 (-$185,604 to $181,823)
Aug-ARI Vs. BUP	$71	0.0002	$468,126 (-$425,881 to $400,934)
Aug-ARI Vs. Aug-BUP	$101	0.0012	$85,817 (-$483,214 to $466,643)

†QALYs were measured using the EQ-5D. QALYs were imputed for patients who withdrew before the end of the acute and continuation phases.

‡95% confidence intervals were obtained from bootstrapping methods.

Supplementary Table 2. Quality of Life, Work, and Social Outcomes by Treatment Group

	Week	N	Switch - BUP	Augment - BUP	Augment - ARI
			Mean (95% CI)		
Cumulative health utility (from EQ-5D)	**0**	1509	-	-	-
	12	1124	0.14 (0.14 to 0.15)	0.15 (0.14 to 0.15)	0.15 (0.14 to 0.15)
QIDS	**0**	1511	16.4 (16.0 to 16.8)	16.3 (15.9 to 16.7)	16.6 (16.2 to 17.0)
	12	1124	8.7 (8.2 to 9.2)	8.3 (7.8 to 8.9)	8.2 (7.6 to 8.7)
Q-LES-Q	**0**	1511	42.8 (41.2 to 44.3)	42.3 (40.7 to 43.8)	42.2 (40.6 to 43.8)
	12	1119	51.5 (49.7 to 53.2)	51.2 (49.4 to 53.0)	53.1 (51.3 to 54.9)
Employment	**0**	1511	0.36 (0.29 to 0.46)	0.34 (0.27 to 0.43)	0.41 (0.33 to 0.51)
	12	1136	0.41 (0.32 to 0.52)	0.37 (0.29 to 0.46)	0.45 (0.37 to 0.56)
Proportion reporting work time missed(WPAI)	**0**	396	0.32 (0.24 to 0.42)	0.43 (0.34 to 0.54)	0.36 (0.28 to 0.46)
	12	314	0.18 (0.12 to 0.28)	0.25 (0.18 to 0.35)	0.28 (0.21 to 0.38)
% impairment at work (WPAI)	**0**	392	50.0 (44.3 to 55.7)	51.5 (45.7 to 57.2)	52.7 (47.2 to 58.2)
	12	307	32.4 (26.3 to 38.6)	36.2 (29.7 to 42.6)	40.0 (34.1 to 45.9)
Proportion reporting work productivity loss (WPAI)	**0**	396	0.32 (0.24 to 0.42)	0.43 (0.34 to 0.54)	0.36 (0.28 to 0.46)
	12	314	0.18 (0.12 to 0.28)	0.25 (0.18 to 0.35)	0.28 (0.21 to 0.38)
% activity impairment (WPAI)	**0**	1511	64.0 (61.5 to 66.4)	62.7 (60.2 to 65.2)	64.1 (61.6 to 66.6)
	12	1117	43.9 (40.9 to 46.8)	45.9 (42.9 to 48.9)	45.0 (42.0 to 48.0)
Work and social adjustment scale (WSAS)	**0**	1443	26.7 (25.7 to 27.6)	26.2 (25.2 to 27.2)	26.7 (25.7 to 27.6)
	12	1074	18.6 (17.4 to 19.8)	19.0 (17.7 to 20.2)	18.8 (17.5 to 20.0)

None of the comparisons tested between treatment groups were significant at $P<0.05$. Mean values were estimated from models adjusted for baseline values, sociodemographic factors, and were imputed for those who withdrew prior to follow-up.

Supplementary Table 3. Mean Monthly Total Health Care Costs by Treatment Group for Societal Perspective

Mean Monthly Total Health Care Costs	Switch - BUP	Augment - BUP	Augment - ARI
	Adjusted Mean (95% Confidence Interval)		
Baseline: 12 months prior			
Drug	$153 (102 to 204)	$157 (106 to209)	$213 (161 to 265)
Outpatient	$1,054 (922 to 1,185)	$1,126 (992 to 1,259)	$1,066 (932 to 1,199)
Inpatient	$372 (162 to 582)	$406 (193 to 618)	$443 (230 to 656)
Patient travel + time	$132 (98 to 165)	$116 (82 to 150)	$127 (93 to 161)
Total	$1,712 (1,410 to 2,015)	$1,807 (1,501 to 2,113)	$1,852 (1,544 to 2,159)
12-week			
Drug	$192 (125 to 258)	$187 (119 to 255)	$264 (195 to 334)
Outpatient	$1,535 (1,356 to 1,714)	$1,681 (1,500 to 1,863)	$1,613 (1,430 to 1,795)
Inpatient	$184 (-85 to 453)	$354 (79 to 628)	$132 (-142 to 406)
Patient travel + time	$146 (71 to221)	$150 (75 to 225)	$201 (125 to 277)
Total	$2,095 (1,696 to 2,495)	$2,398 (1,992 to 2,804)	$2,250 (1,842 to 2,658)

Supplementary Table 4. Total Health Care Costs per Remission by Treatment Group from Societal Perspective

	Total Health Care Costs[†] (95% Confidence Interval)	Remission from Depression	ICER Cost per Remission (95% Confidence Interval[‡])
Switch - BUP N=505	$6,650 ($4,770 to $8,531)	0.22	
Augment-BUP, N=503	$7,281 ($5,431 to $9,131)	0.27	
Augment-ARI, N=503	$6,894 ($5,036 to $8,752)	0.29	
Aug-BUP Vs. BUP	$631	0.047	$13,538 (-$57,555 to $104,560)
Aug-ARI Vs. BUP	$244	0.066	$3,669 ($979 to $15,890)
Aug-ARI Vs. Aug-BUP	-$387	0.020	-$19,473 (-$117,762 to $119,115)

[†]Total health care costs include outpatient visits, inpatient stays, pharmacy costs, travel, and time costs. Mean costs estimated from adjusted models (adjusted for baseline costs and sociodemographics).
[‡]95% confidence intervals were obtained from bootstrapping methods.

Supplementary Table 5. Impact Inventory for Reference Case Analysis

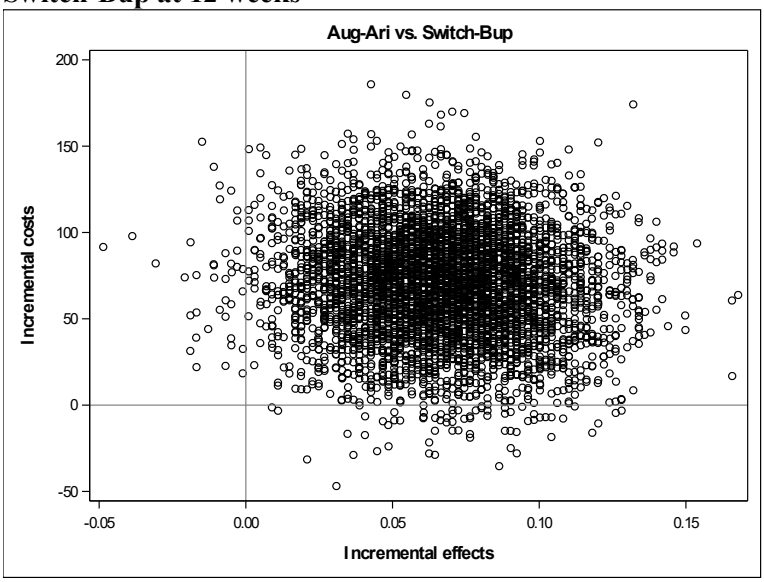
Sector	Outcome	Perspective for CEA	
Health		Health care sector	Societal
	Quality of life	Yes	Yes
	Remission from depression	Yes	Yes
	Health care costs paid by VA and other payers	Yes	Yes
	Patient time costs	No	Yes
	Transportation costs	No	Yes
Non-Health	Lost productivity	No	Yes

Supplementary Table 6. Cost per Utility† Analysis Using Attrition Weights

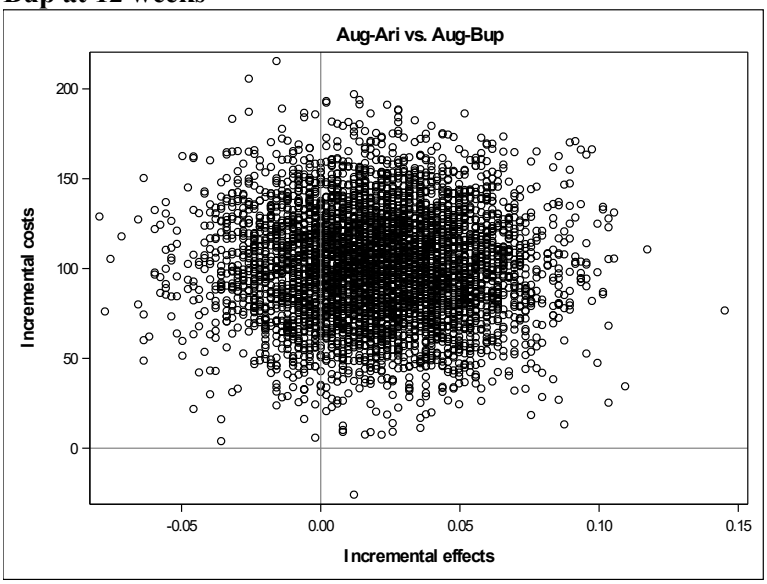
Comparison	Mental health cost difference	Utility difference	ICER Cost per Utility (95% Confidence Interval)
Aug-BUP Vs. BUP	$107	0.0029	$36,256 (-$347,525 to $291,251)
Aug-ARI Vs. BUP	$252	0.0034	$73,295 (-$716,747 to $655,476)
Aug-ARI Vs. Aug-BUP	$145	0.0005	$293,620 (-$750,761 to $748,494)

†Utility was measured using the EQ-5D. Utility among respondents was weighted for attrition to account for patients who withdrew before the end of the acute and continuation phases.

Supplementary Figure 1: Bootstrapped analysis of ICER for Cost per Remission: Aug-Ari vs. Switch-Bup at 12 weeks



Supplementary Figure 2: Bootstrapped analysis of ICER for Cost per Remission: Aug-Ari vs. Aug-Bup at 12 weeks



Supplementary eFigure 3: Bootstrapped analysis of ICER for Cost per Remission: Aug-Bup vs. Switch-Bup at 12 Weeks